Pathology

Marrow Edition 6

Volume 2

MARROW

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// ME521-SLC

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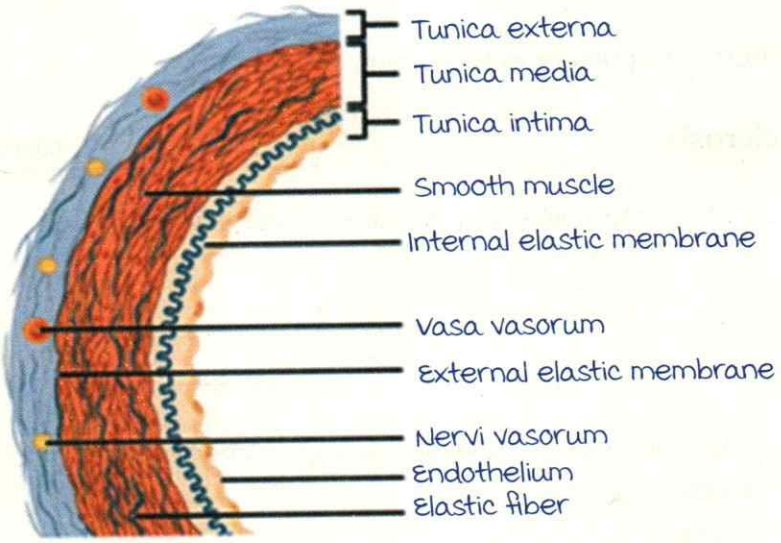
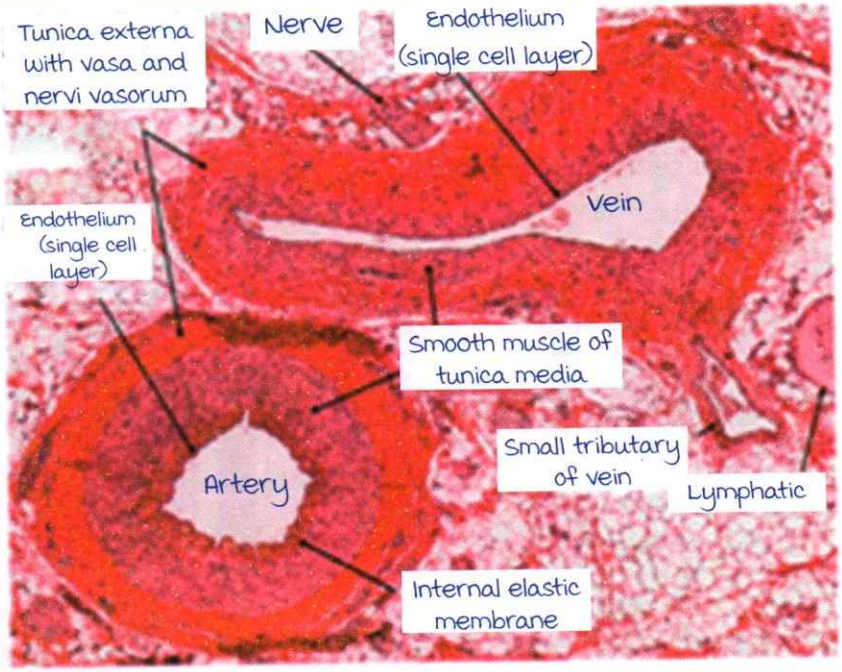
BLOOD VESSELS : SCLEROSIS

Normal histology of a blood vessel 00:01:52





Pathology Tunica Intima : Inner most layer.

Single layer of endothelial cells.

Internal elastic lamina : In between T. intima and media.

Tunica media : Thickest layer.

Composed of smooth muscle cells.

Active space

External Elastic lamina : In between T. media and Adventitia.
Tunica Adventitia : Some fat and vasa vasorum.

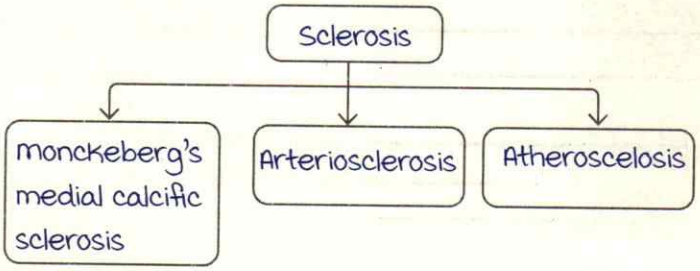
Marker for blood vessels : CD 31, factor 8, vWF, VEGF.
Stain for elastin layer (internal and external elastic Lamina : Verhoff Van Geisan stain).

If RBCs are present in the lumen, it can be a blood vessel.

Sclerosis

00:06:05

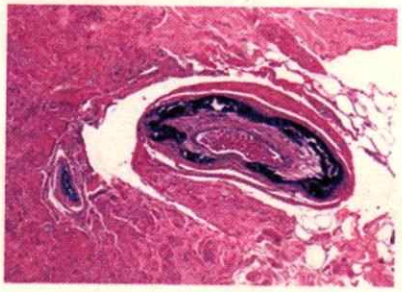
Sclerosis is the thickening or hardening of vessels.



Monckeberg's medial calcific sclerosis :
Seen in elderly.
Sclerosis is seen in tunica media.
Asymptomatic.

Calcification on H & E stains as purple, as calcium stains with basophilic dyes.
Stains for calcium :

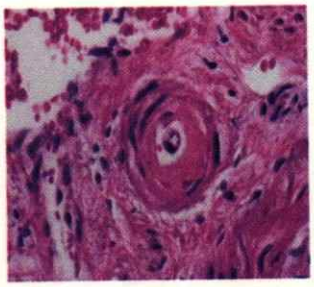
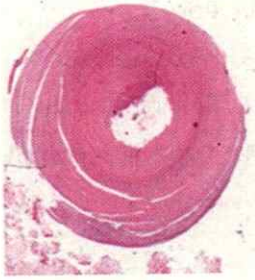
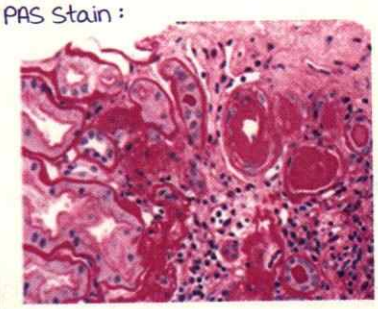
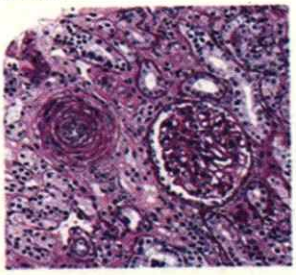
1. Von Kossa.
2. Alizarin Red S.



Arteriosclerosis :
Thickening and hardening of artery.
2 types :

1. Hyaline arteriosclerosis.
2. Hyperplastic arteriosclerosis.

Active space

Hyaline	Hyperplastic
Seen in : Benign hypertension and diabetes mellitus	Seen in : Malignant hypertension
Microscopy : Pink homogenous thickening of the vessel wall that leads to narrowing of lumen.	Microscopy : Proliferation of smooth muscle cells leads to concentric laminated thickening : Onion skin appearance. Fibrinoid necrosis.
	
PAS Stain : 	PAS Stain : 

"Onion skin in medicine"

Malignant hypertension : biopsy.
CIDP : Nerve biopsy.
Primary sclerosing cholangitis : Biopsy.
SLE, spleen : Gross.
Ewing's sarcoma : X-ray.

Tay Sach's disease :
On electron microscopy.

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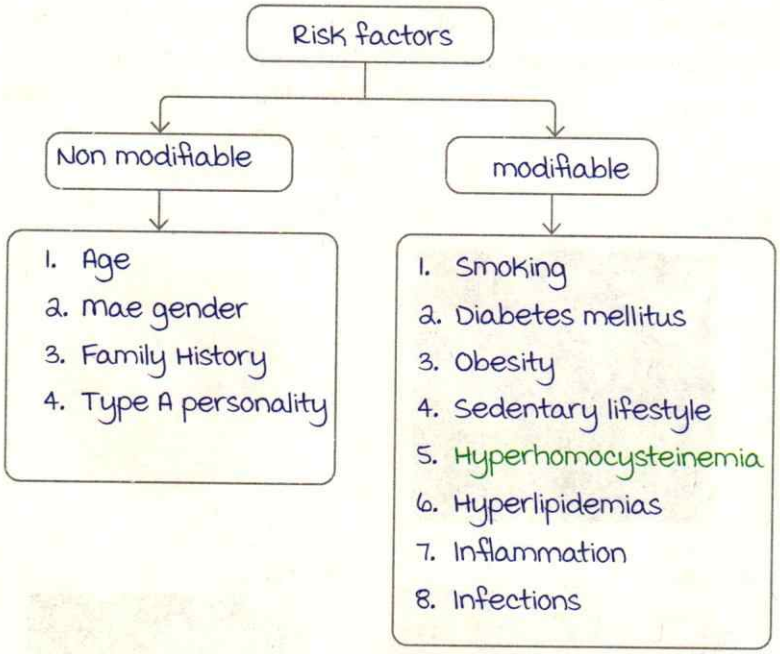
Atherosclerosis

00:14:24

Formation of atheromatous plaque in the vessel wall.

Risk factors :

Same risk factors for myocardial infarction as well.



Most important non-modifiable factor is family history.

In recent times, Hyperhomocysteinemia has emerged to be an important risk factor.

Infections that can lead to increased risk of atherosclerosis :

1. Herpes.
2. Cytomegalovirus.
3. Chlamydia.

Pathogenesis :

Most accepted theory : "Response to injury Hypothesis".

Atherosclerosis is a result to the injury to endothelium.

The three most important causing endothelial injury :

1. Hyperlipidaemia.
2. Inflammation.
3. Hemodynamic disturbances.

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Hemodynamic disturbance :

Whenever there is Laminar non turbulent flow.

↓

There is increase in factor KLF-2 (Kruppel like factor 2)

↓

Increases the synthesis of atheroprotective genes.

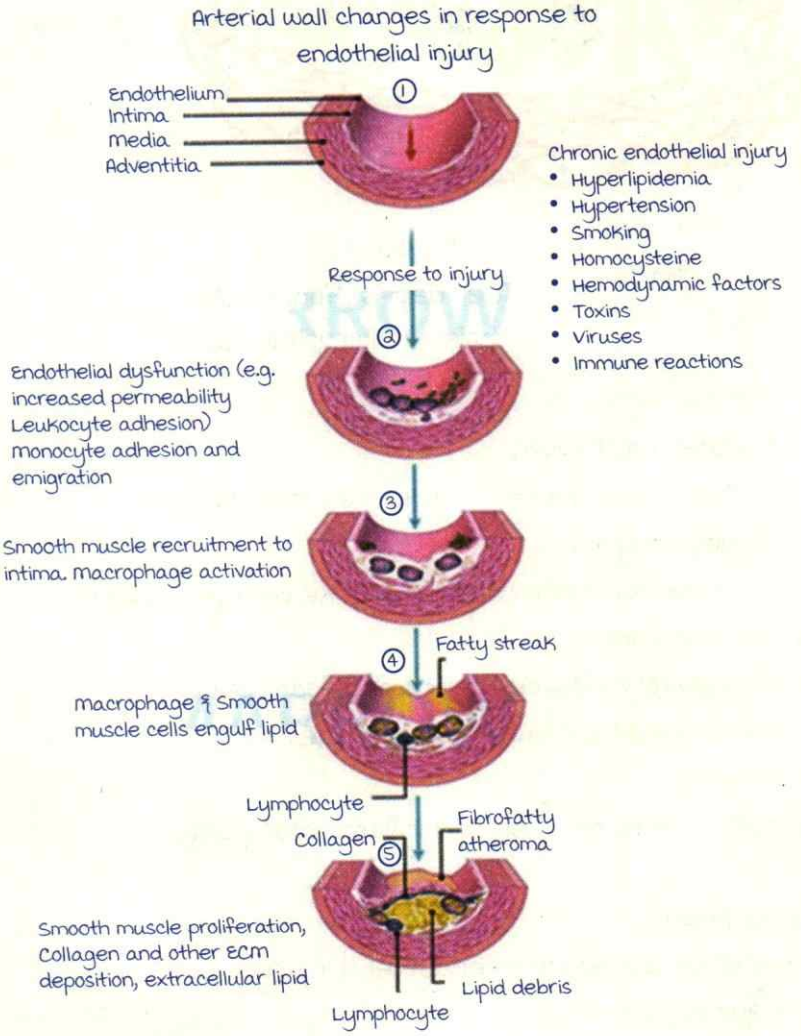
↓

Therefore KLF-2 is atheroprotective.

Most common vessels affected in atherosclerosis :

Abdominal aorta> coronary artery> popliteal artery> internal carotid artery > circle of Willis.

Arterial wall changes in response to injury :



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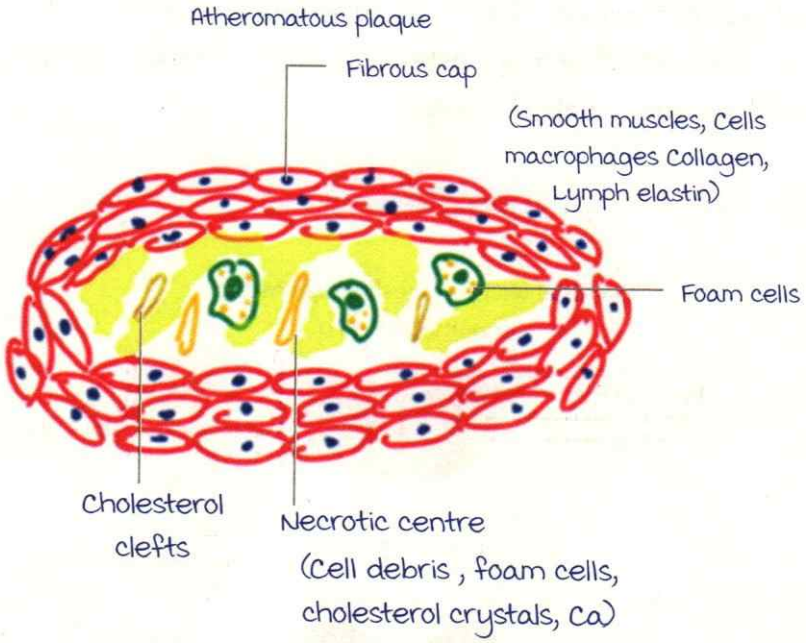
Therefore, response to a chronic endothelial injury produces endothelial dysfunction, macrophage activation and smooth muscle recruitment.

These cells engulf lipid and lead to collagen and other ECM deposition. Along with accumulation of extracellular lipid it leads to the formation of an atheromatous plaque.

Atheromatous plaque

00:25:22



1. Fibrous cap :
   - Outer most layer.
   - Consists of smooth muscle cells, macrophages, lymphocytes.
   - These secrete proteoglycans like collagen, elastin.
2. Necrotic Core :

   Cholesterol clefts, cell debris and foam cells.

   Foam cells : Lipid laden macrophages.
3. Shoulder :

Smooth muscle, collagen and Inflammatory cells.

Fatty streak :

It is the earliest lesion of endothelial injury.

Present in childhood.

Can later develop into atheromatous plaque.

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They are yellow flat lesion seen in vessel wall.

Dietary Habits :
Dietary habits can have a huge impact on development of atherosclerosis.

Atherosclerosis

Vegan Vegetarian Meat - eater

Types of Plaques 00:29:15

Stable Plaque	Vulnerable Plaque
When the main component is the fibrous cap/shoulder.	When the main component is the necrotic core. more dangerous.

Complications : (mnemonic : ACUTE)

1. Aneurysm.
2. Calcification.
3. Ulceration.
4. Thrombosis.
5. Embolism.

Aneurysm 00:32:50

Localized abnormal dilatation of vessel wall.

Types :

1. True aneurysm.
2. False/ pseudoaneurysm.

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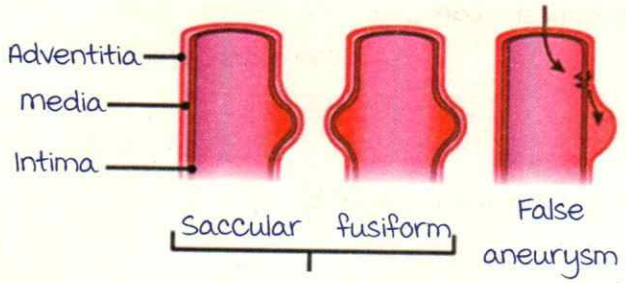
True aneurysm	Pseudo aneurysm
• Involves all three layers. • Due to thinning or weaking of the wall. Example : Atherosclerosis, Anterior transmural MI.	• When there is an extravascular hematoma communicating with an intravascular space. Example : Post MI rupture leads to wall rupture forms a hematoma leading to false aneurysm. It is also called Pulsating hematoma.

Based on shape :

1. Saccular : Spherical outpouching.
2. Fusiform : Cylindrical/ circumferential dilation.



True aneurysms

Dissecting aneurysm

MC cause of abdominal aortic aneurysm : Atherosclerosis.
MC cause of ascending aortic aneurysm : _____

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Abdominal Aortic Aneurysm :

Risk of rupture depends on the size :

<4 cm : Risk is nil.

4–5 cm : Risk is 1% per year.

5–6 cm : Risk is 11% per year.

>6 cm : Risk is 25% per year.

Syndromes associated with Aneurysms :

1. Marfan's syndrome : Defect in fibrillin which leads to cystic medial degeneration.
2. Loeyt Deitz syndrome : Defect in elastin.
3. Ehler Danlos syndrome : Defect in TGF-β signaling pathway.

Syphilitic Aneurysm 00:40:35

Also known as Leutic aneurysm.

Seen in tertiary syphilis.

Usually affects ascending aorta and vasa vasorum.

Shows "tree bark" appearance of vessel wall.

MCQs.

A 44 year old woman dies as a consequence of a 'stroke'. At autopsy, she is found to have a large right basal ganglia haemorrhage. She has an enlarged 550 gm heart with predominantly left ventricular hypertrophy. Her kidneys are small, about 80 gm each, with cortical scarring, and microscopically they demonstrate small renal arterioles that have luminal narrowing from concentric intimal thickening. Which of the following is the most likely condition associated with her findings?

A. Autosomal dominant polycystic kidney disease
B. Diabetes mellitus, type II
C. Hypercholesterolemia
D. Malignant hypertension
E. Monckeberg's medial calcification

Explanation: Onion skin appearance is seen in hyperplastic arteriolosclerosis, found in malignant hypertension.

Active space

44

A 77 year old man with decreasing mental function has developed increasing dyspnea for the past 3 years. On physical examination he has a diastolic murmur. A chest CT scan shows an enlarged heart and prominent aorta. He dies from complications of pneumonia. At autopsy, the thoracic aorta is aneurysmally dilated. A microscopic section of the aorta shows chronic inflammation and luminal narrowing of vasa vasora. There is disruption of the aortic medial elastic fibres. Which of the following conditions is most likely to cause these findings?

A. Hypercholesterolemia.
B. Marfan syndrome.
C. Polyarteritis nodosa.
D. Takayasu arteritis.
E. Tertiary syphilis.
F. ANCA-associated vasculitis.

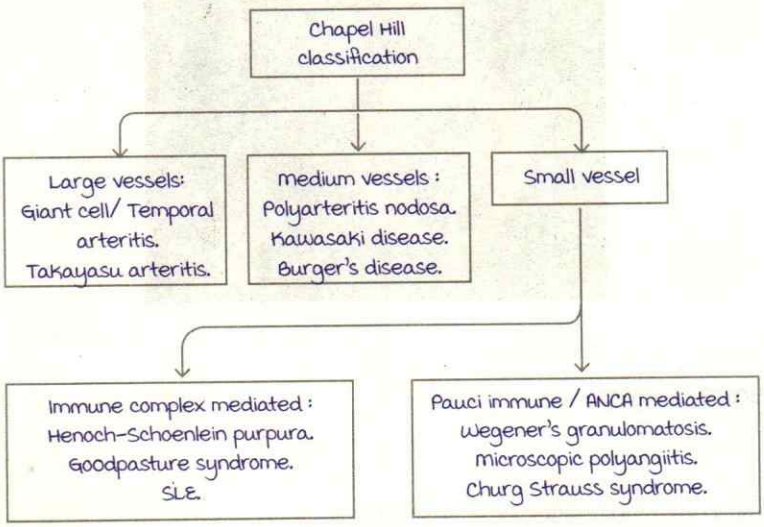
Explanation : Thoracic aorta aneurysm with vasa vasoral narrowing is seen in in syphilitic aneurysm.

Active space

BLOOD VESSELS : VASCULITIS

Vasculitis : Inflammation of vessel wall.

Vasculitis classification :



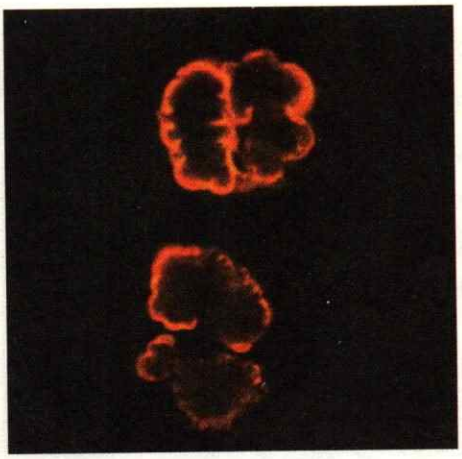
Anti-Neutrophilic Cytoplasmic Antibodies/ANCA 00:03:35

Presence of antibodies against the granules of the neutrophils.

There are two types of ANCA :

C-ANCA : Cytoplasmic ANCA (Anti proteinase-3 ANCA).

P-ANCA : Perinuclear ANCA (Anti myeloperoxidase ANCA).



P-ANCA

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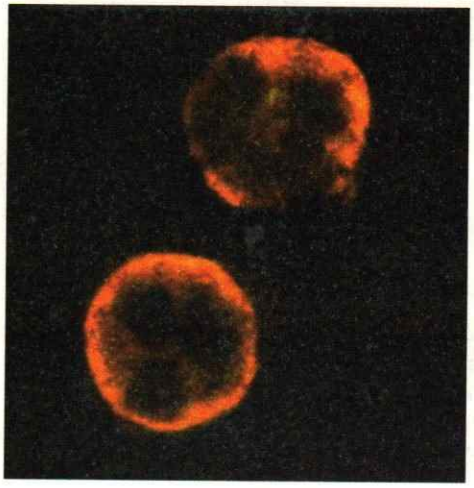
P-ANCA : Seen in microscopic polyangiitis and Churg Strauss syndrome.

C-ANCA : Seen in Wegener's granulomatosis.



C-ANCA

Mnemonic, World Cup :
Wegner's Granulomatosis is :
C-ANCA positive.

On immunofluorescence testing,
P-ANCA shows perinuclear staining.
C-ANCAs show diffusely cytoplasmic staining.

ANCA is not specific to vasculitis as it is also increased in other autoimmune conditions like SLE, Ulcerative colitis or Primary sclerosing cholangitis.

Pathogenesis of vasculitis :

It can be of two types : Non-infectious/immune and Infectious.

Non-infectious are :

- ANCA mediated.
- Hypersensitivity reaction/immune complex mediated.
- T-cell mediated.
- Anti-endothelial antibody mediated.

Active space

Giant cell arteritis

00:09:26

Also known as temporal arteritis.

It is the most common vasculitis associated with the elderly (>50 years).

The most common vessel involved is the _____

Other vessels that can be affected are the ophthalmic artery and vertebral artery.

The most common symptom is a localized headache.

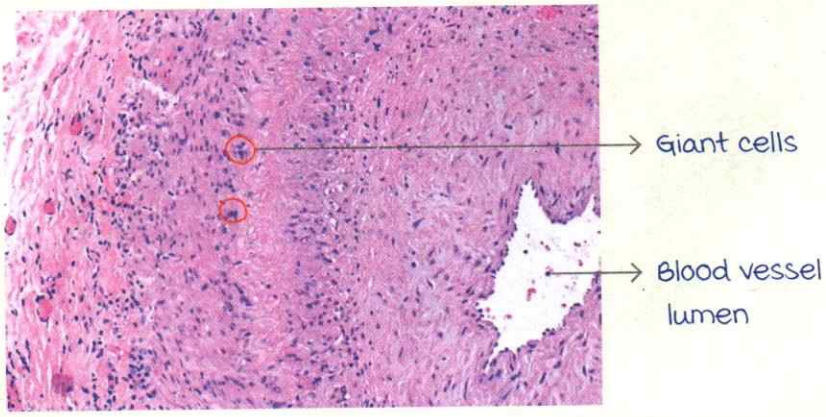
The most specific symptom is jaw claudication.

Other symptoms are fever and weight loss.

It can be associated with polymyalgia rheumatica.

Increased ESR present.

Investigation of choice : Arterial vessel wall biopsy.
A minimum 3 to 5 cm of the vessel wall is taken.



Histopathology :

Granulomatous inflammation.

Giant cells.

Infiltration of the vessel with CD4 + T cells

Fragmentation of internal elastic lamina.

These are best visualized on VVG/Verhoeff Van Gieson's stain.

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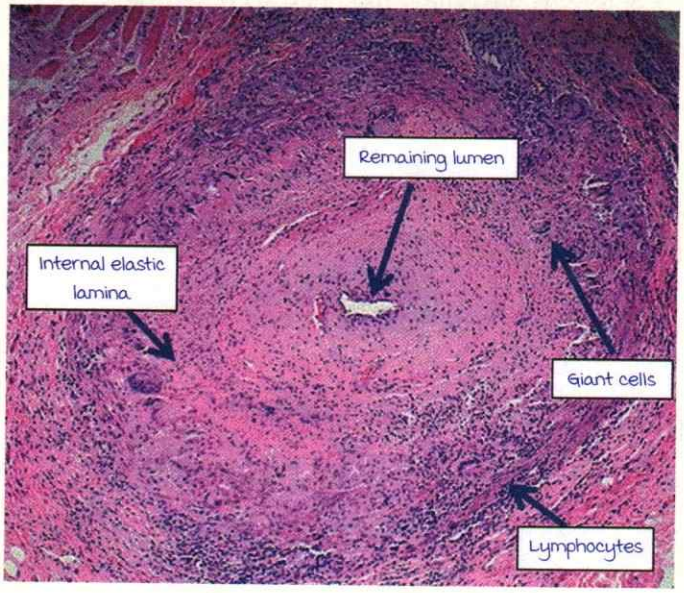
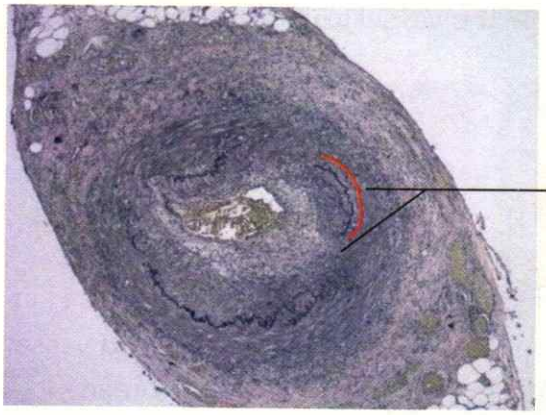
Treatment :

Steroids or immunosuppressant drugs.





Takayasu arteritis

00:17:10

Age affected < 50 years.

Also known as aortic arch syndrome or pulseless disease.

The most common vessel affected is the subclavian artery.

Least common artery affected is the coronary artery.

Clinical presentation :

Loss of pulse in upper extremities.

Asymmetry in BP.

Active space

Histopathology :

Granulomatous inflammation present.

Presence of giant cells.

Polyarteritis nodosa 00:19:48

Medium vessel vasculitis.

Type III hypersensitivity reaction (immune complex mediated).

All organs can be affected : Kidney, heart, GIT, liver.

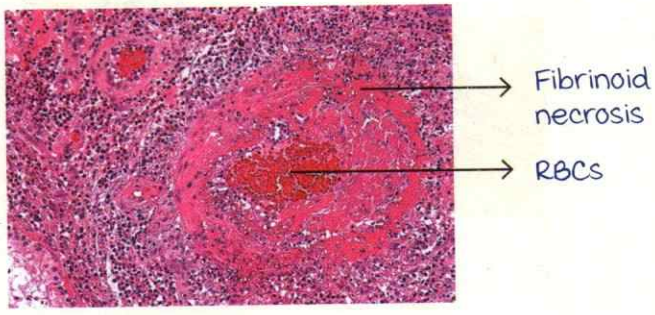
Pulmonary vessels/lungs are never affected.

The most common cause of death is renal failure.

Kidneys can be affected but glomerulonephritis is not seen.

Commonly associated with mononeuritis multiplex.

30% of patients are positive for HbsAg.



Histopathology :

Fibrinoid necrosis in the vessel wall is present.

Transmural segmental necrotizing inflammation.

All stages of inflammation can be seen in a single vessel.

Kawasaki disease 00:26:38

Common in Japanese.

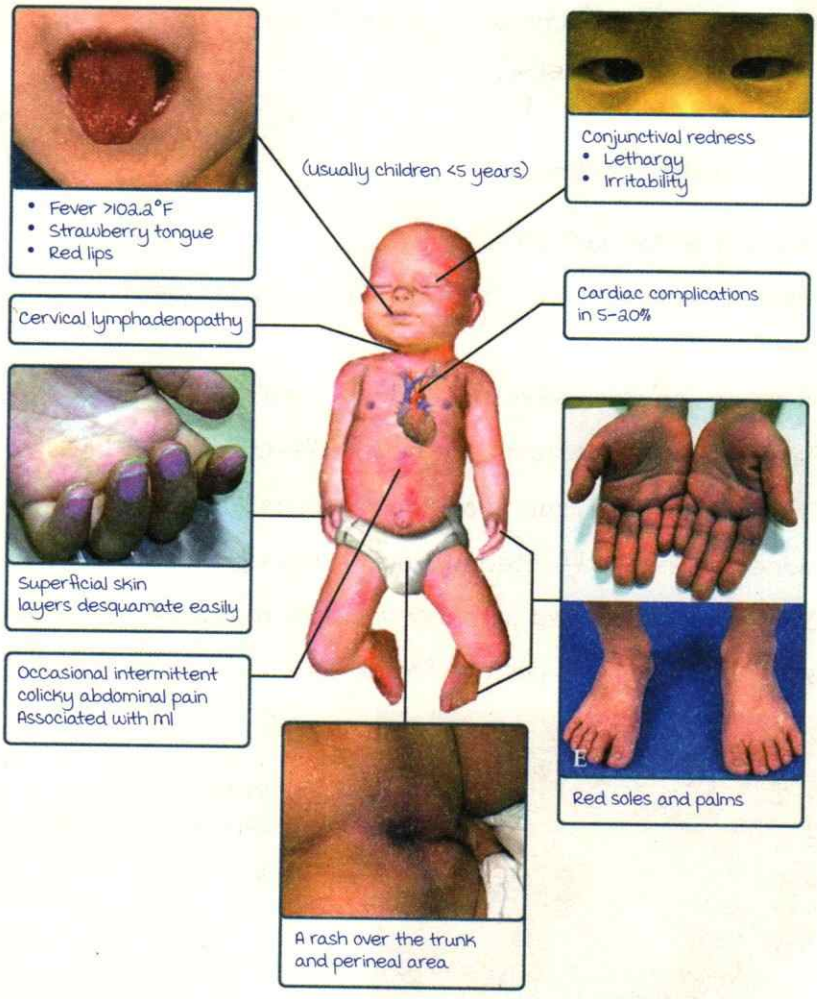
Age <5 years.

Most specific vasculitis in children.

Also known as mucocutaneous lymph node syndrome.

Active space

Kawasaki disease



Diagnostic criteria :

Fever + Any 4 of the following 5 :

Mnemonic : CREAM.

Conjunctivitis.

Rash.

Edema.

Adenopathy.

Mucosal involvement.

Mnemonic : Kawasaki.

K : Conjunctival redness.

A : Age < 5 years.

W : Vasculitis.

A : Adenopathy.

Active space

S : Strawberry tongue, skin rash.

A : Anti-endothelial antibodies.

K : Coronary artery involvement.

I : Increased platelets.

The most commonly affected vessel is the coronary artery. (myocardial infarction can occur in children).

Buerger's disease :

Also known as thromboangiitis obliterans.

Seen in middle aged, male smokers.

Clinical signs :

Intermediate claudication.

Rest pain.

Gangrene.

Can affect all types of arteries, nerves, and veins.

Microscopic features :

- Neutrophilic micro abscess.
- Granulomatous inflammation.

Wegner's granulomatosis 00:35:30

Now called as Granulomatosis with polyangiitis.

3 organs affected are : Lungs, blood vessels and Kidneys.

It has a triad of :

1. Lesions in upper and lower respiratory tract :
   Otitis media.
   Nasal septal perforations.
   Polyps.
   Lung granulomas/cavitary lesions in the lung.
2. Vasculitis.
3. Kidney involvement :
   Focal glomerulonephritis.
   Rapidly progressive glomerulonephritis.

Active space

95% of cases are C-ANCA positive : Can be used to see the recurrence or severity of the disease.

Histopathology :

Granulomatous inflammation with giant cells.

Microscopic polyangitis :

Similar to polyarteritis nodosa.

Involves small vessels.

P-ANCA positive.

Clinically affects lungs.

Glomerulonephritis may be seen.

Also known as Leukocytoclastic (WBCs broken) vasculitis.

Histopathology :

Fragmented neutrophils are present.

Segmental fibrinoid necrosis is present.

Churg Strauss syndrome :

Now called allergic granulomatosis with angiitis.

Associated with bronchial asthma, eosinophilia, allergic rhinitis.

Histopathology : Granulomatous inflammation.

Henoch Schonlein purpura 00:42:25

most common vasculitis in children.

Clinically involves : Skin, joints, GIT, and kidney.

IgA mediated vasculitis.

Causes of granulomatous vasculitis :

- Wegener's granulomatosis.
- Takayasu arteritis.
- Churg Strauss syndrome.
- Temporal arteritis.
- Buerger's disease.

Q. A 65 year old man presents with sudden onset blindness. He gives a history of frequent headaches along

Active space

the sides of his scalp. Which is the investigation you will do to confirm the diagnosis ?

A. Slit-lamp examination.

B. Biopsy of the vessel.

C. ESR.

D. Arteriogram.

Q. A 19 year old young woman who emigrated from Taiwan 8 years ago presents with fever, malaise, myalgias, arthritis and coldness in her upper extremities. She has a weak radial pulse bilaterally, and a magnetic resonance angiogram reveals nearly 75% stenosis of main arteries originating from the aorta. She likely has which of the following conditions?

A. Buerger's disease.

B. Kawasaki disease.

C. Takayasu arteritis.

D. Temporal arteritis.

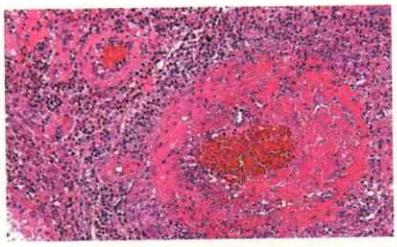
Q. A 33 year old female presents with abdominal pain, fever and malaise for the past 2 months. The patients microscopic image from the biopsy is given below. The amorphous, proteinaceous material in the vessel wall is?

A. Hyaline arteriosclerosis.

B. Fibrinoid necrosis.

C. Caseous necrosis.

D. Hyaline arteriosclerosis.



Q. A 30 year old male smoker presents with gangrene of his extremities. Which one of the following histologic findings from a biopsy of the blood vessel supplying area?

A. Granulomatous inflammation with giant cells.

B. Fragmentation of neutrophils.

C. Fibrinoid necrosis with overlying thrombosis.

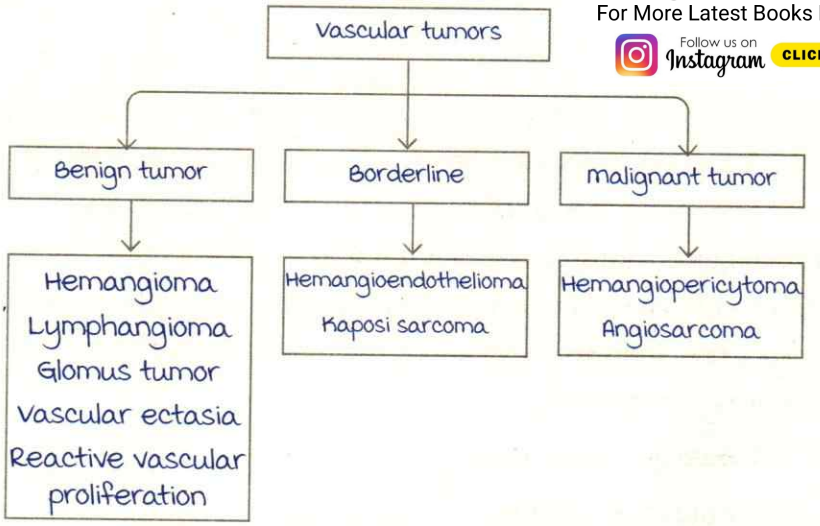
D. Thrombosis with microabscesses.

Active space

VASCULAR TUMORS

Classification of vascular tumors

00:00:24



Vascular ectasia :

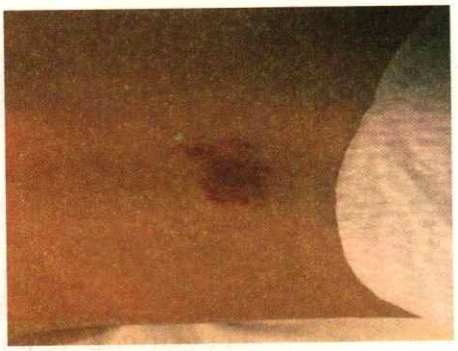
	Nevus flameus	Spider angioma/ telangiectasia	Hereditary hemorrhagic telangiectasia
	mc vascular ectasia. Birth mark.	A spider like lesion	Also known as Osler Weber Rendu syndrome. Autosomal dominant disorder. Defect : TGF β signaling pathway. TGF β : most fibrogenic cytokine.
mc site	Head & neck	Head & neck	
Microscopy	Dilated blood vessels		

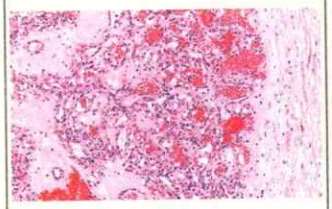
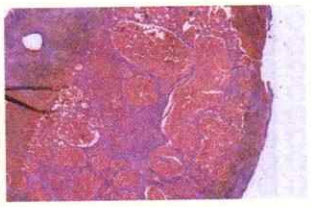
Active space

Hemangioma

00:05:26

Benign blood vessel tumor.
Very common.



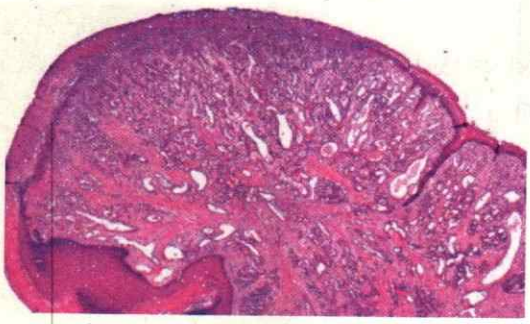
	Capillary hemangioma	Cavernous hemangioma
	More common	Less common
mc site	Superficial (skin/ subcutaneous tissue)	Deeper tissues (liver)
Microscopy	Proliferation of large number of small blood vessels (RBCs in the lumen). 	Proliferation of large dilated vascular spaces/channels. 
	Self regressing	Not self regressing

Clinicopathologic correlation : Von Hippel Lindau (VHL) syndrome (associated with cavernous hemangioma).

Pyogenic granuloma :

- No pus or granuloma.
- Site of lesion : Skin or gingiva.
- Also called lobular capillary hemangioma.
- Microscopy : Cells present in lobules, with proliferation of blood vessels.

Active space



Lobular capillary hemangioma

Granuloma gravidarum :

- Variant of pyogenic granuloma.
- Seen in pregnancy.
- Also a lobular capillary hemangioma.

Lymphangioma

00:12:00

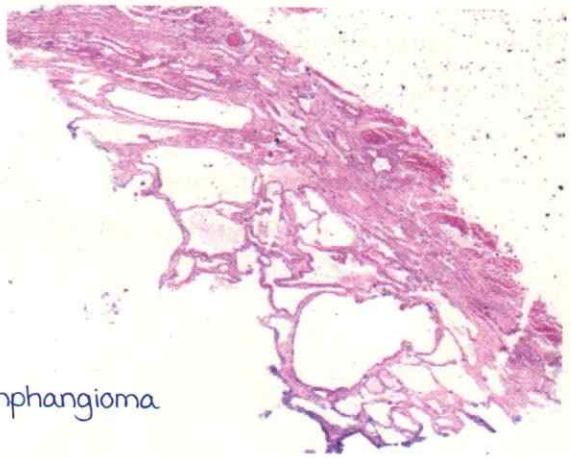
Proliferation of lymphatics.

Blood vessels	Lymphatic vessels
Thicker	Thinner
RBC in lumen	No RBC in lumen. Serous fluid in the lumen can be seen.

2 types :

1. Capillary lymphangioma.
2. Cavernous lymphangioma : Can be associated with Turner's syndrome.

Also called cystic hygroma.



Cavernous lymphangioma

Active space

Reactive vascular proliferations :

Bacillary angiomatosis :

- Causative factor : Bartonella henslae.
- Usually seen in immunocompromised hosts.

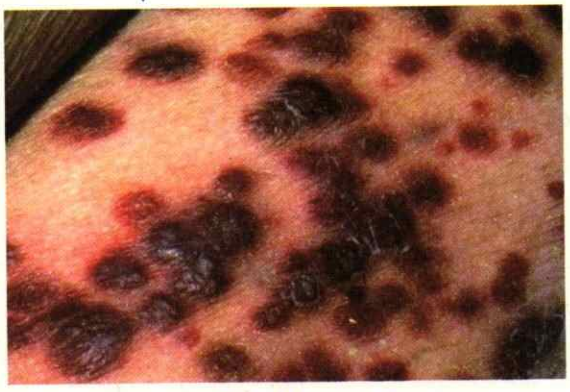
Glomus tumor :

- Arises from glomus body (peri-ungual area).
- Significance : Thermoregulation body.
- Patient presents with very painful tumor in nail bed.

Kaposi sarcoma

00:16:51

Causative factor : Human herpes virus 8 (HHV 8).
2nd MC malignancy in HIV positive patients.
Seen in immunocompromised hosts.



Kaposi sarcoma

Diseases caused by HHV 8 :

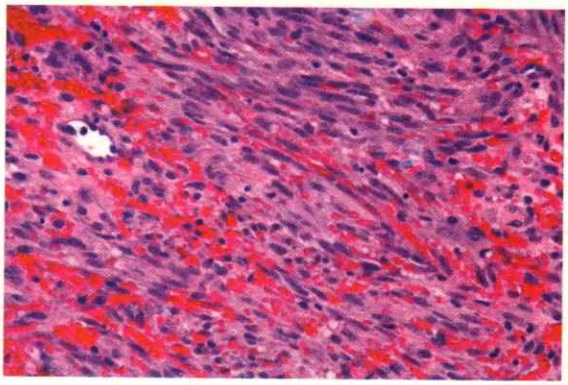
1. Kaposi's sarcoma.
2. Primary effusion lymphoma.
3. Multicentric castleman's disease.
4. Plasmablastic lymphoma.

4 different types :

1. Chronic/classic/European (HIV -ve):
   Skin/subcutaneous tissue.
   No lymph node involvement.
2. African/endemic (HIV -ve) :
   Skin involved.
   Lymph nodes can be involved.

Active space

3. HIV associated (HIV +ve) :
   Deep tissues affected.
   Lymph nodes can also be involved.
4. Transplant associated (HIV -ve) :
   Deep tissues affected.
   Lymph nodes can also be involved.



Kaposi sarcoma

Skin lesions :

3 types :

1. Patch : Flat lesion.
2. Plaque : Slightly raised lesion.
3. Nodule : Raised lesion.

Microscopy :

- Plump spindle cells.
- Slit like vascular spaces.

Angiosarcoma

00:23:38

Highly malignant and aggressive tumor with poor prognosis.

Risk factor : Radiation.

Commonly affects liver : Hepatic angiosarcoma.

Risk factors for Hepatic angiosarcoma :

1. Poly Vinyl Chloride (PVC).
2. Arsenic.
3. Thorotrast.

Microscopy :

Poorly differentiated tumor with highly pleomorphic cells.

Active space

IHC markers :

vWF (von Willebrand factor), CD 31, VEGF (Vascular Endothelial Growth Factor), factor 8.

Stewart Treves syndrome :

- Angiosarcoma which develops in long standing lymphedema.
- Latent period : 10 years.

Lymphangiosarcoma :

Can occur after a modified radical mastectomy with lymph node dissection.

MCQs :

Q An elderly lady underwent mastectomy and axillary lymph node dissection for breast carcinoma 10 years back. She now presents with multiple, confluent, hemorrhagic, necrotic and elevated purple black papules over the right upper limb. What is the most likely diagnosis?

A. Mondor's disease.
B. Zuska's disease.
C. Stewart Treves syndrome.
D. Tietze's syndrome.

Q A 23 year old HIV positive male is seen by his physician. The patient is concerned about the development of multiple red to purple skin plaques that have become nearly confluent on his arms and legs. The skin disorder is most likely :

A. Angioedema.
B. Angiosarcoma.
C. Kaposi's sarcoma.
D. Osler weber rendu disorder.

Active space

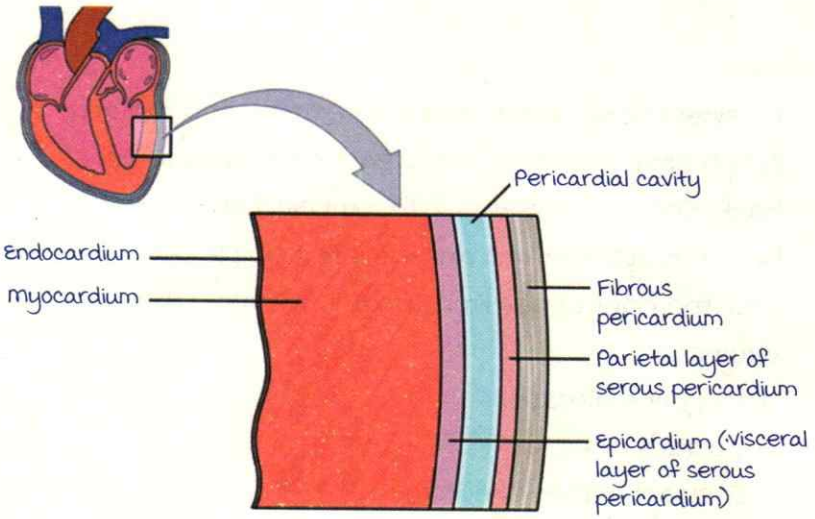
CARDIOVASCULAR SYSTEM : PART 1

Normal blood flow :

Deoxygenated blood from SVC & IVC → right atrium → right ventricle → Lungs → oxygenated blood → left atrium left ventricle → aorta → systemic circulation.

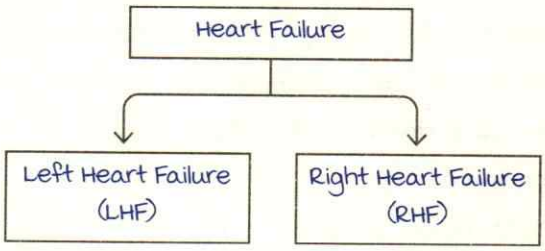
Layers of heart :

- Pericardium.
- Myocardium.
- Endocardium.



Heart failure

00:04:13



Lungs most affected (due to backpressure).

Lungs : Pulmonary congestion and edema.

Morphology :

- Gross : Wet, bloggy and edematous.

Active space

- Microscopy : Heart failure cells (hemosiderin laden macrophages).

Stain with Prussian blue (Perl's stain).

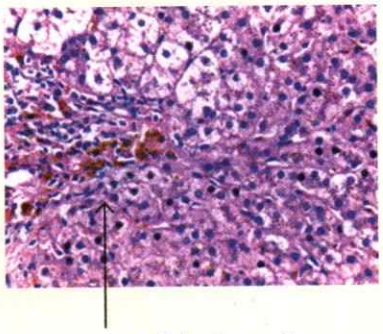
Kidney : Acute tubular necrosis.

MCC of RHF : Left heart failure.

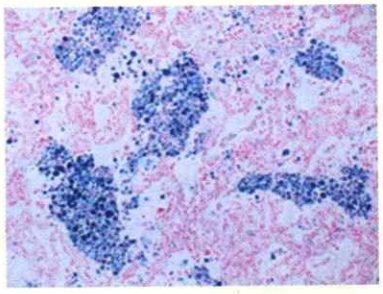
MCC isolated RHF : Pulmonary hypertension.

Liver and spleen affected.

- Liver : Congestive hepatomegaly → Nutmeg liver.
- Spleen : Congestive splenomegaly → Gamma gandy bodies (contain calcium, hemosiderin and fibrosis).

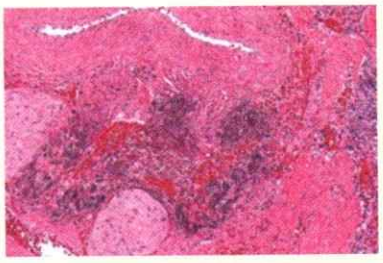


Hemosiderin cells



Heart failure cells

Nutmeg liver



Gamma gandy bodies

Ischemic heart disease :

1. Angina pectoris.
2. Myocardial infarction.
3. Sudden cardiac death.
4. Chronic ischemic heart disease.

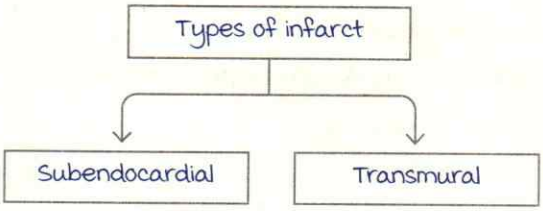
Active space

Myocardial Infarction/MI

00:14:50

Area of coagulative necrosis in heart.

It is wedge shaped.



- Involves the subendocardial zone (least perfused zone).
- Non-ST segment elevation infarct.

- Involves all 3 layers of heart.
- Also called ST segment elevation infarct.

Clinical features : Chest pain radiating to left shoulder, nausea, vomiting, diaphoresis, dyspnea.

Investigations :

A. ECG :

1. ST segment elevation : Transmural infarct.
2. Non-ST segment elevation : Subendocardial infarct.
3. T wave inversion.
4. Pathological Q waves.

B. Cardiac enzymes :

1. Myoglobin :
   - One of the earliest to increase in MI.
   - Non specific.
   - Rises in 1 hour, falls in 24 hours.
   - Not good for monitoring patient.
2. H-FABP :
   - Heart Fatty Acid Binding Protein.
   - Earliest to increase.

Active space

3. CK-MB :
   - Rises in 2-4 hours, falls in 2-3 days.
   - Good marker for re-infarction.
4. Troponins : I and T.
   - Troponin I : Best marker.
   - They rise in 2-4 hours, fall in 7-10 days.
   - Best marker for re-infarction.
5. LDH :
   - Normally LDH2 > LDH1.
   - In MI : LDH 1 > LDH2 (LDH flip).

Morphological changes in MI

00:27:50

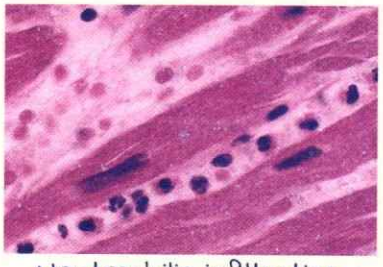
Time	Gross features	Light microscope	Electron microscope
Reversible injury			
0-½ hour	None	None	Relaxation of myofibrils : glycogen loss; mitochondrial swelling
Irreversible injury			
½ - 4 hours	None	Usually none; variable waviness of fibers at border	Sarcolemmal disruption; mitochondrial amorphous densities
4-12 hours	Dark mottling (occasional)	Early coagulation necrosis; edema; hemorrhage	
12-24 hours	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; early neutrophilic infiltrate	

Active space

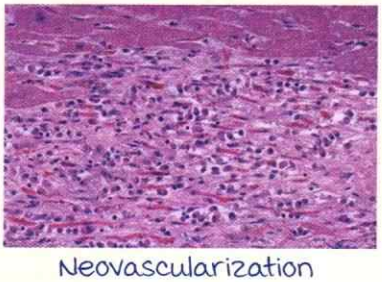
1–3 days	Mottling with yellow tan infarct center	Coagulation necrosis, with loss of nuclei and striations; brisk interstitial infiltrate of neutrophils	
3–7 days	Hyperemic border; central yellow tan softening	Beginning disintegration of dead myofibers, with dying neutrophils: early phagocytosis of dead cells by macrophages at infarct border	
7–10 days	Maximally yellow tan and soft, with depressed red tan margins	Well developed phagocytosis of dead cells; granulation tissue at margins	
10–14 days	Red gray depressed infarct borders	Well established granulation tissue with new blood vessels and collagen deposition	
2–8 weeks	Graywhite scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity	
>2 months	Scarring complete	Dense collagenous scar	

First 4 hours : no gross changes.

Earliest light microscopy changes : Waviness of fibers.



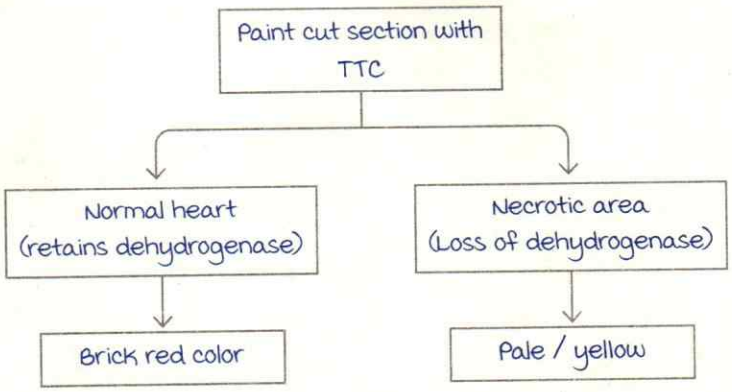
Neutrophilic infiltration (1–3 days)

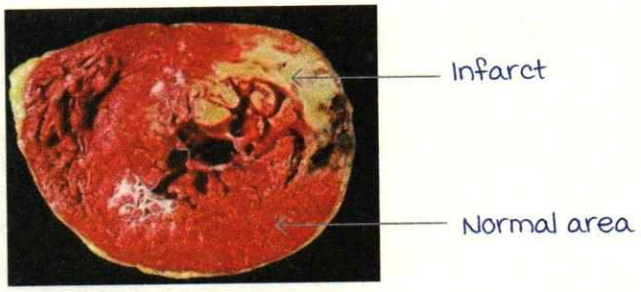


Neovascularization (7–10 days)

If MI <12 hrs, Triphenyl Tetrazolium Chloride (TTC) stain can be used.

Active space



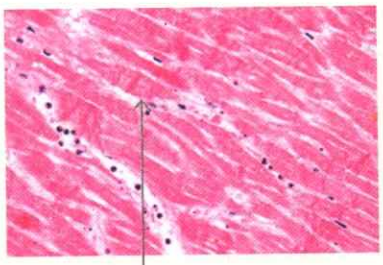


Complications after MI :

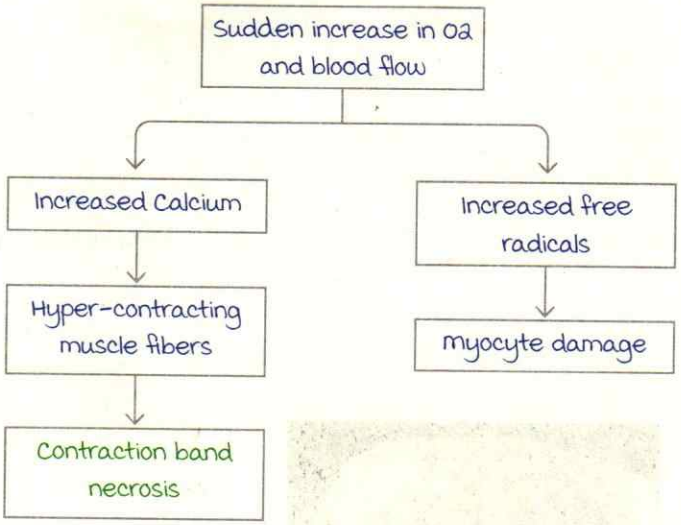
Mnemonic : ACTRAPID.

- Aneurysm.
- Contractile dysfunction.
- Thrombosis.
- Rupture.
- Arrythmias (<1 hour - VF; >1 hour- SVT).
- Papillary muscle dysfunction.
- Dressler's syndrome (autoimmune fibrinous pericarditis occuring 2-3 days / weeks after MI).

Ischemia reperfusion injury 00:47:20



Active space



Active space

CARDIOVASCULAR SYSTEM : PART 2

Carditis

00:00:22

Inflammation of the heart.

Types :

1. Pericarditis.
2. Myocarditis.
3. Endocarditis.

Endocarditis :

Inflammation of the endocardium.

Diseases :

1. Rheumatic heart disease.
2. Infective endocarditis.
3. Non Bacterial Thrombotic Endocarditis (NBTE).
4. Libman Sachs endocarditis.

They all present as verrucae/vegetations on the heart wall.

Rheumatic Heart Disease (RHD)

00:02:12

Age : 5 to 15 years.
Multisystem inflammatory disorder.
Clinically present with history of sore throat.
Occurs 2-3 weeks after a streptococcal sore throat.
Organism : β hemolytic streptococci.
Strains of Streptococci are : 1 ,3 ,5 ,6 ,18.

Pathogenesis :
It is a type 2 hypersensitivity reaction : Antibody mediated.
(mnemonic for type 2 hypersensitivity reaction →
my Blood Group is Rh Positive).
The streptococcal M protein cross reacts with the glycoprotein on the heart and joints by molecular mimicry.

Active space

The most common valve affected : Mitral valve.
Least common valve affected : Pulmonary valve.

Acute rheumatic fever usually presents with mitral regurgitation.
Chronic RHD presents with : Mitral stenosis.

Revised Jones criteria :
Major criteria :

1. Migratory polyarthritis :
   Non erosive arthritis (usually involves large joints).
   Most common and earliest manifestation.
2. Pancarditis : All layers of the heart are involved.
3. Subcutaneous nodules : Painless.
4. Erythema marginatum : Raised rash, sparing the face.
5. Sydenham's chorea : Involuntary purposeless jerky movements.

Minor criteria :
Clinical parameters :

1. Fever or arthralgia.

Lab parameters :

1. Increased CRP.
2. Increased ESR.
3. Prolonged PR interval.

Supportive evidence for diagnosis :

1. Raised ASO titer.
2. Positive throat swab for streptococci.

Morphology of heart in RHD

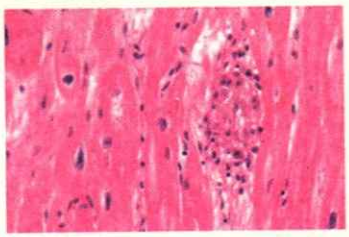
00:11:23

Presents with pancarditis (All three layers are affected).

1. Pericardium :
   Fibrinous pericarditis.
   "Bread and Butter" pericarditis.

Active space

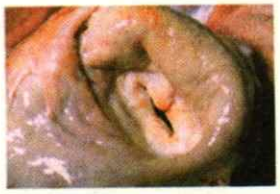
2. Myocarditis and endocarditis :
   Aschoff bodies are seen.
   - Pathognomic of RHD.
   - Comprises of :
     1. Fibrinoid necrosis.
     2. Inflammatory cells.
     3. Anitschkow cells.



Anitschkow cells/Caterpillar cells : They are macrophages with slender, wavy, ribbon-like nuclei.
Aschoff bodies can be seen in all layers.
But maximally seen in myocardium.

3. The mitral valve in mitral stenosis has a fish mouth appearance.
   Therefore, called fish mouth stenosis/button hole stenosis.

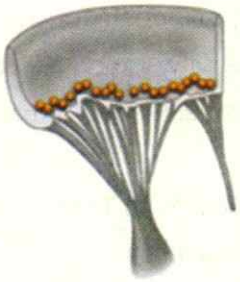
   Stenosis is due to fibrosis and calcification.



4. In mitral regurgitation, the wall of left atrium is thickened.
   This is called as Subendocardial jets/McCallum plaques.
   Because of regurgitation of blood back into left atrium.

5. Mitral valve thickening or commissural fusion and shortening and thickening of chordae tendinae.

6. Vegetations : Small, warty, verrucous and sterile seen along the lines of closure of valve leaflets.



Rheumatic heart disease

Active space

Infective Endocarditis (IE)

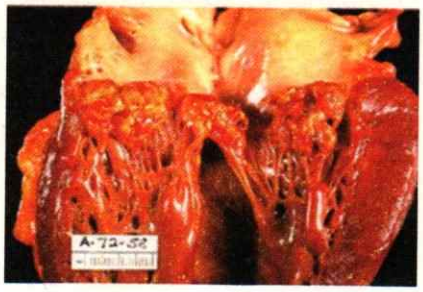
00:22:18

Acute IE	Subacute IE
Occurs in a normal heart valve. Caused by highly virulent organism like Staphylococcus aureus.	Usually occurs on previously damaged heart valve. Caused by less virulent organism like Streptococci.

Clinical presentation :

1. Fever.
2. Splenomegaly.
3. Roth's Spots : Retinal hemorrhages.
4. Osler's node : Painful subcutaneous nodules on pulp of digits.
5. Janeway lesions : Non tender macules on palms and soles.
6. Splinter hemorrhages.

Vegetations :
Large, bulky, infected, friable, destructive present along the line of closure of leaflets.
They are destructive to the underlying chordae tendinae. Since friable, it can easily embolize.



Non Bacterial Thrombotic Endocarditis (NBTE) / Marantic endocarditis :
Can be seen in patients with debilitating diseases like :

1. Pancreatic cancer.
2. Metastatic cancer.
3. AML-M3.

Active space

Vegetations :

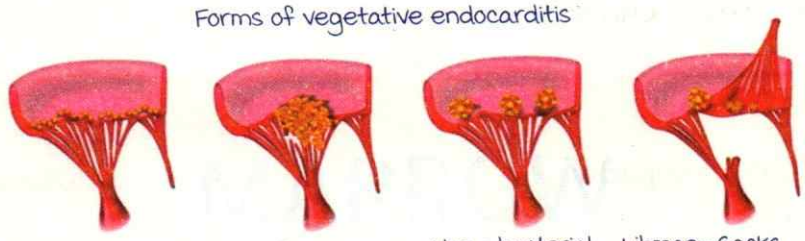
Small, bland, non destructive, friable present along the lines of closure of the valve leaflets.

Libman Sachs Endocarditis (LSE) :

Seen in SLE.

Vegetations are present on both surfaces of valve leaflets, but more on the lower side.

Forms of vegetative endocarditis



Rheumatic heart disease | Infective endocarditis | Non – bacterial thrombotic endocarditis | Libman– Sacks endocarditis

The rheumatic fever phase of rheumatic heart disease (RHD) is marked by small warty vegetations along the lines of closure of the valve leaflets.

Infective endocarditis (IE) is characterized by large, irregular masses on the valve cusps that can extend onto the chordae tendinae.

Nonbacterial thrombotic endocarditis (NBTE) typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present.

Libman Sacks endocarditis has small or medium sized vegetations on either or both sides of the valve leaflets.

All these vegetations are sterile except infective endocarditis.

Myocarditis :

Inflammation of myocarditis.

Coxsackie A and B can lead to myocarditis.

Trichinella spiralis is the most common helminth leading to myocarditis.

Active space

Pericarditis :

Types :

Acute pericarditis	Chronic pericarditis
1. Caseous pericarditis seen in TB. 2. Hemorrhagic : seen either in TB or malignancy. 3. Fibrinous : RHD 4. Serous : RHD or SLE	Chronic constrictive pericarditis seen in TB.

Cardiomyopathy

00:33:33

A disease of the cardiac muscle.

Types :

1. Dilated.
2. Hypertrophic.
3. Restrictive.

Dilated cardiomyopathy (DCM) :

Most common type of cardiomyopathy.

Causes :

1. Idiopathic.
2. Alcohol : Most common cause of DCM.
3. Cobalt.
4. Cardiotoxic drugs like Adriamycin, Doxorubicin.
5. Myocarditis.
6. Hemochromatosis. (Can cause both DCM and restrictive, but DCM > restrictive).
7. Postpartum.
8. Genetic :

   Mutation of sarcolemmal proteins : Titin gene mutation.

   Titin : Largest protein in human body.

Gross pathology :

Dilatation of all four chambers of the heart.

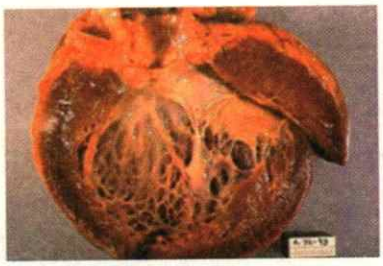
Leading to a flabby hypo-contracting heart.

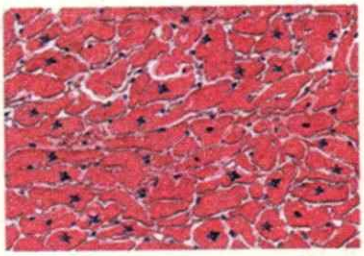
Active space

Histopathology :

1. Hypertrophied muscle fibres.
2. If the DCM is due to Titin mutation : Presence of Ninja star nuclei.

Histologic appearance of ninja-stars like nuclei in dilated cardiomyopathy





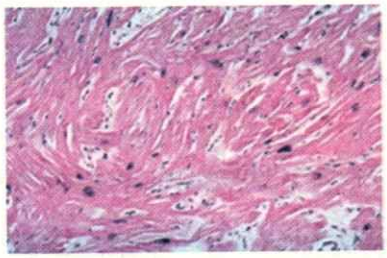
Ninja - stars ✶ ✶ ✦ ✶

Takotsubo cardiomyopathy 00:41:50

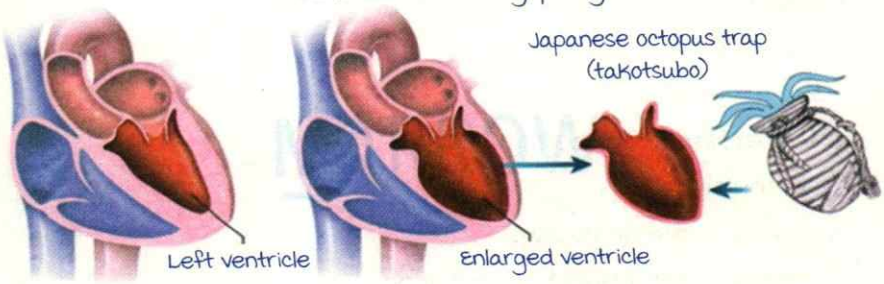
Type of DCM.
Also known as Broken Heart syndrome.

Due to _____ there is release of large amounts of catecholamines.
These catecholamines cause the selective ballooning and hypertrophy of the left ventricle.

The heart shape in this DCM looks like a Japanese octopus trap called Takotsubo.



Takotsubo cardiomyopathy



Normal heart
Normal shape of left ventricle when it contracts

Takotsubo cardiomyopathy
shape of the left ventricle becomes similar to the octopus trap

Active space

Arrhythmogenic right ventricular cardiomyopathy :
Autosomal dominant disorder.
Selective right ventricular hypertrophy.
Due to mutation of plakoglobin or desmosomes.

Naxos syndrome.

1. Arrhythmogenic right ventricular cardiomyopathy.
2. Wooly hair.
3. Hyperkeratosis of palms and soles.
   Occurs due to plakoglobin mutation.

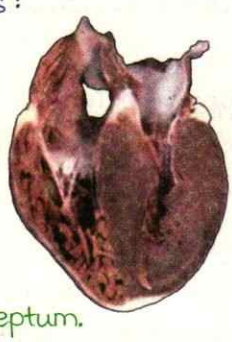
HOCM

00:48:04

HOCM : Hypertrophic Obstructive Cardiomyopathy.
Causes :
Genetic : mutations in sarcolemmal proteins :

- Myosin binding protein C.
- Beta myosin heavy chain.

Most common cause of sudden cardiac death in young athletes.



Gross pathology :
Selective hypertrophy of interventricular septum.
It is called "banana split" configuration or "banana like heart".

Histopathology :
Hypertrophied muscle fibers.
Myofiber disarray : The arrangement is known as "HelterSkelter arrangement of muscle fibers".

Restrictive cardiomyopathy :
Causes :

1. Idiopathic.
2. Sarcoidosis.
3. Metastatic cancer.
4. Amyloidosis.
   Most common cause.
   ATTR/ transthyretin deposition.
5. Radiation.
6. Hemochromatosis.
7. Loeffler's Endomyocarditis.

Active space

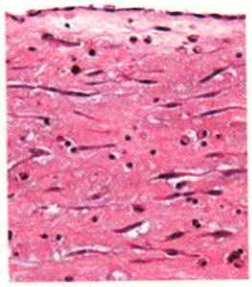
Endomyocardial fibroelastosis :
Seen in children <2 years of age.
Seen associated with mumps infection.

Tumors of heart

00:56:10

Most common tumor of the heart : Secondaries or mets.
Most common primary tumor of the heart : Myxoma.
Most common tumor of the heart in children : Rhabdomyoma.
Most common heart valve tumor : Papillary fibroelastoma.
(This showed sea anemone like projections).

Myxoma :
Usually seen in left atrium.
Causes ball valve obstruction.



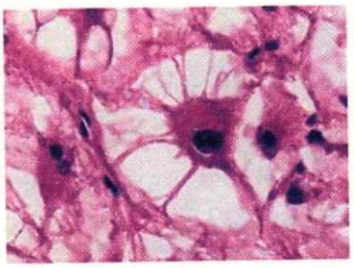
Gross pathology :
Gelatinous appearance.
Histopathology :
Myxoma/lepidic cells in a mucopolysaccharide background.

Syndromes associated with myxoma :

1. Carney's syndrome.
2. GNAS mutations.

McCune Albright syndrome is also associated with GNAS mutation.

Rhabdomyoma :
Most common cardiac tumor in children.
Can be associated with
Tuberous sclerosis.



On histopathology :
Spider cells are seen.
Spider cells have glycogen.
Hence, they are PAS +

MCQs :

A 19 year old woman has had increasing malaise for the past 5 months. On physical examination she has a cardiac murmur characterized by a mid-systolic click. An echocardiogram demonstrates mitral insufficiency with upward displacement

Active space

of one leaflet. There is aortic root dilation to 4 cm. She has adislocated right ocular crystalline lens. A year later she dies suddenly and unexpectedly. The medical examiner finds a prolapsed mitral valve with elongation, thinning, and rupture of chordae tendinae. A mutation involving which of the following genes is most likely to be present in this patient?

A. Beta myosin.
B. CFTR.
C. FGFR.
D. Fibrillin.
E. Spectrin.
F. Dystrophin.

Answer : Fibrillin.
Explanation : The diagnosis is marfan's syndrome. Associated with fibrillin gene mutation.

A 22 year old man has had increasing malaise over the past 3 weeks. On physical examination his vital signs show T : 39.2°C, PR : 105/minute, RR : 30/minute, and BP : 80/40 mm Hg. On auscultation of his chest, a loud systolic cardiac murmur is heard, and his lungs have bibasilar crackles. Needle tracks are seen in his left antecubital fossa. He has splinter haemorrhages noted on fingernails, as well as painful erythematous nodules on palmar surfaces. A tender spleen tip is palpable. A chest radiograph shows pronounced pulmonary edema. Which of the following laboratory test findings is most likely to be present in this patient's peripheral blood?

A. Creatine Kinase-MB of 8% with a total CK 389 U/L.
B. Positive blood culture forPseudomonas aeruginosa.
C. Total serum cholesterol of 374 mg/dL.
D. Blood urea nitrogen of 118 mg/dL.
E. Antinuclear antibody titre of 1:512.

Answer : Positive blood culture for Pseudomonas aeruginosa.
Explanation : Diagnosis is infective endocarditis. Therefore culture positivity is possible.

A 55 year old man presented to the emergency with progressive dyspnea. His wifereports that he had chest pain

Active space

7 days back which had lasted for 2 days. You suspect that patients chest pain was due to myocardial infarction. If so, bloodlevels of which of the following enzymes would be elevated now?

A. CPK.
B. SGOT.
C. Troponin.
D. Myoglobin.

Answer : Troponin.
Explanation : Troponin levels are still elevated 7 days after MI.

A 17 year old girl is short in stature for her age. She has not yet shown any changes of puberty. On physical examination her vital signs include T : 37°C, RR : 18/minute, P : 75/minute, and BP : 165/85 mm Hg. She has a continuous murmur heard over both the front of the chest as well as her back. Her lower extremities are cool with diminished pulses and poor capillary filling. She has a webbed neck. A chest radiograph reveals a prominent left heart border, no edema or effusions, and rib notching. Which of the following cardiovascular abnormalities is she most likely to have?

A. Shortening and thickening of chordae tendineae of the mitral valve.
B. Narrowing of the aorta past the ductus arteriosus.
C. Supravalvularnarrowing in the aortic root.
D. Lack of development of the spiral septum and partial absence of conus musculature.
E. Single large atrioventricular valve.

Answer : Narrowing of the aorta past the ductus arteriosus.
Explanation : The diagnosis is of Turner's syndrome. There are two associated cardiac conditions with Turner's

1. Coarctation of aorta.
2. Bicuspid aortic valve.

A 17 year old girl experiences syncope while out running for exercise one afternoon, as she has done for many years. Physical examination, chest radiograph, head CT scan, CBC, and chemistry panel are all normal. Over the next year, she develops mild dyspnea and fatigue. She experiences several

Active space

episodes of near syncope. After another syncopal episode, she is referred to acardiologist who orders an EKG that shows changes of left ventricular hypertrophy and broad Q waves. An echocardiogram reveals left ventricular and septal hypertrophy, small left ventricle, and reduced septal excursion. The septum has a 'ground glass' appearance. Which of the following is the most likely microscopic feature of her disease process?

A. Aschoff bodies.
B. Lymphocytic infiltrates.
C. Pericarditis.
D. Myofiber disarray.
E. Atheroma formation.

Answer : Myofiber disarray.
Explanation : The diagnosis is HOCM. microscopic disarray is seen in HOCM.

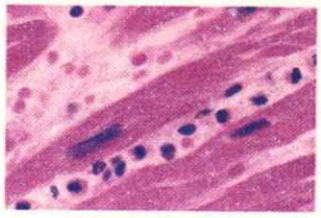
Two brothers were arguing over a property dispute when the elder of the two complained of chest pain and collapsed. He was taken to the hospital but was declared brought dead. The condition responsible for the death of this patient is :

A. Constrictivecardiomyopathy.
B. Restrictive cardiomyopathy.
C. Dilated cardiomyopathy.
D. Arrhythmogeniccardiomyopathy.

Answer : Dilated cardiomyopathy.
Explanation : Sudden emotional stress can cause Takotsubo cardiomyopathy which is a type of DCM.

The heart of a patient who had suffered a myocardial infraction is subjected to a histopathological examination. The microscopic image is given below. What time following infarction would you observe this?

A. 30 minutes to 4 hours.
B. 4 to 12 hours.
C. 12 to 24 hours.
D. 3 to 7 days.

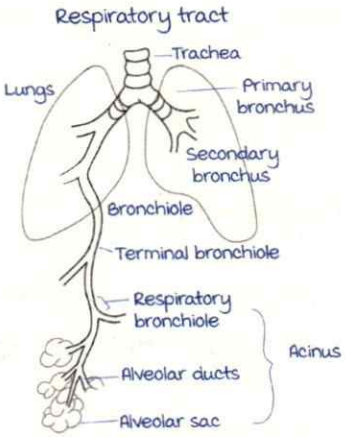


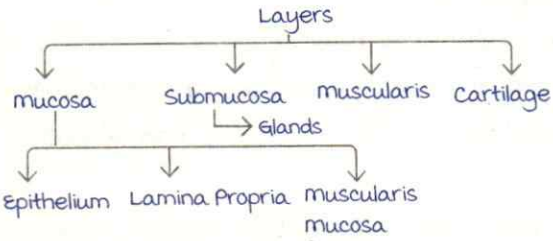
Answer : 12 to 24 hours.
Explanation : Neutrophils are seen in the muscle fibres.

Active space

OBSTRUCTIVE LUNG DISEASE

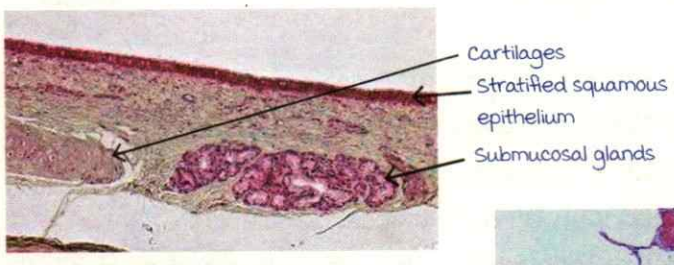
Respiratory bronchiole + alveolar ducts + alveolar sac → Acinus (functional unit of lung) → Affected in emphysema.



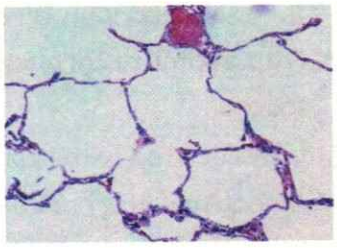


The entire respiratory tract is lined by pseudo stratified ciliated columnar epithelium.
Except vocal cords (stratified squamous epithelium) & alveoli (type 1 & type 2 pneumocytes).

Type 1 pneumocytes	Type 2 pneumocytes
95% cells	5% cells
Flat cells	Prominent/globular cells
	They produce surfactants & help in healing after injury.



Histology of respiratory tract

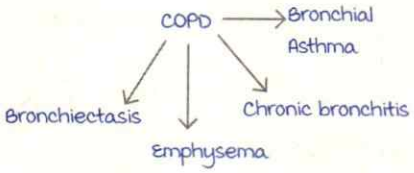


Alveolar biopsy

Active space

Pores of Kohn are present in between alveoli which help in diffusion of oxygen & other materials.

COPD :



Emphysema

00:08:03

Irreversible enlargement of airspaces (Acini) distal to the terminal bronchiole with destruction of walls (without fibrosis).

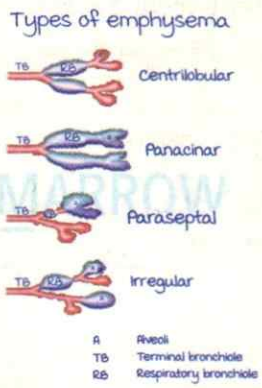
Risk factors (pathogenesis) :

- Smoking : Increases elastase activity.
- Alpha 1 antitrypsin deficiency : Decreases anti proteases → Increases elastase activity → Destruction of wall → Emphysema.

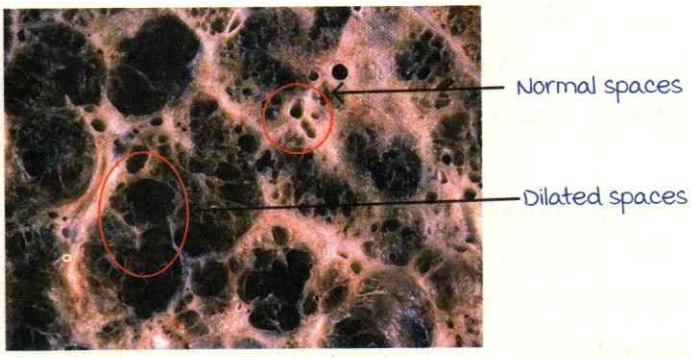
In lungs there is a delicate balance between the elastase & anti elastase.

Types :

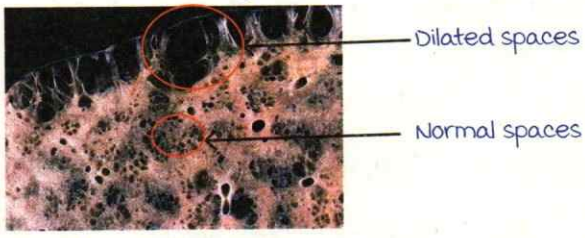
- Centrilobular/centriacinar : Dilated respiratory bronchioles but air ducts ,alveolar sac are spared.
  1. mc type of acinar clinically .
  2. mc smoking associated emphysema.
  3. Usually affects upper lobe of lungs.
- Pan acinar : All bronchioles, air ducts & alveolar sacs are involved.
  1. Usually affects lower lobe of lungs.
  2. Associated with α 1 anti-trypsin deficiency.
- Para septal/distal acinar : Distal acini affected, central spared.
  1. Associated with spontaneous pneumothorax.
- Irregular : any part of the acini are affected.



1. MC type seen on autopsy.



Centrilobular emphysema



Para septal acinar

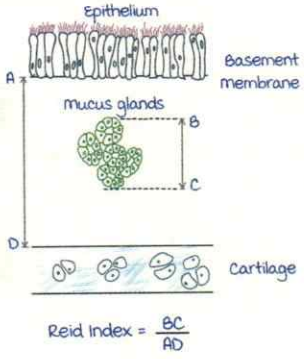
Histology : Broken septa/alveolar walls → Floating septa.
Clinically, barrel shaped chest, flattened diaphragm is seen.
The patients are called pink puffers (no cyanosis).

Chronic bronchitis

00:19:59

Persistent productive cough for atleast 3 consecutive months for atleast 2 consequent years in the absence of any other identifiable cause.

MC differential : Tuberculosis.



90% are smokers, which irritates the mucosa → mucus gland hypertrophy occurs → Increased mucus production → Productive cough & increased reid Index.

Reid index : Ratio of thickness of mucus gland layer to the thickness of wall between epithelium & cartilage.
Normal = 0.4.
Increased in chronic bronchitis.
Goblet cell hyperplasia & basement membrane thickening can also be seen.

Active space

Bronchial asthma

00:25:25

Hyperresponsiveness of airways as there is reversible bronchoconstriction & inflammation of airways.

Pathogenesis : Type I hypersensitivity reaction.

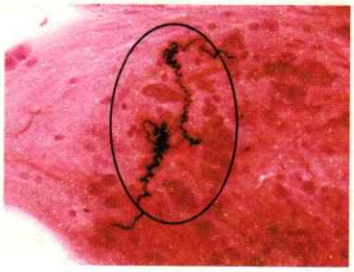
Genetic components :

- Gene for atopy is on chromosome 5.
- Polymorphism in IL 13 & Adam 33 gene Matrix metalloprotease.
- Increased YKL 40 associated with increased severity of bronchial asthma.

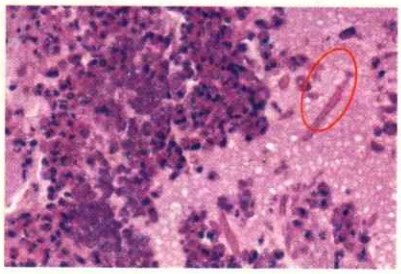
Pathology :

Sputum Microscopy

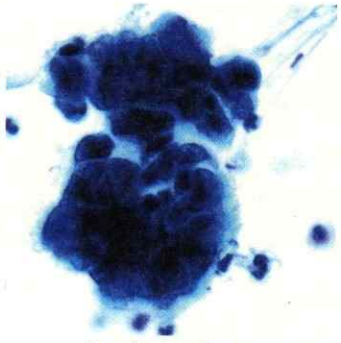
Curshman spirals	Charcot Leyden crystals	Creola bodies
↓	↓	↓
Whorled mucus plugs	Composed of eosinophillic membrane protein galectin 10	Sloughed mucus epithelium



Curshman spirals



Charcot leyden crystals



Creola bodies

Histology :

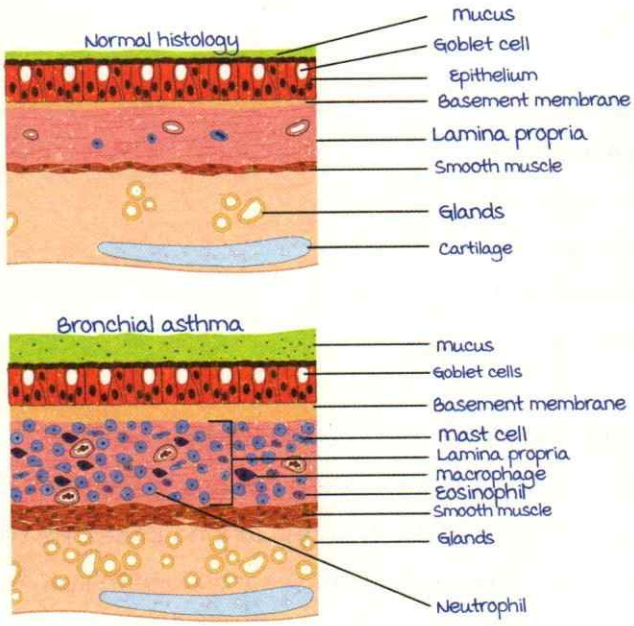
The process is called as Airway remodelling.

- Increased mucus production.
- Goblet cells hypertrophy.
- Thickened basement membrane.

Active space

- Lamina propria with inflammatory cells.
- Smooth muscle hypertrophy.
- Submucosal gland hypertrophy.

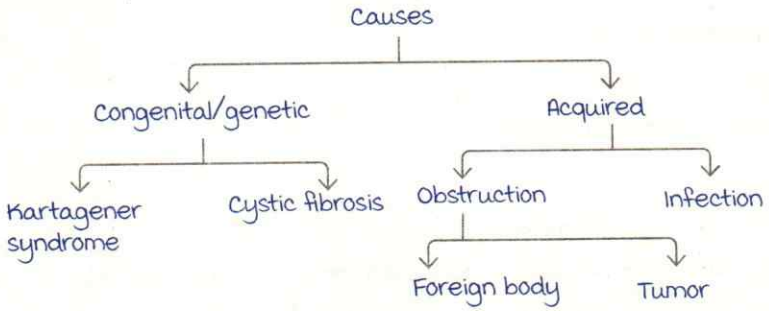
Reid index : Normal.



Bronchiectasis

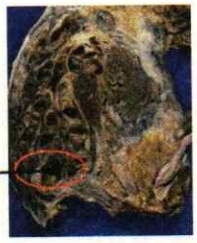
00:37:36

Abnormal permanent dilatation of bronchi & bronchioles.



Kartagener syndrome :

- Also known as Immotile Cilia syndrome/primary ciliary dyskinesia.
- Defect in dynein arm of cilia.
- Triad : Bronchiectasis, sinusitis & situs inversus.
- Male and female infertility may also be present.



Active space

Lower lobes (bilaterally) are usually affected.
When we put a probe in these dilated spaces → In a normal person, probe stops 2-3 cms before pleura.
If my patient has bronchiectasis, the probe almost reaches the pleura.

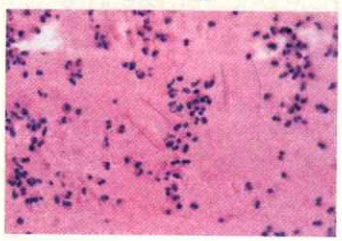
Complications :

- Lung abscesses.
- Brain abscess.
- Empyema.
- Amyloidosis : AA amyloidosis produced from serum amyloid associated in the liver.

Q. A 27 year old man is being evaluated for cough and dyspnoea for 2 months. He is not a smoker. Work up revealed emphysematous changes at lung bases. He reports that his father and uncles were diagnosed with liver failure and lung disease at relatively young age. Where is the gene encoding the defective protein located ?
A. Chromosome 1.
B. Chromosome 13.
C. Chromosome 14.
D. Chromosome 15.
Answer : Chromosome 14.

Centriacinar emphysema occurs MC in smokers.
Alpha 1 anti trypsin deficiency leads to both liver & lungs disease & the location for this mutation is chromosome 14.

Q. A 35year old woman presented with recurrent episodes of breathlessness, wheeze and chest tightness. Auscultation of the chest revealed bilateral wheeze. Sputum microscopy reveals the following. What is the most likely diagnosis ?
A. Sarcoidosis.
B. Chronic bronchitis.
C. Bronchial asthma.
D. Asbestosis.
Answer : Bronchial asthma.



Active space

Charcot leyden crystals can be seen in the image.
In sarcoidosis , we will see non-caseating granulomas or asteroid bodies or schaumann bodies.
Chronic bronchiectasis : Reid index is increased.
In asbestosis, asbestos bodies are seen.

Clinical scenario :
A 44 year old woman working in a bakery ,presents with episodic cough, wheeze and shortness of breath with stuffy, itchy runny nose and watering eyes. She realized that rice bran worsened her symptoms → she is allergic to rice bran.
Chest x ray is normal, FEV1/FVC ratio was low.
Skin prick testing was positive to flour, red bran.

Ans : Skin prick test positive indicates an allergic element.
Other tests → Atopic asthma can be suspected, sputum examination can be done to look for Curshman spirals , charcot leyden crystals & Creola bodies.
Genetic testing for chromosome 5 or Endobronchial biopsy can also be done for diagnosis.

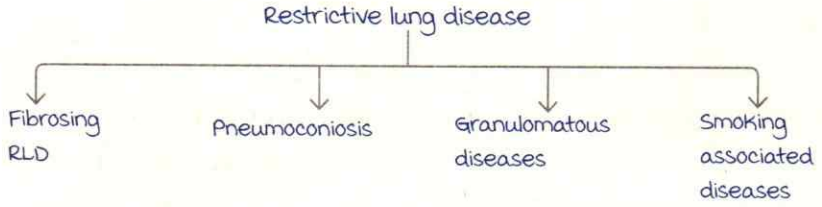
Clinical scenario :
A 3 year old male child presented with history of fever and shortness of breath, presented with recurrent respiratory and pneumonic infections. On examination, apex of heart was felt on the right fourth intercostal space along midclavicular line.
Chest x ray was suggestive of dextrocardia. USG abdomen showed liver and GB on the left side while spleen was on the right side. Diagnosis?

Ans : Dextrocardia is suggestive that the child has Situs inversus along with lots of infections.
Other organs are reversed as well suggestive of Kartagener syndrome.

Active space

RESTRICTIVE LUNG DISEASE

Total lung capacity is decreased in Restrictive Lung disease/ RLD but FeV/FVC is normal.



Pneumoconiosis

00:01:14

These are occupational lung disorders.

Development depends on :

- Size of the particle → (0 to 5) microns → most pathogenic. Not cleared by ciliary apparatus.
- Solubility of particle.
- Duration of exposure (longer duration - increased risk).
- Other synergistic factors like smoking.

Categories :

- Coal worker's pneumoconiosis.
- Silicosis.
- Asbestosis.

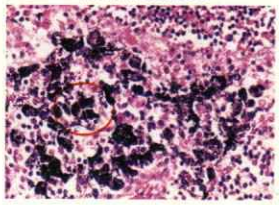
Most will affect the upper lobe of lung except asbestosis which affects the lower lobe of lung.

Coal worker's pneumoconiosis :

Usually seen in coal-mine workers.

Usually presents in upper lobe of lungs.

Anthracosis



Manifestations :

- Asymptomatic anthracosis → Associated with deposition of black carbon pigment.
- Simple coal workers pneumoconiosis : Can manifest as coal macules or coal nodules.

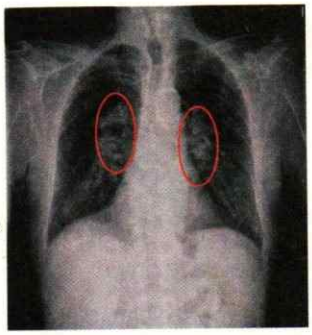
Active space

- Progressive massive Fibrosis : Entire lung undergoes fibrosis.

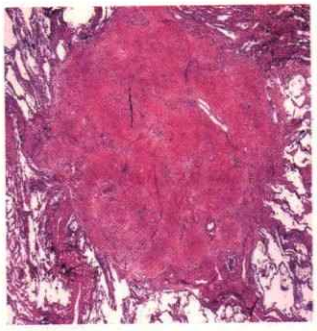
Caplan Syndrome : Coal worker's pneumoconiosis or silicosis + Rheumatoid arthritis.

Silicosis :

- m/c pneumoconiosis in the world.
- Seen in sand blasters & usually affects upper lobe of lungs.
- AKA Miner's/Grinder's disease.
- Silicosis is synergistic with TB.
- Increased risk of lung cancer can be seen.
- Incidence of lymph node enlargement especially hilar LN.
- X-ray : Egg shell calcification.
- Grossly : Starts as fibrotic nodule → Coalesce to form collagenous scar.
- Histopathology : Whorled collagen fibres.
- Birefrengent silica particles (SiO_2) are best seen on polarised microscopy.
- Fried egg appearance : Also seen in
  Bone marrow biopsy of hairy cell leukemia &
  Biopsy of oligodendroglioma.



Egg shell appearance

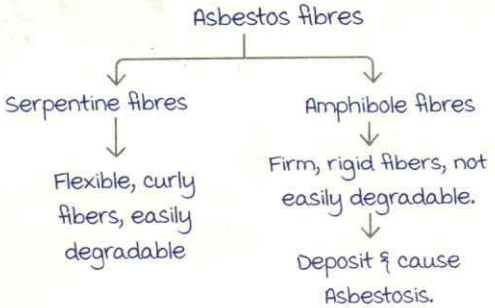


Whorled collagen fibres

Asbestosis :

Usually occurs in construction workers/shipping industry.

Usually affects lower lobe of lungs.

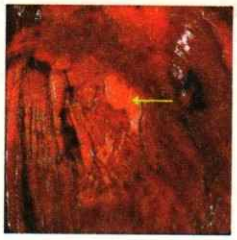


Amphibole fibres are more pathogenic than serpentine.

Active space

Diseases caused by asbestos :

- Pleural plaque → m/c & earliest lesion.
- Pleural effusion.
- Lung cancer (lung adenocarcinoma → m/c type of malignancy) with 15–20 years latent period of development.
- Malignant mesothelioma (most specific malignancy caused by Asbestosis) with 25–40 years latent period of development.



Psammoma bodies can be seen. Also seen in :

- Papillary carcinoma of thyroid.
- Papillary renal cell carcinoma.
- Prolactinoma.
- Serous cystadenocarcinoma of ovary.
- Meningioma.

Calretinin : Tumor marker used for malignant mesothelioma.

Also used in :

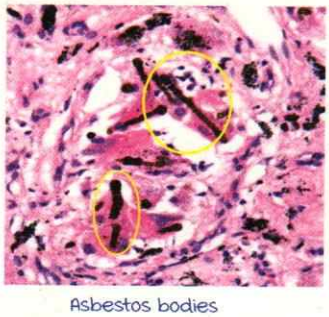
- Laryngeal cancer.
- Gastric carcinoma.
- Renal cell carcinoma.

Histopathology : Asbestos bodies/ferruginous bodie seen.

Asbestos bodies are asbestos fibres & if they get coated with iron → Ferruginous bodies (Prussian blue positive).

They are dumbbell-shaped, beaded, fusiform rod-like structure.

Asbestos bodies in Prussian Blue stain



Asbestos bodies

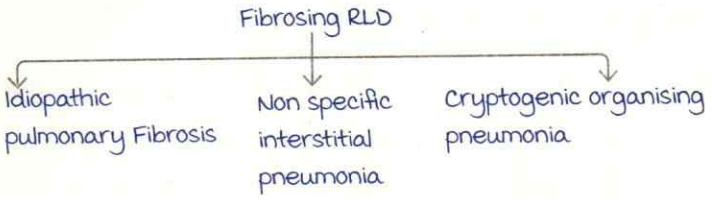
Other pneumoconiosis :

- Baritosis : Barium toxicity.
- Byssinosis : Cotton toxicity.
- Baggassosis : Sugarcane toxicity.
- Siderosis : Iron toxicity.
- Berylliosis : Beryllium toxicity, produces non-caseating granulomas, D/D for Sarcoidosis.

Active space

Fibrosing RLD

00:23:11



Idiopathic pulmonary fibrosis is also known as Usual Insterstitial Pneumonia (UIP).

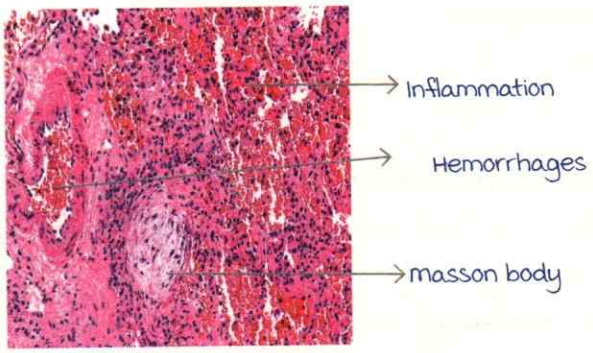
TGF-β mutations can be seen.

Generalised fibrosis is seen in lung parenchyma.

Non specific interstial pneumonia : Can be associated with connective tissuedisorders.

Cryptogenic organizing pneumonia : AKA Bronchiolitis Obliterans Oranising Pneumonia (BOOP).

Histopathology → masson bodies (loose fibrous plaque/plug) can be seen in BOOP.



Clincal scenarios

00:23:11

Match the following :

1. silicosis	A. Basal lobes are involved.
2. mesothelioma	B. malignant pleural effusion without mediastinal shift.
3. Caplan syndrome	C. Initially demonstrated in coal workers.
4. Asbestosis	D. Crazy pavement.

Answer :

Silicosis → Crazy pavement appearance.

Mesothelioma → malignant pleural effusion without

Active space

mediastinal shift.

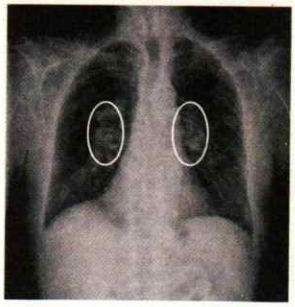
Caplan syndrome → Initially demonstrated in coal workers.

Asbestosis → Basal lobes are involved.

Q. A 66 year old man has had increasing dyspnea for the past year. He is retired from the construction business. There are some rales auscultated in both lungs on physical examination. A chest radiograph reveals bilateral diaphragmatic pleural plaques with focal calcification as well as diffuse interstitial lung disease. A sputum cytology shows no atypical cells, only ferruginous bodies. Pulmonary function studies reveal a low FVC and a normal FEVI/FVC ratio. These findings are most likely to suggest prior exposure to which of the following environmental agents?

A. Cotton fibers.
B. Silica dust.
C. Fumes with iron particles.
D. Asbestos crystals.
E. Beryllium.
F. Black mold spore.

Q. A 28 year old non smoker presented to emergency with cough, progressive dyspnea for 1 year, works in stone crushing industry.
Past history received ATT 1 year ago for 6 months.
Examination hyper resonant note on percussion.
Lab tests : LFT, KFT, CBC (normal).
sputum for AFB was negative.
Chest X-ray shows calcifications.
BAL : Revealed macrophage laden silicotic particles. Diagnosis?



Answer : Silicosis.

Active space

GRANULOMAS AND INFECTION OF LUNGS

Sarcoidosis 00:01:07

- Common granulomatous disease in western countries.
- Diagnosis of exclusion.
- Females >> Males.
- Average of presentation : 30-40 years.
- Multisystem disorder.

Clinical features :

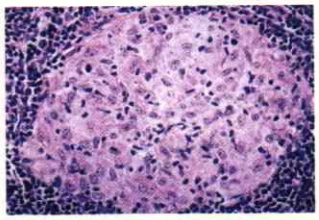
- Fever, weight loss.
- Ocular → Uveitis, sicca syndrome, Keratitis.
- Lymph nodes affected : Hilar lymph nodes enlargement.
- Skin involvement.
- Bone marrow : myelophthisic anemia.
- Genitals involvement.
- Salivary glands involvement.
- MC affected organs : Lungs.

Pathogenesis :

Type IV hypersensitivity reaction (cell mediated).
Increased levels of CD4 + TH_1 cells leading to granuloma formation (INF gamma/ IL-12).
HLA-A_1 and HLA B8 association.

Biopsy :

- Non caseating granulomas.
- Slipper shaped nuclei (epitheloid cells).
- Naked granuloma (absence of lymphocytic collar).

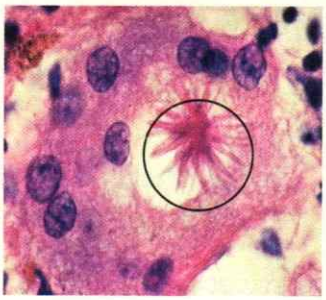


Non caseating granulomas

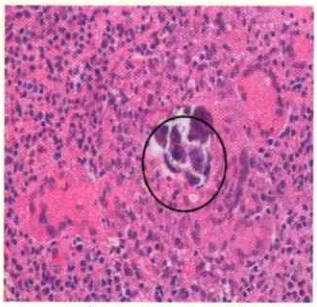
Inclusions of sarcoids :

Active space

Schaumann bodies : Basophilic due to calcium concretions.



Asteroid body



Schaumann body

Biochemical tests :

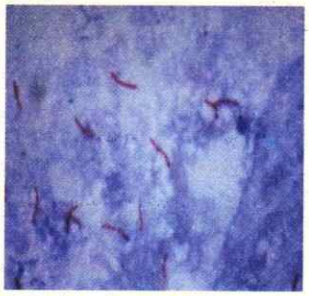
- Increased CD4 to CD 8 cell ratio.
- Kveim's test positive.
- Increased serum calcium : metastatic calcification.
- Increased level of angiotensin converting enzymes.

Hypersensitive pneumonitis 00:10:45

Type III and Type IV hypersensitivity reaction.
Caused by inhalation of organic dust like moulds or hay.

Tuberculosis 00:12:08

- Caused by mycobacterium tuberculosis.
- C/F : Fever, night sweats, weight loss, chest pain, dyspnea & cough.
- Virulence factor : Cord factor.



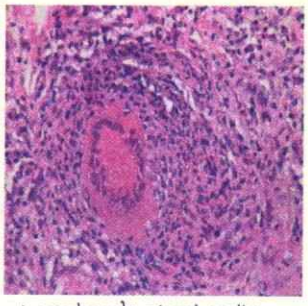
AFB bacilli on ZN stain

- FNAC of lymph nodes :

Cheesy material : Caseous necrosis.
Caseating granulomas.

- Acid fast bacilli on ZN stain.

Other AFB : Cryptosporadium, Isospora, Nocardia & hooklets of hydatids.
Acid fastness is due to mycolic acid in the membrane.



Langhan's giant cells

- Biopsy of lymph nodes :

Caseating granuloma.

Active space

Giant cell is called langhan's giant cells (necklace or horse shoe arrangement of nuclei).

Treatment → ATT.

Types of tuberculosis :

Primary TB :

- Occurs in children or occurs after first exposure.
- Usually affects lower part of upper lobe and upper part of lower lobe.
- Leison is called as Gohn's foci.
- Gohn's foci + lymphnode : Gohn's complex.
- Fibrosis + calcification in gohn's complex : Ranke's complex.
- Rich's focus : Involvement of TB in brain.
- Simmon's focus : Involvement of TB in liver.
- Weigert's focus : Involvement of TB in lymphnodes.

Secondary (reactivation) TB :

- Occurs in children.
- In previously sensitized individuals/ repeat exposure.
- Puhl's focus : Supraclavicular lesion of reactivation of Tb.
- Assmann's focus : Infraclavicular lesion.

Miliary TB :

- 1-2 mm millet shaped lesions.
- Poor prognosis.
- Spread to other organs → Hematogenous.

Miliary TB

Pneumonia

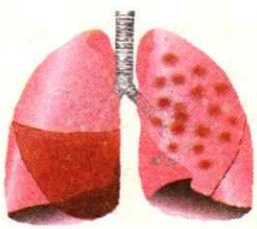
00:26:09

Infection of lung parenchyma.

2 types : Lobar pneumonia and lobular bronchopneumonia.

Lobar pneumonia → Entire lobe affected.

Bronchopneumonia → Patchy infiltrate.



Active space

Also classified into typical and atypical pneumonia.

Typical pneumonia	Atypical pneumonia
Bacteria	Viruses.
Lots of exudate	Less exudates
Neutrophil	Lymphocyte

Stages of pneumonia :

4 main stages :

1. Stage of congestion : 1-2 days.
2. Stage of red hepatization : 2-4 days.
3. Stage of grey hepatization : 5-8 days.
4. Stage of resolution : 8-10 days.

Stage of congestion :

Lung is congested with RBC's.

Stage of red hepatization :

Red in colour due to RBC.

Hepatization is due to liver like consistency (firm) due to fibrin.

Stage of grey hepatization :

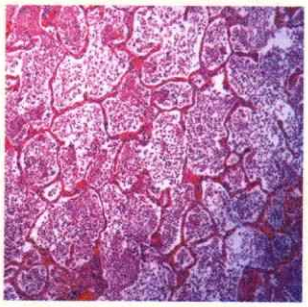
Disintegration of RBC's, producing grey colour.

Hepatization is due to liver like consistency (firm) due to fibrin.

Stage of resolution : MC outcome.

Biopsy → Inflammatory cells.

Alveoli are engorged.



Biopsy - Pneumonia

MCC of community acquired pneumonia : Streptococcus pneumoniae.

MCC of hospital acquired pneumonia : _____

Active space

Other infections

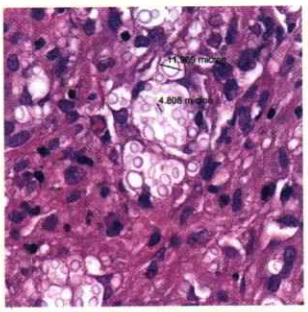
00:32:38

Covid 19

On HPE : Diffuse alveolar damage.

Histoplasmosis :

- Seen in bird breeders.
- Gross : Tree bark appearance.
- HPE : Caseating granuloma.
  cysts of histoplasma.

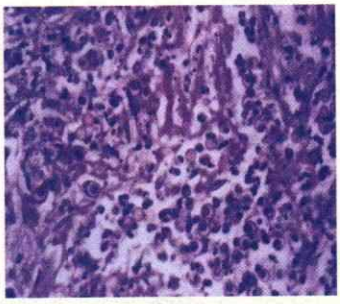


Histoplasmosis

Blastomycosis :

Characteristic appearance of →

- Double walled thick cysts with a dense basophilic core.
- Figure of 8 appearance.
- Gomori methanamine silver stain.



Blastomycosis

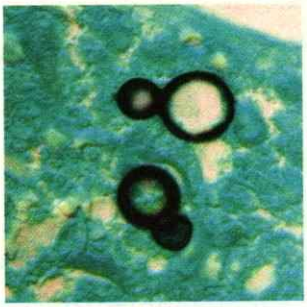
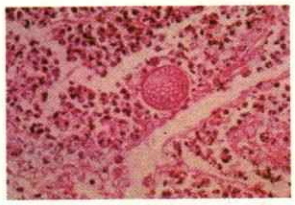


Figure of 8 on Gomori methanamine silver stain

Coccidiomycosis :

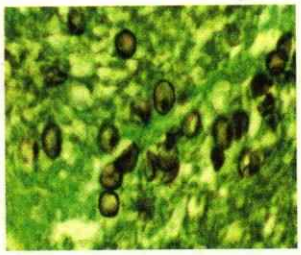
Caseating granuloma.



Coccidiomycosis

Pneumocystis carnii :

- Produces frothy sputum in immunosuppressed like HIV.
- Ping pong ball appearance/ cup and saucer appearance.

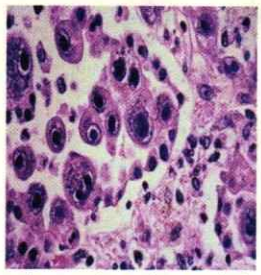


Pingpong ball appearance

Active space

CMV pneumonia :

- Owl's eye inclusions.
- Intranuclear basophilic inclusions.



Intranuclear basophillic inclusions

Pulmonary alveolar proteinosis

00:39:49

Disorders of surfactant.

Rare disease.

3 types :

Congenital or neonatal :

- Mutation of ABC A3 gene.
- Defective development of lamellar body leading to defective production of type II pneumocytes resulting in surfactant abnormalities.

Autoimmune pulmonary alveolar proteinosis :

- MC type (90%).
- Defect in GM-CSF signalling pathway.

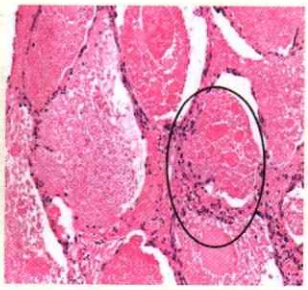
Entire surfactant starts accumulating in intra broncheolar space.

Secondary PAP :

- Rare.
- Associated with hematological malignancies.

HPE :

Homogenous pink material in the alveoli.



Pink homogenous material in alveoli

Active space

MCQs :

Q. A 70-year-old woman at an extended care facility for the past two years has increasing inability to perform activities of daily living. She can no longer recognize family members. She is lethargic and spends most of her days in a wheelchair or in bed. She develops an acute febrile illness and is noted to be coughing up increasing quantities of yellowish sputum. Her temperature is 38°C. A chest x-ray shows infiltrates involving the left lower lobe. A sputum sample shows numerous neutrophils and gram-positive diplococci. Which of the following infectious agents is most likely to cause her pulmonary disease?

A. Pneumocystis jiroveci.
B. Listeria monocytogenes.
C. Mycobacterium tuberculosis.
D. Legionella pneumophila.
E. Streptococcus pneumoniae.

Q. A 50-year-old woman has lived in Oslo, Norway all her life and worked as a seamstress. She is a non-smoker, but she has had increasing shortness of breath, fever, weight loss, and night sweats for the past 4 months. On physical examination her temperature is 37.6°C. There are fine rales auscultated in all lung fields. A chest radiograph reveals hilar lymphadenopathy and a reticulonodular pattern of small densities in all lung fields. She demonstrates anergy by skin testing to mumps and Candida antigens. A transbronchial biopsy is performed that microscopically shows numerous small pulmonary interstitial non-caseating granulomas. Which of the following is the most likely diagnosis?

A. Histoplasmosis.
B. Sarcoidosis.
C. Berylliosis.
D. Tuberculosis.

Q. A 41-year-old man with a 6 Kg weight loss over the past 3 months now has had worsening fever, non-productive cough, and dyspnea for the past 3 days. His temperature is 38.2°C and there are diffuse rales

Active space

in both lungs on auscultation. A chest radiograph shows patchy infiltrates in both lungs. Laboratory studies show WBC count 3250/microliter with 81 segs, 3 bands, 5 lymphs, and 11 monos. His CD4 lymphocyte count is 79/microliter. Cryptosporidium parvum organisms are found in a stool specimen. A bronchoalveolar lavage is performed, yielding fluid that microscopically demonstrates pink, foamy exudate with little inflammation. Which of the following additional findings on microscopic examination is he most likely to have in the BAL specimen?

A. Acid fast bacilli.
B. Branching septate hyphae.
C. Multiple cysts with GMS stain.
D. Hemosiderin-laden macrophages.
E. Short gram positive rods.

Active space

LUNG TUMORS

Most common lung tumor : Metastasis.

Most common carcinoma which metastasizes to the lung : Breast carcinoma.

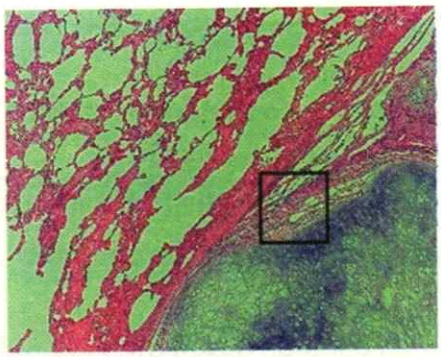
Most common Primary lung tumor : _____

Pulmonary hamartoma 00:02:25

Solitary 3-4cm well circumscribed lesion.

On X-ray : Coin shaped lesions seen.

Hamartoma is an abnormal proliferation of cells.



H & E :

Consist of connective tissue elements and epithelium.

Most common connective tissue element is cartilage.

Classification of lung cancer 00:05:30

They are classified as follows,

- Small cell lung carcinoma.
- Non-small cell lung carcinoma : Squamous cell and adeno carcinoma of lung.
- Large cell lung carcinoma.

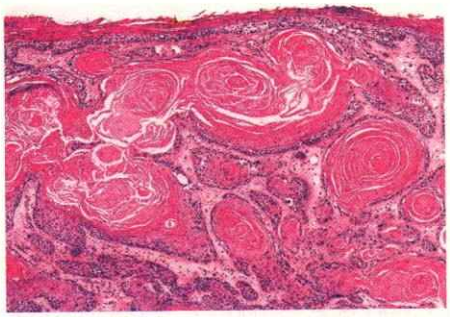
Squamous carcinoma of lung (SCC).

Male >> Females.

Associated with smoking.

Centrally located.

Produce cavitary lesions or Intra bronchial mass-producing obstruction.



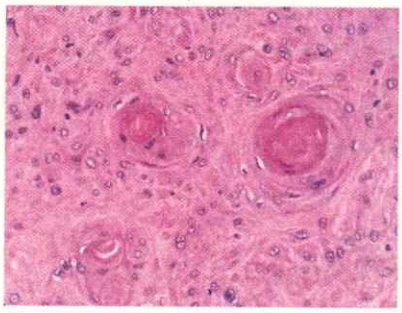
Active space

Pathogenesis :

Mutation in P53, Rb, CDKN2A, Loss of chromosome 3p, 9p and 17p.

Squamous cell carcinoma more commonly associated with para neoplastic syndrome :

Hypercalcemia due to PTH related peptide.



Precursor lesions : Squamous dysplasia Or carcinoma insitu.

H & E :

Desmosomes and Keratin pearls.

SCC can be of three types :

- Well differentiated : Pearls seen.
- Moderately differentiated : Individual cell Keratinization seen.
- Poorly differentiated : Keratin pearls not seen.

Poorly differentiated carcinoma can be diagnosed by immuno histo chemistry markers : Cytokeratin, P63 and P40 (most sensitive and specific marker).

Adeno carcinoma of lung

00:17:42

Most common lung carcinoma overall.

Usually seen in women.

Seen in non-smokers.

Peripherally located.

Para neoplastic syndrome associated : migratory thrombophlebitis.

Genetics : Mutation in EGFR, ALK, MET, RET, K-RAS.

Precursor lesions :

- Atypical adenomatous hyperplasia.
- Adenocarcinoma insitu.

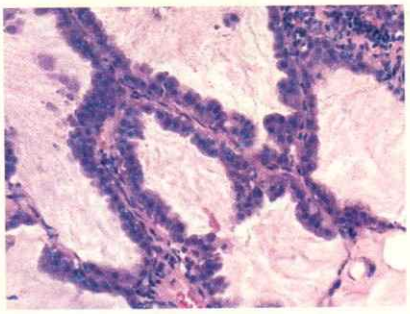
Atypical adenomatous hyperplasia :

Lesion is less than or equal to 5mm.

Dysplastic pneumocytes lining the alveolar epithelium.

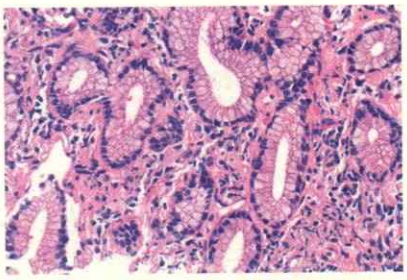
Active space

Adenocarcinoma insitu :



Also known as bronchioalveolar carcinoma. < 3mm.
Tumor cells grow along the bronchioalveolar lining.
Butterflies on the fence appearance.
Filigree pattern/Lepidic pattern.

H & E :



Glands lined by malignant cells.

Types : Well, moderately and poorly differentiated adeno carcinoma.

Immuno histo chemistry markers to diagnose poorly differentiated adeno carcinoma : TTF-1, NAPSIN-A.

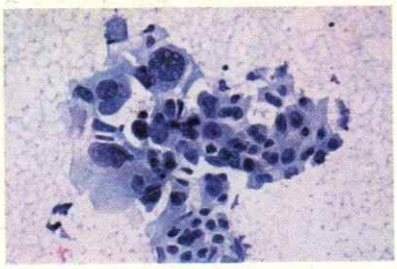
Small cell carcinoma of lung

00:27:20

Strongest association with smoking.
Males >> Females.
Centrally located (Sometimes located in the periphery).
Worst prognosis.
Highly chemo sensitive.
Produces maximum para neoplastic syndrome :
Cushing syndrome, SIADH (most common).

Genetics :
Mutation in P53, Rb and L-myc association (Amplified).

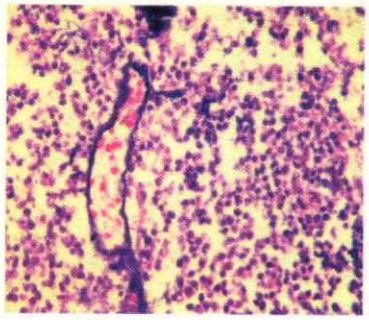
H&E :



Small cells, scanty cytoplasm.
Hyperchromatic nucleus.
Nuclear moulding.
Necrosis.
Azzopardi effect.
Granular chromatin : Salt and pepper chromatin.

Active space

Azzopardi effect :
Fragile cells break & releases DNA which deposits in the blood vessel wall producing basophilic staining.



Immuno histochemistry markers :

- Neuron specific enolase.
- Synaptophysin.
- Chromogranin.

These markers can be used for any neuro endocrine tumors.
Electron microscopy : Dense core neurosecretory granules.

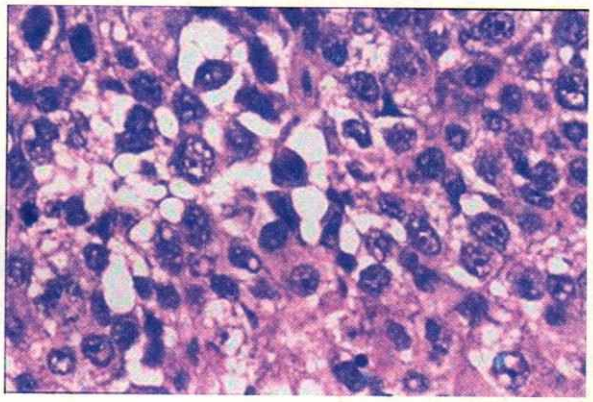
Neuro endocrine tumors :

- Small cell carcinoma of lung.
- Carcinoid tumor.
- Phaeochromocytoma.
- Paraganglioma.
- Carotid body tumor.

Large cell lung cancer

00:39:30

Sheets of large highly pleomorphic cells.
Centrally as well as peripherally located.
Diagnosis of exclusion.



Active space

Feature	SCC	Adeno CA	Small cell CA	Large cell CA
Incidence	M>F	F>M	M>F	M>F
Location	central	Priphearal	Central	Peripheral
Smoking ass	Smoking ass	Non smokers	Strongest ass with smoking	Both
Parane-oplastic syndromes	Hyper-calcemia	Migratory Thrombo-phlebitis	Cushings syndrome, IADH	Gynecomastia
Pathogen-esis	P53	K ras, EGFR, ALK	L-myc	
H&E	Keratin pearls, desmo-somes	Glands lined by pleomorphic cells	Small cells, salt and pepper chroma-tin, nuclear moulding, Azzopardi effect	Large, pleomorphic cells
IHC	CK, P63, P40	TTF 1, NAPSIN A	NSE, chromo, synapto	

Clinical presentation of lung cancer 00:44:26

Most common symptom is cough.
Other symptoms : Dyspnea and hemoptysis.
Lung carcinoma at the apex : Compress the cervical sympathetic chain (Horner's syndrome).
This tumor at the apex is called as Pancoast tumor.

Horner's syndrome :

Ptosis.
Miosis.
Enophthalmos.
Anhydrosis.
Loss of cilio spinal reflex.

Spread of lung cancer :

- Directly involves the recurrent laryngeal nerve : Hoarseness.

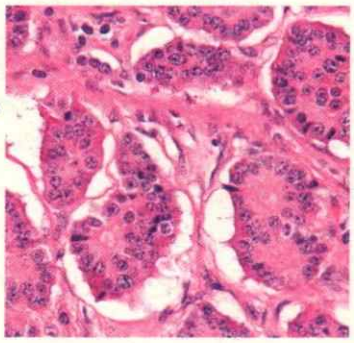
Active space

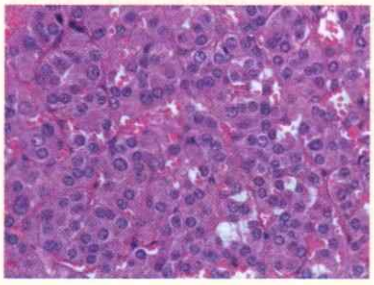
- Lymph node involvement : Hilar lymph nodes.
- metastasis : Liver (more common), brain and adrenal gland.

Carcinoid tumor of lung

00:48:46

Arises from the Kulchitsky cells.
Only 10% carcinoid tumor produces carcinoid syndrome.
Clinically :
Flushing, sweating, diarrhea.
H&E :
Cells are present as rosette like or nest like.
Salt and pepper chromatin.





Types :
Typical carcinoid tumor.
Atypical carcinoid tumor.

Typical	Atypical
<2 miosis per 10 high power fields.	2-10 miosis per 10 high power fields.
Less pleomorphic.	more pleomorphic.
Less necrosis.	more necrosis.

Malignant mesothelioma

00:53:46

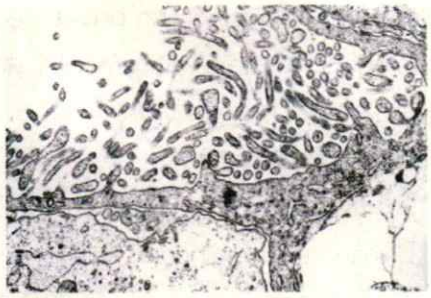
Risk factor : Asbestosis exposure.
Latent period : 25-40 years.
History of working in a shipping industry usually present.
Genetics : mutation in P53, SV-40 virus involvement.
H&E :
3 types of cells can be seen,

- Spindle cells.
- Epithelioid cells.
- Sarcomatoid cells.

Active space

Immuno histochemistry markers : Calretinin

Electron microscopy : Long slender microvilli or tonofilaments.



Asbestosis exposure leads to,

- Malignant mesothelioma.
- Adenocarcinoma lung.

Differentiating features :

Malignant mesothelioma	Lung adenocarcinoma
Asbestosis exposure for 25-40 years.	Exposure for 10-30 years
Calretinin +	Calretinin -
Vimentin +	Vimentin -
TTF 1 -	TTF 1 +
On EM : Long slender microvilli	Short, plump villi

MCQs :

Q. A 56 year old chronic smoker, presents with cough and hemoptysis. Mass is resected. What is the possible marker?

A. Cytokeratin.

B. Vimentin.

C. EMA.

D. Napsin.

Q. A 60 year old man with greyish white tumor located at central bronchus causing obstruction and bronchiectasis. Biopsy will show :

A. Spindle cells.

B. Contains all three germ layers.

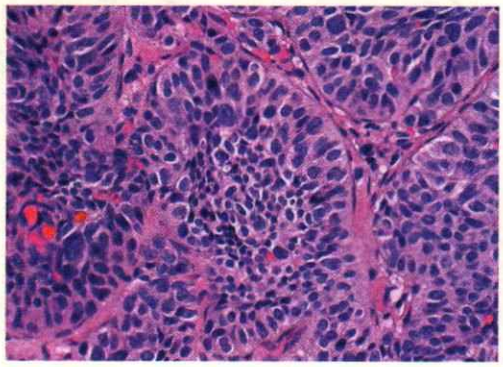
C. Abundant osteoid matrix formation.

D. Small round cells with hyperchromatic nuclei and nuclear moulding.

Active space

Q. A 35 year old women presented with coughing, dyspnea, flushing, diarrhea for a month. Histopathology of mass is given below. mitosis was 5/hpf and is chromogranin positive. What is the diagnosis?

A. Small cell carcinoma.
B. Large cell carcinoma.
C. Typical carcinoid.
D. Atypical carcinoid.



Q. Lymphoma like picture in lung cancer is seen in which subtype?

A. SCC.
B. Adenocarcinoma.
C. Small cell carcinoma.
D. Large cell carcinoma.

Q. Incorrect statement about small cell lung cancer :

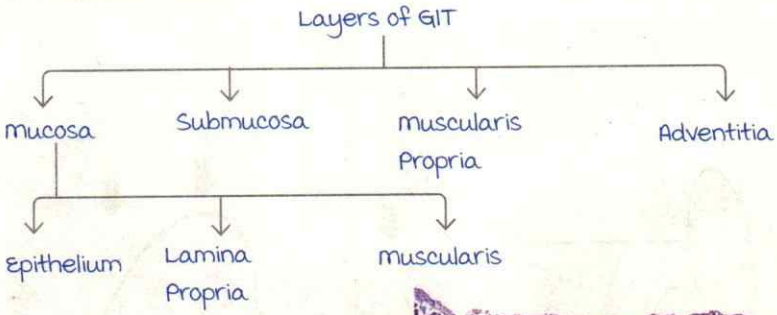
A. Not associated with smoking.
B. Surgical resection alone is the treatment of choice.
C. Associated with paraneoplastic syndromes.
D. Contains neurosecretory granules.
E. Most patients have distant metastasis at the time of diagnosis.

Active space

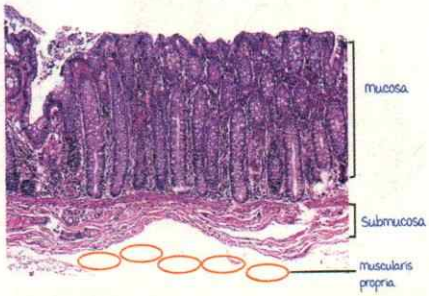
ESOPHAGUS

Histology of GIT

00:01:24



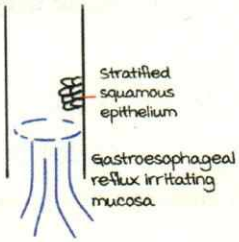
Exceptions :
No submucosa in gall bladder.
No serosa in esophagus.



Lesions of esophagus

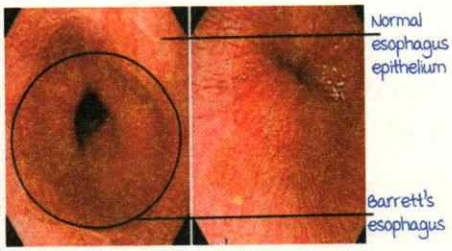
00:03:06

Barret's esophagus :
Also known as Columnar Lined Oesophagus (CLO).
metaplasia (reversible change in which one differentiated cell type converts into another).
Esophagus is normally lined by stratified squamous epithelium → Columnar epithelium (barret's esophagus).



This occurs due to :
Gastro-oesophageal reflux disease /GERD.

Types :
Short segment :
metaplasia involves <3 cm.
Long segment :
metaplasia involves >3 cm.



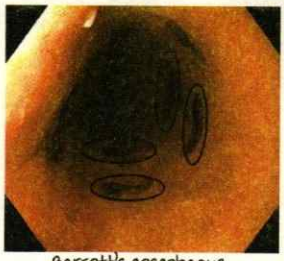
Active space

Microscopy :

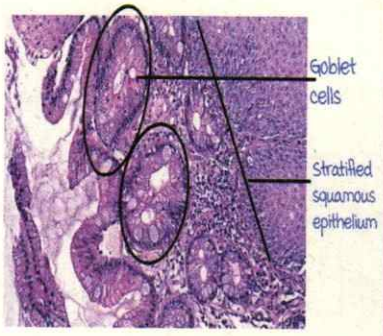
- Intestinal metaplasia.
- Goblet cells containing mucin (stained by Alcian blue) seen.

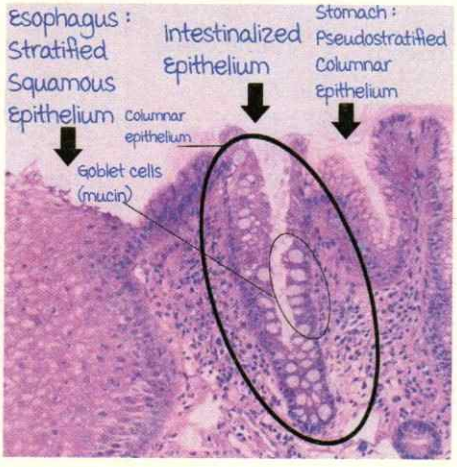
Special stain for Barrett's esophagus is Alcian blue.

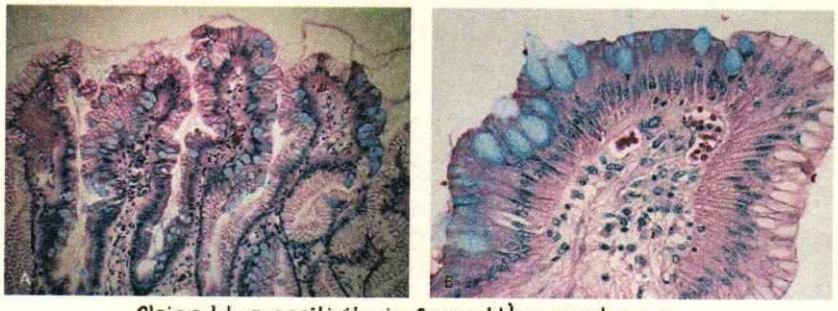
On endoscopy : Red velvety appearance.



Barrett's oesophagus







Alcian blue positivity in Barrett's oesophagus

Hallmark of Barrett's esophagus is presence of goblet cells.
Dysplasia of Barrett's esophagus can lead to increased risk of adenocarcinoma of esophagus.

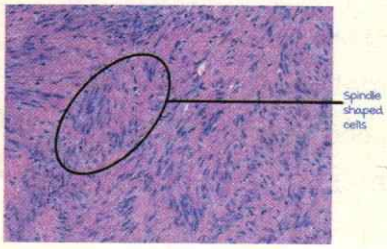
Tumors of esophagus 00:12:29

m/c benign tumour of oesophagus : Leiomyoma.

Origin : Smooth muscle.

Histology :

Spindle shaped cells with cigar shaped nuclei.



Active space

IHC marker : Smooth muscle Actin (SMA).

Malignant tumour : Leiomyosarcoma (IHC marker : Vimentin).

Carcinoma esophagus

00:14:53

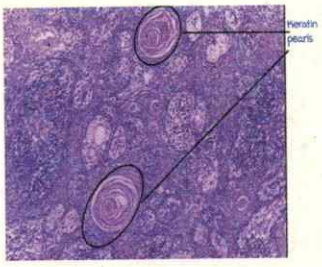
Squamous cell carcinoma (SCC)	Adenocarcinoma
middle 1/3 rd of esophagus	Lower 1/3 rd of esophagus
Overall MC	m/c in western world
Risk factors	
Smoking , alcohol Preservative rich food Smoked food Tylosis Achalasia cardia Vitamin E & Selenium deficiency Zenker's diverticulum Corrosive injury Plummer Vinson syndrome	Smoking , alcohol GERD CREST syndrome Barrett's esophagus P53 & Rb mutation can also be seen H. pylori is protective.

SCC :

Histology : Keratin pearls & Desmosomes can be seen.

Keratin pearls are eosinophilic and have nuclei (to differentiate from psammoma bodies).

Marker : Cytokeratin (CK) & p63.

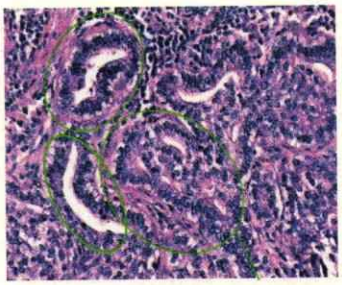


Adenocarcinoma :

Glands lined by pleiomorphic cells.

Most important prognostic factor :

Depth of invasion.



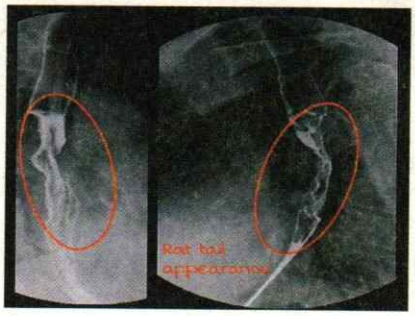
Adenocarcinoma — Glands lined by pleiomorphic cells

Clinical Features :

- Dysphagia (solids >> liquids).
- weight loss.
- Anorexia.

Active space

Barium swallow : Rat tail appearance.



Clinical scenario :

Q. A patient with recurrent gastritis has been diagnosed with Helicobacter Pylori infection. Which of the following is true in this patient?

A. Increased risk of adenocarcinoma esophagus.

B. Decreased risk of adenocarcinoma esophagus.

C. Increased risk of SCC esophagus.

D. Decreased risk of SCC of esophagus.

H.Pylori is protective against adenocarcinoma.

Q. A 58 year old man has had increasing difficulty swallowing for the past 6 months and has lost 5 Kg. No abnormal physical examination findings are noted. Upper GI endoscopy reveals a nearly circumferential mass with overlying ulceration in the mid esophageal region. Biopsy of the mass reveals pink polygonal cells with marked hyperchromatism and pleomorphism. Which of the following is the most likely risk factor for development of his disease?

A. Iron deficiency.

B. Helicobacter pylori infection.

C. Chronic alcohol abuse.

D. High fruit diet.

E. Zenker diverticulum.

Hints : Circumferential mass suggestive of SCC.

Plummer Vinson syndrome

00:14:53

Also known as Patterson Kelly Brown syndrome.

Seen in middle aged females.

Characterised by a triad of :

- Oesophageal web.
- Atrophic glossitis.
- Iron deficiency anemia.

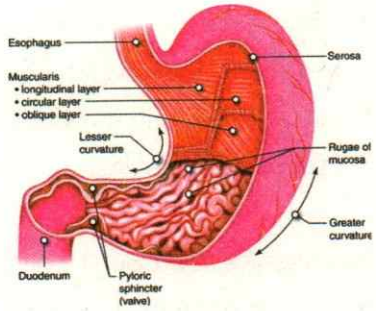
Active space

STOMACH

Anatomy of stomach 00:00:20

Parts :

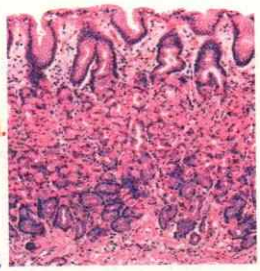
- Cardia.
- Greater curvature of stomach.
- Lesser curvature of stomach.
- Fundus.
- Body.
- Antrum or pyloric antrum.



Inside, it has large number of rugae or folds.

On microscopy, stomach has various areas and different types of cells.

- Foveolar cells : Secrete neutral mucin.
- Fundus and body of stomach :



Upper layer : Parietal cells (eosinophilic).
Parietal cells secretes intrinsic factor & Hcl.
Below : Chief cells (basophilic).
Chief cells produce pepsinogen.
Parietal & chief cells : mostly in the fundus & body of stomach.

Gastritis 00:03:39

Inflammation of gastric mucosa (gastric epithelium).
2 types : Acute and chronic.

Acute gastritis	Chronic gastritis	
Shorter duration.	Longer duration.	
Causes : Smoking, alcohol, aspirin, NSAIDS and stress.	Broadly 2 types : Type A & B.	
	Type A : Seen in 10%. Autoimmune.	Type B : Seen in 90%. Caused by H.pylori
HPE : Neutrophils in the epithelium.		

Active space

Type B chronic gastritis :

1. H. pylori induced gastritis.

H. pylori :

- Gram negative spiral shaped bacteria.
- It has tuft of flagella at one end.

Pathogenic factors :

- Cag A and Vac A : Carcinogenic.
- It also produces enzyme called Urease.
- Flagella helps in movement.
- Produces adhesins.

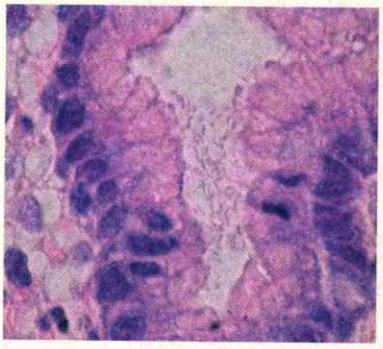
Diseases caused by H. pylori :

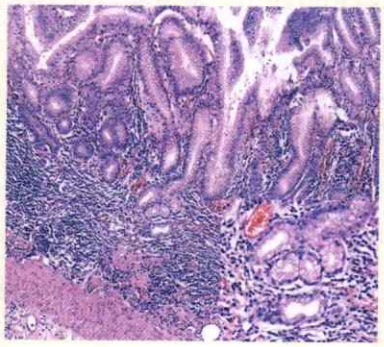
- Chronic gastritis (type B).
- Gastric adenocarcinoma (m/c malignancy by H.pylori).
- Marginal zone lymphoma/ MALToma (most specific malignancy by H.pylori).
- Protective against :

Antral biopsy is done in most of the cases.

On HPE :

- Intra epithelial neutrophils.
- Sub epithelial plasma cells.
- Lymphoid follicles/ lymphocytic aggregates in sub epithelium.
- Neutrophils invades gastric glands, forming pit abscesses.
- H. pylori is present over the mucosa as it cannot penetrate the gastric mucosa.





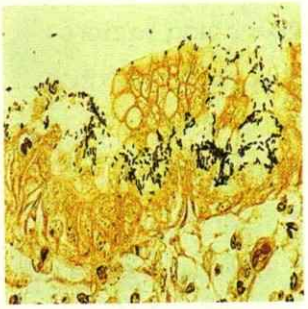
Special stains :

- Warthin starry silver stain.
- Modified geimsa stain

Active space

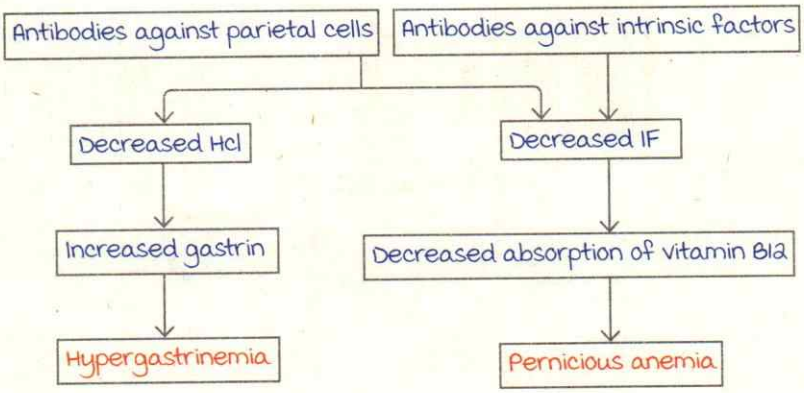
- Steiner stain.
- Diff Quik stain.

warthin starry silver stain



2. Type A chronic gastritis :

- 10% cases.
- Autoimmune gastritis.
- Antibodies are usually against parietal cells or
- Antibodies against intrinsic factor.



C/F :

- Features of vitamin B_{12} deficiency.
- Features of atrophic gastritis.
- Increased risk of other auto immune disorders.

Gross examination : Loss of rugal folds.

On HPE : Lymphocytes and plasma cells in the mucosa.

Peptic ulcer

00:19:04

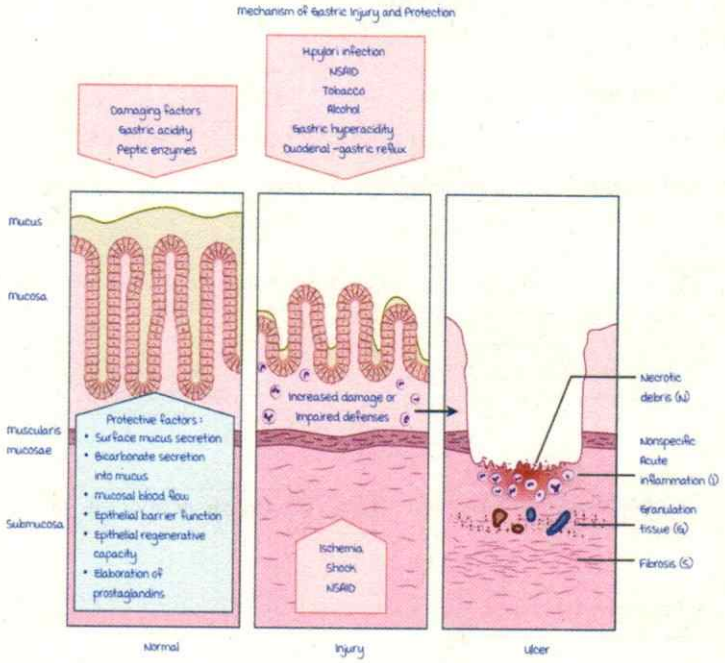
Protective factors :

- Surface mucus secretion.
- Bicarbonate secretion into mucus.
- Mucosal blood flow.
- Epithelial barrier function.
- Epithelial regenerative capacity.
- Elaboration of prostaglandins.

Active space

Damaging factors :

- H. pylori infection.
- NSAID's.
- Tobacco.
- Alcohol.
- Gastric hyperacidity.
- Duodenal gastric reflux.



This diagram illustrates the progression from more mild forms of injury to ulceration that may occur with acute or chronic gastritis. Ulcers include layers of necrosis(N), inflammation (I), and granulation tissue(G), but a fibrotic scar (S) which takes time to develop, is only present in chronic lesions.

Increased damaging factors & the protective factors unable to protect gastric epithelium leads to ulcer.

Peptic ulcer has 4 different zones :

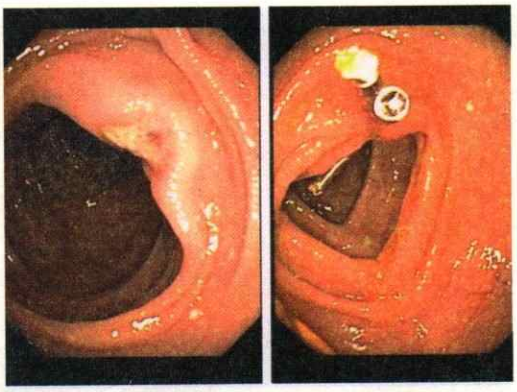
1. Zone of necrotic debris.
2. Zone of inflammatory cells.
3. Zone of granulation tissue : Neovascularization.
4. Zone of fibrosis.

2 types :

Gastric and duodenal ulcer.

Active space

Gastric ulcer	Duodenal ulcer
Less common.	most common.
Common site : Cardia near incisura angularis.	Common site : DI duodenum.
Poor prognosis.	Better prognosis.
more malignant potential.	No malignant potential.
m/C complication : Bleeding.	m/C complication : perforation.



Gastric adenocarcinoma 00:23:43

Risk factors :

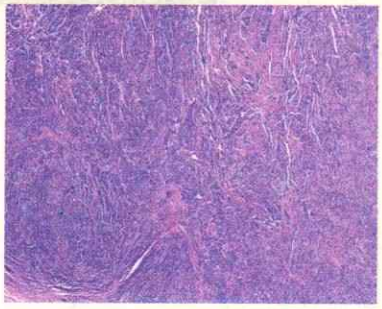
- Smoking.
- Alcohol consumption.
- Consumption of smoked food/fish (hence higher incidence amongst Japanese).
- Preservative rich food.
- H. pylori.
- Menetrier's disease.
- Gastric resections.
- Polyps.
- Gastritis.

Active space

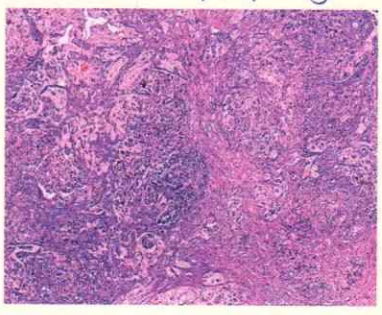
Lauren's pathological classification :

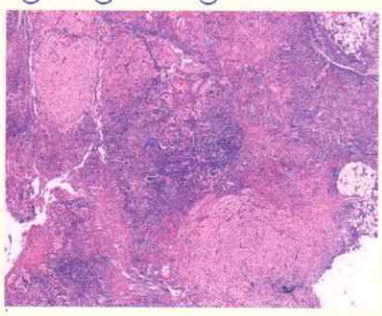
Intestinal	Diffuse
Polypoidal.	Diffuse infiltrative masses.
Environmental.	Familial.
Gastric atrophy, intestinal metaplasia.	Blood type A.
Men > women.	Women > men.
Increasing incidence with age.	Younger age group.
Gland formation.	Poorly differentiated, signet ring cells.
Hematogenous spread.	Transmural/ lymphatic spread.
Microsatellite instability APC gene mutation.	CDH I gene mutation leading to decreased E cadherin.
p53, p16 inactivation.	p53, p16 inactivation.

Adenocarcinoma :
Glands lined by pleomorphic cells. (large cells with hyperchromatic nuclei, loss of polarity, abnormal mitoses.



Signet ring cell is produced by intracellular mucin that pushes the nucleus to the periphery forming a signet ring.



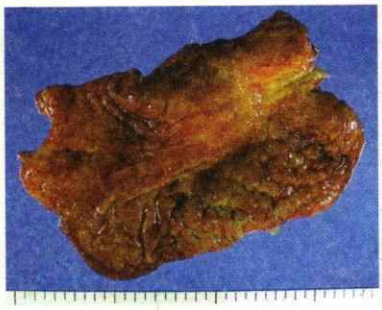


Linitis plastica :
Last stage of diffuse gastric carcinoma.
Leather bottle appearance.

Active space

No intramural mass.

Totally invades the wall leading to thickening of the wall, wall becomes rubbery and appears as leather bottle.



Metastasis of diffuse type of gastric carcinoma :

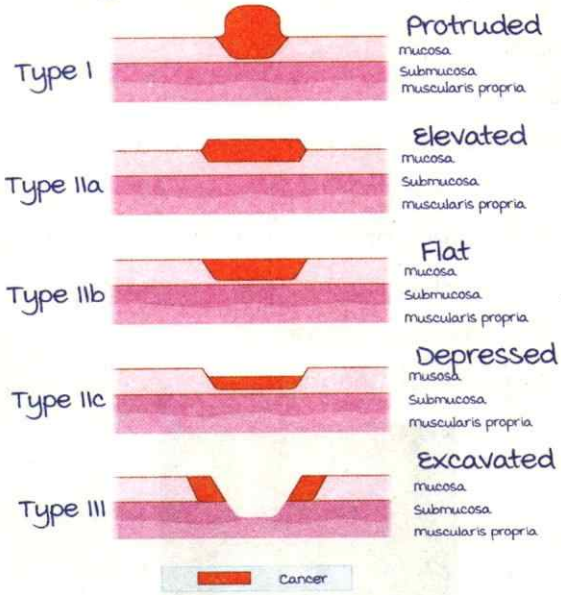
Krukenberg's tumor :

- It produces bilateral symmetric enlargement of ovary.
- Intact capsule.

HPE : Sheets of signet ring cells.

Early Gastric cancer (Japanese classification) :

Pathologic types of early gastric cancer according to Japanese classification system



Best prognosis of early gastric cancer (Japanese

Active space

classification) : Protruded type.

Late Gastric cancer (Boremann classification) :

Borrman's classification of Stomach cancer

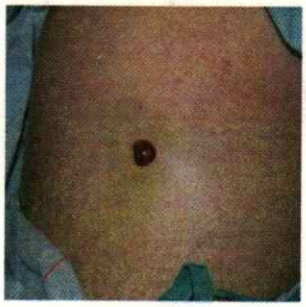
	Type I Polypoid or fungating cancers
	Type II Fungating or ulcerated with surrounding elevated borders
	Type III Ulcerating lesions infiltrating the gastric wall
	Type IV Linitis plastica : diffusely infiltrating
Type V : Unable to be classified	

Best prognosis of advanced gastric cancer (borrmann's classification) : Polypoidal type.

Worst prognosis : Linitus plastica.

C/F :

- Dyspepsia.
- Weight loss.
- Anorexia.
- Left supraclavicular lymph node enlargement : Virchow's node.
- Left axillary lymph node enlargement : Irish node.
- Periumbilical nodule : Sister Mary joseph nodule.
- Ovary : Krukenberg's tumor.
- Can reach pouch of Doughlas : Bloomershelf lesions.



Active space

Gastro Intestinal Stromal Tumor (GIST) 00:37:25

m/c mesenchymal tumor of stomach.

It arises from gut pacemaker cells (interstitial cells of cajal).

Genetics :

- C Kit mutation.
- PDGFR A mutation (oncogene that is amplified).
  (PDGFR B : Seen in brain tumors.)
- SDH B enzyme mutation.

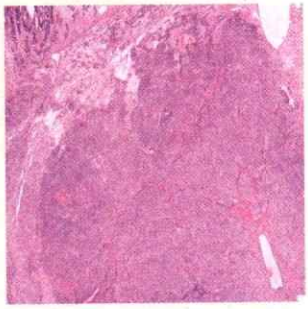
Syndromes associated :

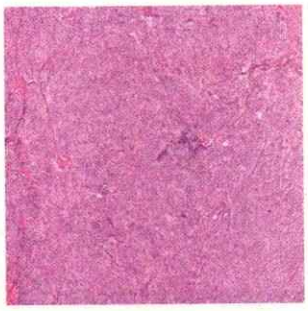
Carney's syndrome :

- GIST.
- Pulmonary chondroma.
- Paraganglioma.

Gross appearance : Soft and well circumscribed tumor.

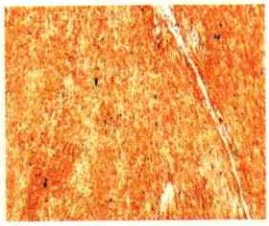
HPE : Spindle cells (m/c) and epitheloid cells (least common).





Markers :

- CD 117 (C Kit) : most sensitive marker.
- DOG 1 : most specific marker.
- CD 34.



Prognostic factors :

Size of tumor :

< 5cm : Good prognosis.

> 10cm : Poor prognosis.

Mitosis :

> 10/hpf : Poor prognosis.

Location :

Gastric GIST : Good prognosis.

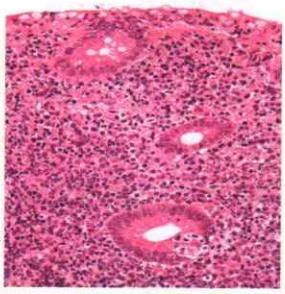
Intestinal GIST : Poor prognosis.

Active space

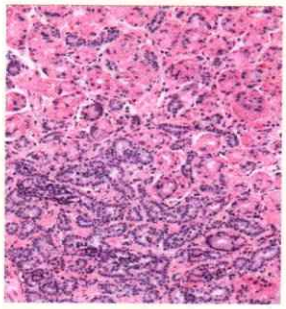
MALToma

00:44:16

Mucosa associated lymphoid tissue (MALT) tumor.
M/C type of gastric lymphoma : DLBCL.
M/C site of extra nodal lymphoma : Stomach.
M/C site for MALT tissue : Peyer's patches.



Genetics :
t(11 : 18) is most common.
t(1 : 18).
t(14 : 18) : Increased MLL expressed.
HPE : Lymphoepithelial lesion (lymphocyte entering the epithelium).
Marker : CD 43+.



Carcinoid tumor :
HPE :
- Nests of monomorphic cells.
- Salt and pepper chromatin.

Markers :
- NSE.
- Synaptophysin.
- Chromogranin.

On electron microscopy : Dense core neurosecretory granules.

MCQ's:

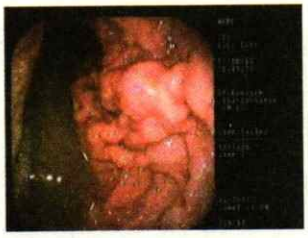
Q. A 50 year old man has had persistent nausea for 5 years with occasional vomiting. On physical examination there are no abnormal findings. He undergoes upper GI endoscopy, and a small area of gastric fundal mucosa has loss of rugal folds. Biopsies are taken and microscopically reveal well-differentiated adenocarcinoma confined to the mucosa. An upper GI endoscopy performed 5 years previously showed a pattern of gastritis and microscopically there was chronic inflammation with the presence of plasma cells. Which of the following is the most likely risk factor for his neoplasm?
A. Inherited APC gene mutation.

Active space

B. Helicobacter pylori infection.
C. Chronic alcohol abuse.
D. Use of non steroidal anti inflammatory drugs.
E. Vitamin B12 deficiency.

Q. A 50 year old woman presents with complaints of abdominal pain and diarrhea. On examination, her face appears flushed and her pulse is 120/min. increased levels of 5HIAA are observed in a urinary sample. Which of the following is not a prognostic factor for this condition?
A. Degree of histological differentiation .
B. Mitotic rate.
C. Type of hormone secreted.
D. Ki67 proliferative index.

Q. The upper gastrointestinal endoscopy of a patient is shown below. Excessive secretion of which of the following is associated with this condition?



A. TGF alpha.
B. PDGF beta.
C. PDGF alpha.
D. TGF beta.

Q. Not true about GIST :
A. Stomach is the most common site.
B. High propensity of malignant change.
C. Associated with c Kit mutation.
D. Histology shows spindle shaped cells.

Active space

INTESTINAL DISORDERS

Malabsorption syndrome :

Clinical features :

- Steatorrhea : Frothy, greasy, bulky stools.
- Abdominal pain.
- Diarrhea.

Celiac disease

00:01:48

Gluten sensitive enteropathy.

Dietary restriction (patient cannot have) :

Barley.

Rye.

Oats.

Wheat.

Patient can have rice or maize.

Pathogenesis :

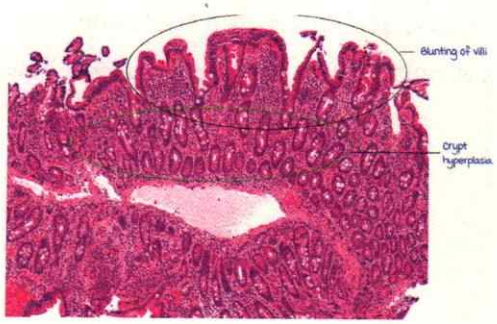
Site for biopsy : Duodenum.

(for H. pylori : Biopsy is taken from antrum).

α-gliadin polypeptide → Cannot be digested by enzymes.

HLADQ2/DQ8 polymorphism seen.

Increased IL-15 → Increased proliferation of CD8+ T lymphocytes.



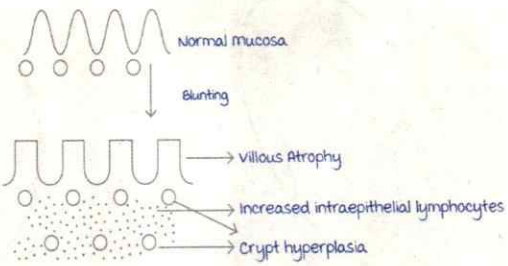
Clinical features :

- Steatorrhea.
- Abdominal pain.
- Diarrhea.
- Increased risk of dermatitis herpetiformis (subepidermal bullous skin disorder).
- Increased risk of enteropathy associated T-cell lymphoma.

Active space

Microscopy :

Villous atrophy.
Crypt hyperplasia.
Increase in number of intraepithelial lymphocytes.



Marsh score : Higher the score → Poorer the prognosis.

Antibodies associated with celiac disease :

Anti gliadin antibody.
Anti endomysial antibody (most specific).
Anti tissue transglutaminase antibody (most sensitive).

Tropical sprue disease :

Seen in people travelling to tropical countries.
Causative organism : E. coli.
Also known as environmental enteropathy.
Affects all part of bowel :

Duodenum : Site of iron absorption.
Jejunum : Site of folic acid absorption.
Ileum : Site of vitamin B_{12} absorption.

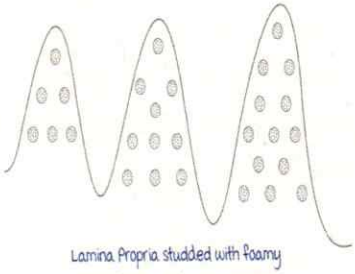
} Deficiency of iron, folic acid & vitamin B 12

Whipple's disease

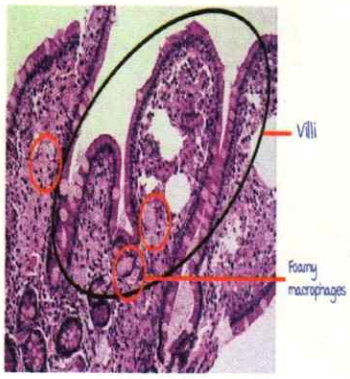
00:13:09

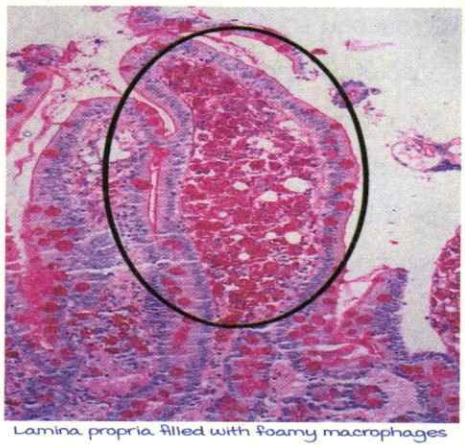
Causative organism : Actinomycetes (Trophyrema whipplei).
Gram positive organism.
It ia a rare & multisystem disorder affecting GIT, lymph nodes, CNS, joints (arthralgia).

Histopathology :
Lamina propria studded with foamy macrophages containing organism → PAS + diastase resistant.


Lamina Propria studded with foamy macrophages containing organisms

Active space




Lamina propria filled with foamy macrophages

Foamy macrophages D/D : TB (differentiated by history & staining : ZN stain positive).

Pseudomembranous colitis 00:17:33

Seen in patients with long standing Cephalosporin/antibiotic therapy.

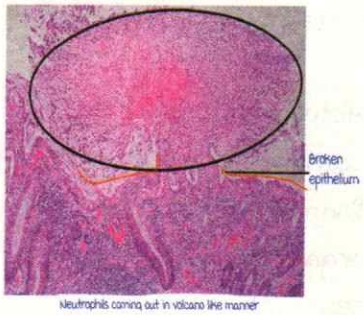

Pseudomembranous enterocolitis

Causative organism : Clostridium difficile.

Pathogenesis :
Antibiotics given for long time → Decreased gut flora → Overgrowth of clostridium difficile → Releases toxins → Damages epithelium.

Gross features :
Dirty, yellow necrotic material on the intestine.

Microscopy :
Neutrophils coming out of damaged epithelium in a volcano like fashion.

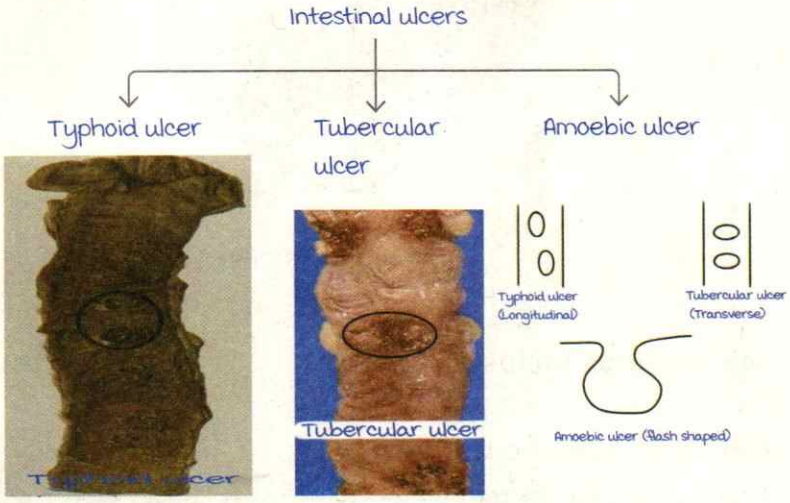


Neutrophils coming out in volcano like manner

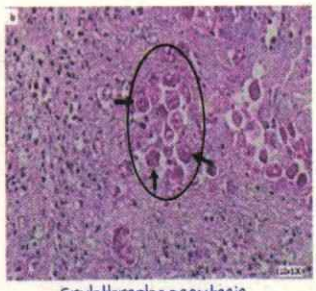
Active space

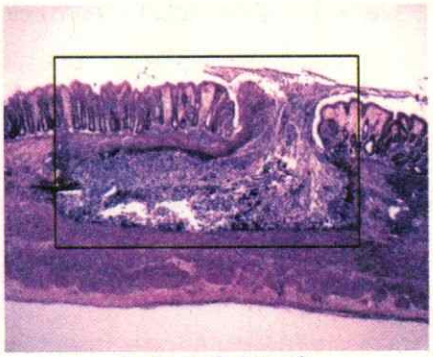
Intestinal ulcers

00:21:44

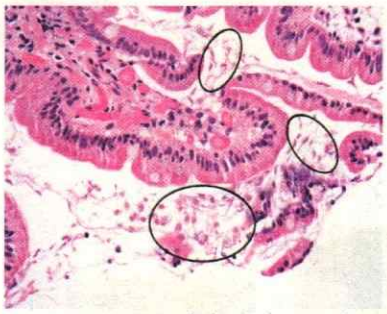


	Typhoid ulcer	Tubercular ulcer	Amoebic Ulcer
Causative organism	Salmonella Typhi	mycobacterium TB	E. Histolytica
MC site	Ileum	Ileocaecal valve	Caecum, liver : Anchovy sauce pus
Shape	Longitudinal Ulcer	Transverse Ulcer	Flask shaped ulcer (cannot proliferate beyond muscularis mucosa)
Strictures	Less common	more common. Fibrosis can also be seen.	
microscopy		Granulomas. Acid fast bacilli.	Erythrophagocytosis (engulfment of RBCs by macrophages)


Erythrophagocytosis


Amoebic ulcer (flask shaped)

Active space



Giardiasis (Pear shaped)

Microvillous inclusion disease

00:28:21

Autosomal recessive disease.

Caused by Myo 5B gene mutation.

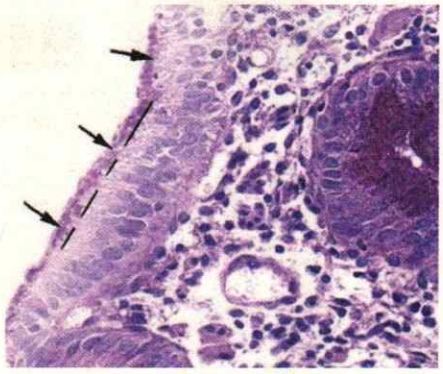
Usually affects <3 months age.

Presents with intractable diarrhoea.

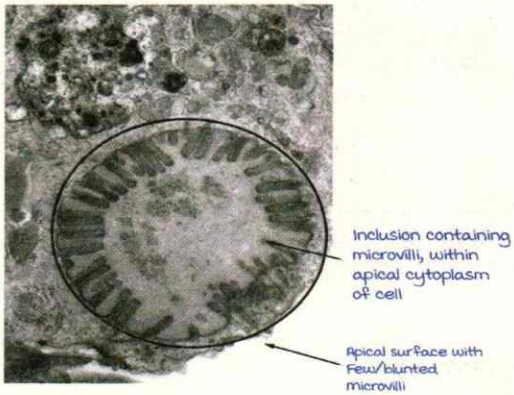
Histology : Inclusions in villi.

Electron microscopy : Inclusions in villi.

IHC marker : Villin.



Inclusions in villi



Clinical scenarios :

Q. A 32 year old male presented with thin stools with mucus, feverish feeling and lower abdominal pain. The stool examination shows leucocytes. What is the most likely cause ?

A. Giardia.

B. Staphylococcus.

C. Cryptosporidium.

D. Entamoeba.

Hints : Characteristic history of thin stools with mucus, feverish feeling suggests entamoeba.

Active space

Q. A 32 year old patient presented with complaints of diarrhea, abdominal pain and weight loss. Hb was decreased. Small intestinal biopsy was taken and image is shown below. most likely diagnosis is :

A. Whipple's disease.

B. Giardiasis.

C. Celiac disease.

D. Entamoeba.

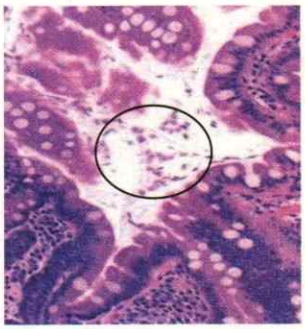
Hints : Whipple's disease will have a history of arthralgia + villi will be shown properly in the images.

The pear shaped organism shown is suggestive of giardiasis.

For celiac disease, image will show crypt hyperplasia + blunting of villi.

For Entamoeba, flask shaped ulcer will be shown.

Q. Which of the following is a histopathological feature of Whipple's disease :



A. Granuloma in lamina.

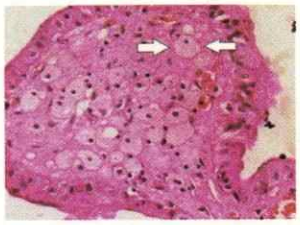
B. Infiltration of histiocytes in lamina.

C. Macrophages with PAS positive material in lamina.

D. Eosinophils in lamina.

Hints : Granuloma in lamina is suggestive of Crohn's disease.

Q. A 35 year old HIV positive man is referred for evaluation of malabsorption. A duodenal biopsy shows the following finding. Which special stain can further be used to confirm the diagnosis ?



A. PAS.

B. Acid fast.

C. Alcian blue.

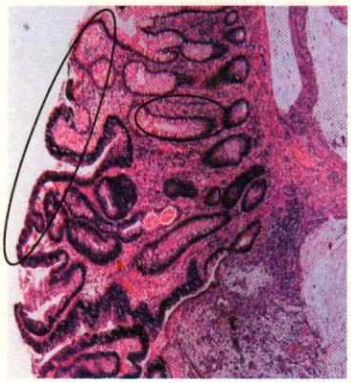
D. Mucicarmine.

Hint : HIV positive suggestive more towards TB diagnosis which would be positive for ZN stain (acid fast bacili).

Active space

55

Q. A 36 year old male patient presented to the clinic with a history of diarrhea and poor appetite. He has been having 4 to 5 episodes of non bloody, loose stools per day for the last 3 months. A duodenal biopsy is taken and histopathology is shown. Which of the fowling is the most common cancer associated with this condition ?



A. B cell lymphoma.

B. T cell lymphoma.

C. Carcinoid.

D. Adenocarcinoma.

Hint : Crypt hyperplasia & blunting of vili is suggestive of celiac disease.

It increases risk of enteropathy associated T-cell lymphoma.

Active space

INFLAMMATORY BOWEL DISEASE

Introduction 00:01:22

Inflammatory bowel disease (IBD) :
Crohn's disease & Ulcerative colitis.

Epidemiology :
Females > Males.
Bimodal age distribution : 15 to 20 years & elderly age group.
more common in western countries & in Caucasians.

Pathogenesis :
Etiology is not completely understood.
most acceptable hypothesis : Hygiene hypothesis
(Poor development of the mucosal immunity due to intake of the diet rich in preservatives).

Genetic factors :

- NOD2 gene polymorphism leading to increased activation of NF-Kβ pathway (growth signaling pathway) causing increased cell proliferation and the development of IBD.
- ATG 16 L1 (Autophagy related 16 L1).
- IL-23 gene polymorphism : Protective for both IBD.
- IRGM (Immunity related GTPase M).

Crohn's disease	Ulcerative colitis
MC site : Ileum, ileocecal valve, caecum.	Rectum (retrograde spread from the colon).
Transmural (all layers of the bowel wall is involved).	Submucosal.

Morphology of the Crohn's disease 00:06:57

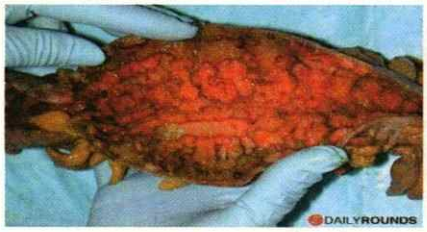
Gross appearance :

- Aphthous ulcers (earliest lesion) which coalesce with each other to form snake like ulcers called serpinginous serpentine ulcers.

Active space

- Deep and knife like ulcers (transmural involvement).
- Skip lesions (non continuous lesion) : most characteristic.
- Creeping fat : mesenteric fat oozes out & encircles over the serosal surface.
- Cobblestone appearance of the mucosa : Islands of regenerating mucosa which appear like cobblestone.
- Rubbery thick intestinal wall.

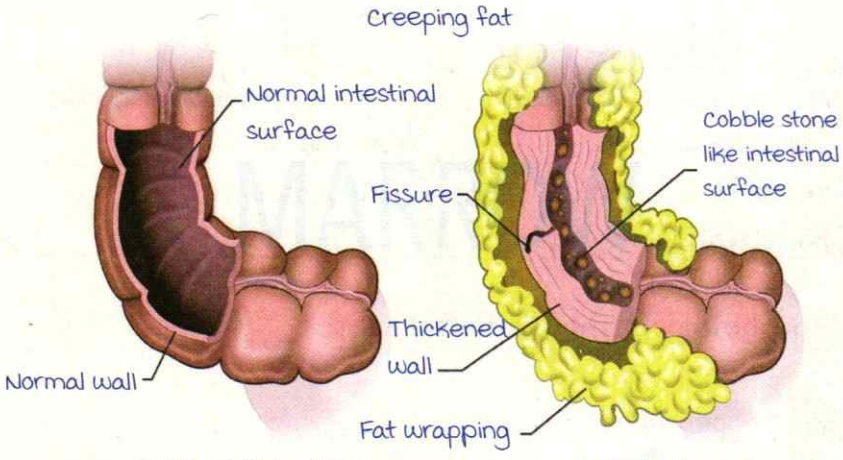
Skip lesion



Cobblestone appearance

Cobblestone appearance

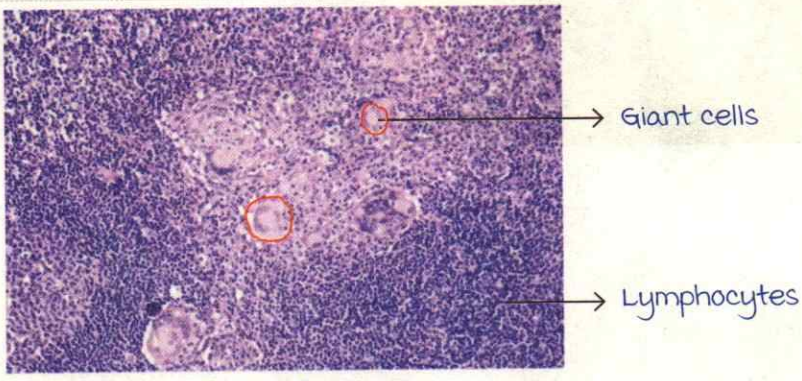
Creeping fat



Active space

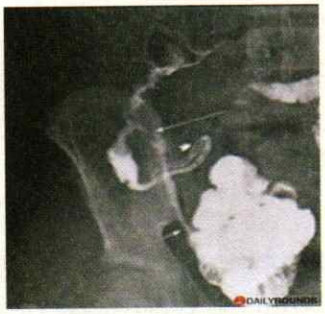
Microscopy features of the crohn's disease 00:13:50

- Transmural.
- Ulcers.
- Non caseating granulomas (in 35 to 40% cases).
  1. Most important cell : Epitheloid cell (macrophage).
  2. Most important cytokine : INF-γ.
  3. Other components : Collar of lymphocytes, giant cells.
- Cryptitis : Presence of inflammatory cells in crypt lining.
- Crypt abscesses : Accumulation of abundant inflammatory cells in the lumen of the crypt.



Histology of Crohn's disease

String sign of Kantor is seen on the barium scan due to formation of fissure/fistula/stricture/sinus. more common in Crohn's disease than in ulcerative colitis.



Morphology of ulcerative colitis 00:17:57

MC sites : _____

Continuous lesions are seen (surgery can be done).

Submucosal.

Spreads in a retrograde manner.

Superficial, broad based ulcers.

Backwash ileitis : The extension of the disease from the rectum and colon till the terminal ileum.

Gross : Pseudopolyps (due to regenerating mucosa).

Active space

mucosal bridges : Formed due to the fusion of tips of the pseudopolyps.

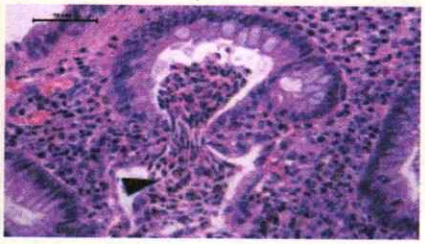
Also known as toxic megacolon (obstructed bolus of food leads to the release of toxins which cause distension of the colon).

Microscopy :

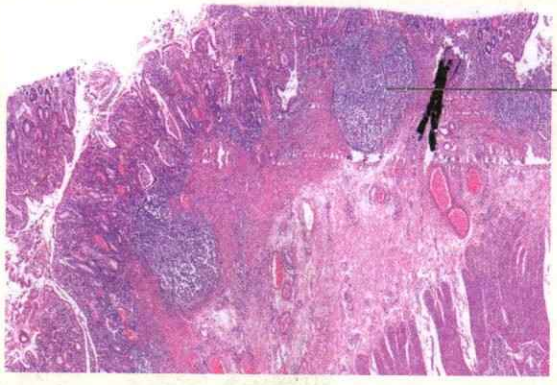
- Ulcer is more prominent.
- Submucosal involvement.
- Cryptitis
- Crypt abscess

} more common and prominent in ulcerative colitis than in crohns disease

Pseudopolyps



Crypt abscess



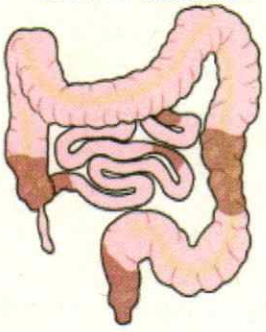
Inflammatory cells in submucosa

Histology : Ulcerative colitis

Cryptitis can also be seen in :

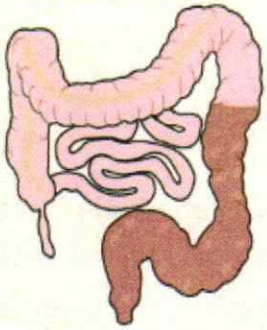
- Radiation colitis.
- Diverticular diseases.

Crohn's disease



Skin lesions

Ulcerative colitis



Continuous colonic involvement, beginning in rectum

Active space

Surgical resection is easier in ulcerative colitis because the lesion are continuous.

Clinical presentation in IBDs 00:25:35

- Fever.
- Abdominal pain.
- Diarrhea.
- Extraintestinal manifestations :

Organ system	manifestation
Dermatologic	• Erythema nodosum • Pyoderma gangrenosum • Oral ulcers (like apthous stomatitis)
Hepatobiliary	• Primary sclerosing cholangitis (MC in ulcerative colitis) • Fatty liver • Autoimmune liver disease • Cholelithiasis
Ophthalmologic	• Anterior chamber complications are more common like : • Episcleritis • Scleritis • Uveitis • Iritis • Conjunctivitis
Hematologic	• Anemia of chronic disease • Iron deficiency anemia • Clotting abnormalities • Abnormal fibrinolysis • Thrombocytosis • Thromboembolic events
Renal	• Calcium oxalate nephrolithiasis (Crohn's disease)

Active space

Musculoskeletal	• Migratory polyangitis • Sacroilitis • Ankylosing spondylitis

Crohn's disease vs ulcerative colitis

00:27:51

Feature	Crohn's disease	Ulcerative colitis
Site	Ileum, caecum	Rectum – colon
HLA	HLA DR1	HLA DR2
Risk factor	Smoking	Smoking is protective (also in endometrial cancer)
Cell	CD4 Th 1	CD4 Th 2
Gross	Skip lesions + Cobblestone appearance Deep knife ulcer – – Thick rubbery wall Transmural	– – Superficial broad based Pseudopolyps Mucosal bridges Toxic megacolon Submucosal
Microscopy	Non caseating granuloma Cryptitis + Cryptitis abscess + Ulcers	– Cryptitis +++ Crypt abscess +++ more prominent
Complications	Stricture + Fissure + Fistula + Sinuses + Colon cancer (less prominent)	– – – – Colon cancer (more prominent)
Radiology	String sign of Kantor	Lead pipe/hose pipe appearance
Antibody	Anti-saccharomyces cerevisiae. Anti-flagellin antibody.	p-ANCA

Active space

Newer update : Crohn's disease and ulcerative colitis both have equal risk of development of colon cancer called Colitis associated neoplasia (CAN).

P-ANCA associated vasculitis :

- Microscopic polyangitis.
- Churg-Strauss syndrome.

C-ANCA associated vasculitis :

- Wegener's granulomatosis.

Recent updates :

Early onset IBD :

Seen in infants and children.

Due to mutation in genes for epithelial transport or immunity.

Mutation in IL-1 or IL-10 receptor.

Indeterminate colitis :

IBD in which there is difficulty in distinguishing between ulcerative colitis or Crohn's disease.

MCQs :

Q. A 32 year old woman has a 10 year history of intermittent, bloody diarrhea. She has no other major medical problems. On physical examination there are no lesions palpable on digital rectal examination, but a stool sample is positive for occult blood. Colonoscopy reveals a friable, erythematous mucosa with focal ulceration that extends from the rectum to the mid-transverse colon. Biopsies are taken and all reveal mucosal acute and chronic inflammation with crypt distortion, occasional crypt abscesses, and superficial mucosal ulceration. This patient is at greatest risk for development of which of the following conditions?

A. Acute pancreatitis.
B. Diverticulitis.
C. Sclerosing cholangitis.
D. Appendicitis.
E. Perirectal fistula.
F. Non-Hodgkin lymphoma.

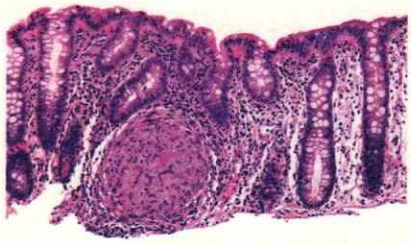
Active space

56

Q. Which of the following is a feature of Crohn's disease ?

A. Pseudopolyps can be seen .
B. Non-caseating granulomas are present.
C. Backwash ileitis may be associated with Crohn's disease.
D. Both B and C.

Q. A 45 year old female presented with recurrent episodes of bloody diarrhea which has revealed geographical ulcers on colonoscopic examination. Colon biopsy was taken and histopathology is shown below. What is the most likely diagnosis in this case?



A. Adenocarcinoma of colon.
B. Crohns disease.
C. Non hodgkins lymphoma.
D. Pseudomembranous colitis.

Active space

POLYP AND COLORECTAL CANCER

Polyp

00:00:58

Protrusion of the mucosa : True protrusion.

Pseudopolyp is seen in ulcerative colitis : Not a true protrusion.

Classification :

Clinical classification :

- Sessile (no stalk). → more malignant potential.
- Pedunculated (stalk). → less malignant potential.

Morphological classification

- Neoplastic polyps : Adenomatous.
- Non neoplastic polyps : Hyperplastic. inflammatory. Hamartomatous.

Types of polyps

00:04:06

1. Hyperplastic polyp :

Occurs in 6th or 7th decade.

Most common site is left colon.

Pathogenesis : Piling up of cells due to delayed shedding.

H / E :

- Serrated architecture of glands limited to upper layers only.
- Lumen is not round.
- Star shaped lumen present.
- It is non neoplastic.

Differential diagnosis:

Sessile serrated adenoma :

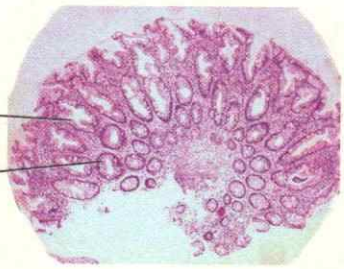
Neoplastic.

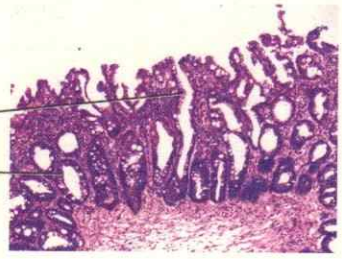
Serrated architecture of glands in entire length.

Active space

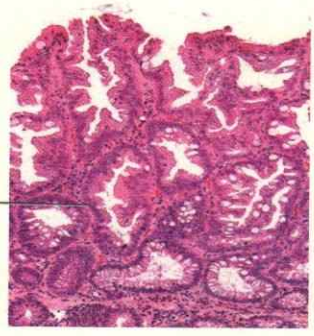
most common site : Right colon.

Hyperplastic polyp :





Sessile serrated adenoma :



2. Inflammatory polyp :
Cause : Repeated cycles of injury & healing.
Most common example : Solitary rectal ulcer.
H & E : Mixed inflammatory infiltrate.

3. Hamartomatous polyps :

Peutz Jeghers Syndrome :
Autosomal Dominant.
Pathogenesis : LKB1 / STK 11 gene mutation.
Clinical presentation :
- Multiple hamartomatous polyps.
- Perioral melanosis.

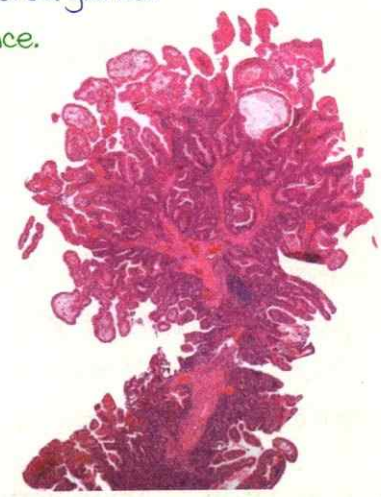
Active space

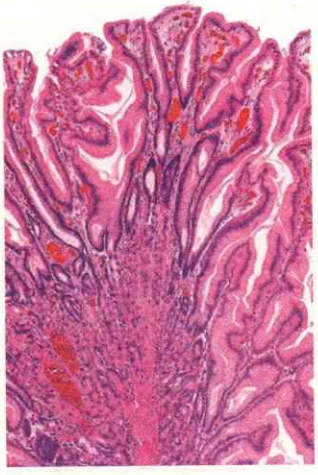
- mucocutaneous hyperpigmentation.
- Increased risk of sex cord stromal tumors.
- Increased risk of pancreatic, breast, thyroid & colon cancers.

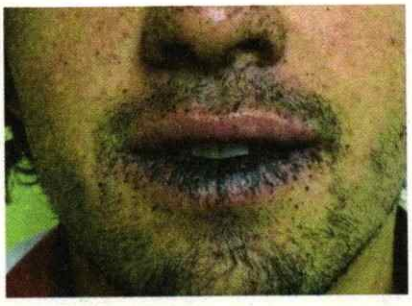
H & E :.

Arborizing pattern of smooth muscle mixed with lamina propria with scattered glands.

Christmas tree appearance.



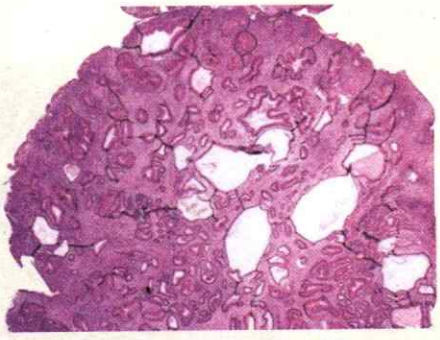




Juvenile polyposis syndrome :

- Occurs in age : <5 years.
- Most common site : Rectum.
- Presentation :

  Bleeding per rectum.
- Autosomal Dominant.
- SMAD 2 & 4 gene mutation.
- 3-100 polyps in rectum.



Dilated glands in Juvenile Polyposis

H & E :

Cystically dilated glands.

Active space

Cronkite Canada syndrome :

Non hereditary.

Presentation :

- Multiple hamartomatous polyps.
- Dermatological manifestations :
  - Hair loss.
  - Nail atrophy.
  - Abnormal skin pigmentation.

Cowden Syndrome :

PTEN gene mutation on Chromosome 10.

Clinical features :

Mnemonic : PTEN.

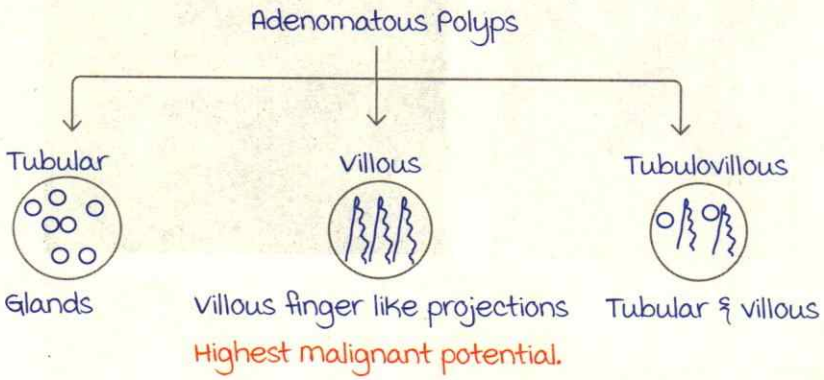
P : Multiple Hamartomatous polyps.

T : Trichilemomma (thickening of skin), Thyroid cancers.

E : Endometrial cancers.

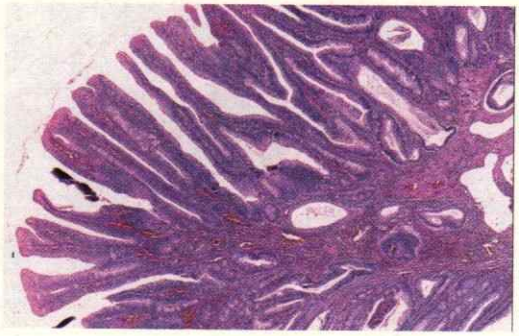
Adenomatous / Neoplastic Polyp

00:18:36



Villous Adenoma :

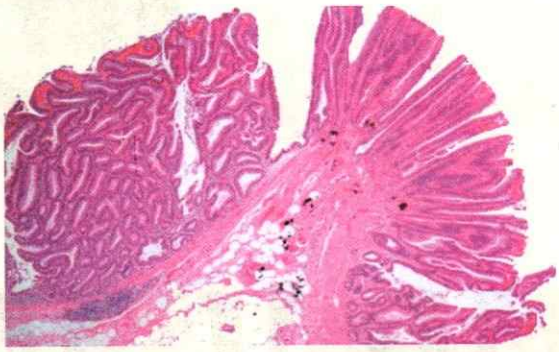
Finger like projections



Active space

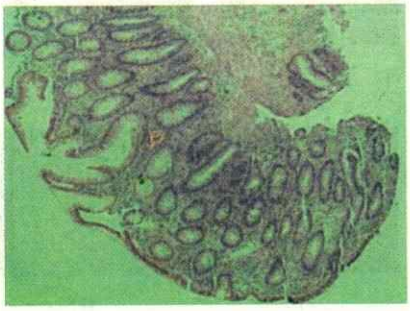
Tubulovillous Adenoma :

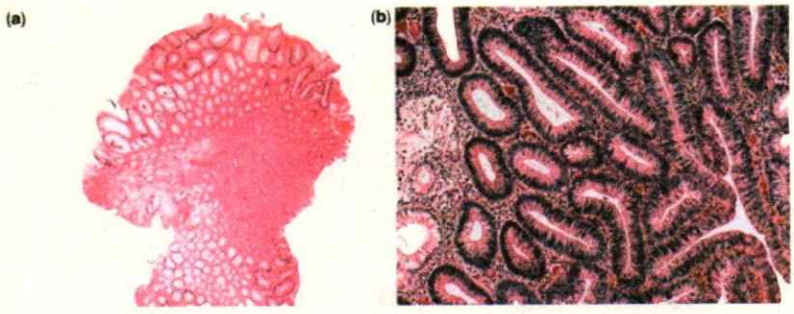
Both Tubules & villi are seen.



Tubular adenoma :

Only tubules are seen.





Familial Adenomatous Polyposis / FAP :

Autosomal dominant.

Pathogenesis :

- Adenomatous polyposis coli /APC (Adenomatous Polyposis Coli) gene (tumor supressor gene) mutation on chromosome 5.
- This leads to development of multiple polyps in intestine.

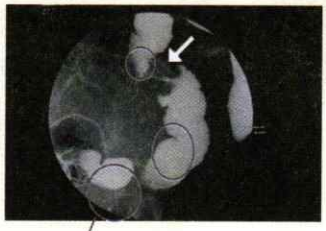
Diagnosis :

- > 100 polyps.
- Congenital hypertrophy of retinal pigment epithelium.

Active space

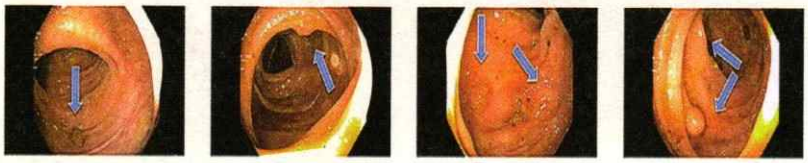
Attenuated FAP : If upto 30 polyps.

Almost 100% of Familial Adenomatous Polyposis if untreated will progress to a colon cancer.

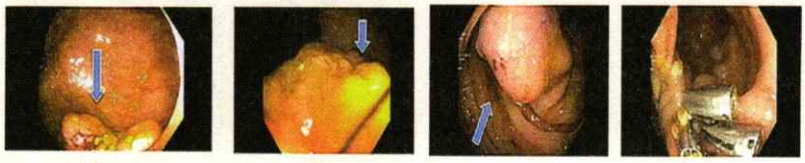


Polyps in FAP

Polyps :



(A) (B) (C) (D)



(E) (F) (G) (H)

FAP Associated Syndromes :

1. Turcot syndrome :
   Multiple adenomatous polyps + brain tumours (like medulloblastoma & Glioblastoma).
2. Gardner syndrome :
   Polyps + bone tumours (Osteomas) + desmoid tumours + epidermal cysts + thyroid lesions.

Colon cancer / Adenocarcinoma of cancer 00:25:36

Common Clinical scenario :

Elderly patients presenting with alteration in bowel habits & microcytic hypochromic anemia.

Average age > 60 years.

Risk factors :

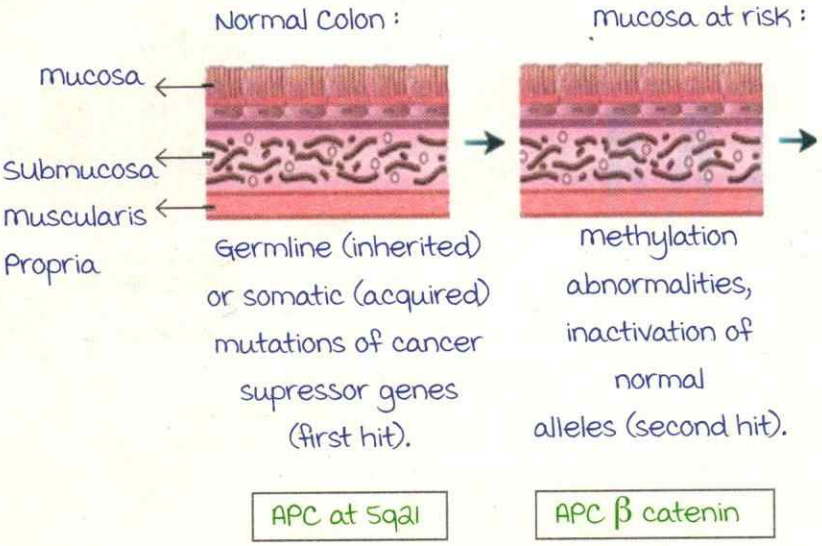
- Inflammatory bowel disease.
- Smoking.
- Alcohol.
- Consumption of nitrites.
- Family history of colon cancer.
- Adenomatous Polyps.

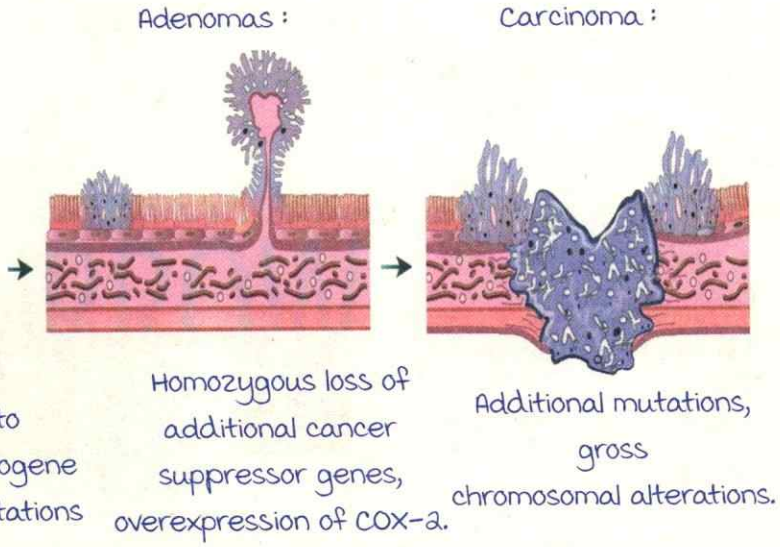
Active space

Types of Colon cancer :

1. Polypoidal tumours
   Developed from Adenoma carcinoma sequence (multistep).
2. Hereditary nonpolyposis colorectal cancer :
   Caused by microsatellite instability defect.

Adenoma Carcinoma Sequence : multistep carcinogenesis.





Active space

Mnemonic for adenoma carcinoma sequence : AK 53.

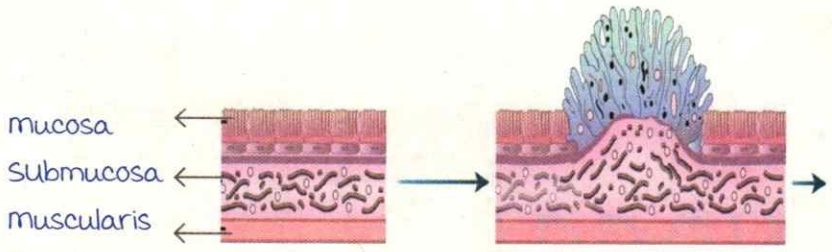
APC : First mutation.

K RAS (Oncogene).

P 53.

Mismatch repair pathway :

Normal colon : Sessile serrated adenoma :



Germline (inherited) or somatic (acquired) mutations of mismatch repair genes.	Alteration of second allele by LOH, mutation or promoter hypermethylation.	Microsatellite instability.

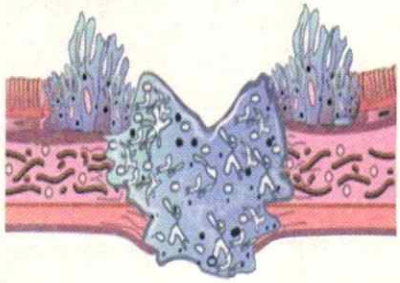
Mismatch repair genes :

MLH1, MSH2, MSH6, PMS1, PMS2

Carcinoma :

Mutations in genes that regulate growth, differentiation, apoptosis.

TGFBR11, BAX, BRAF, TCG-4, IGF2-R.



Tumour which develops is Hereditary Non Polyposis Colorectal Cancer (HNPCC).

Can also lead to Lynch Syndrome :

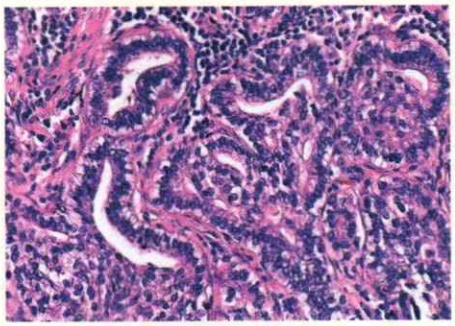
Mnemonic : CEO

Colon cancer.

Active space

Endometrial cancer.

Ovarian cancer.



H & E :

Adenocarcinoma :

Glands lined by pleomorphic cells.

Glands lined by dark blue cells with hyper chromatic nuclei & prominent nucleoli.

When cells secrete excess mucin : Mucinous carcinoma of colon.

Has poorer prognosis, because the chance of tumour spreading to the other sides are more.

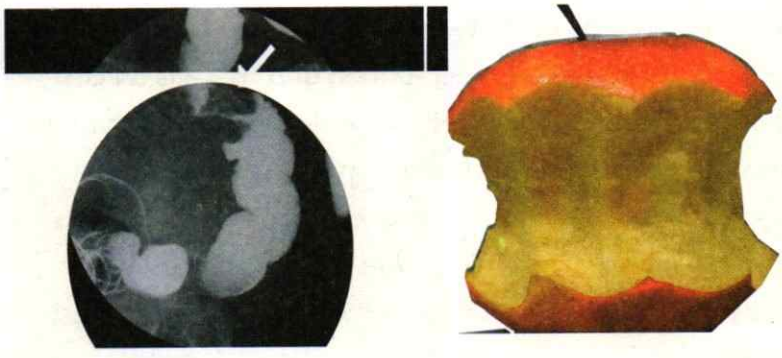
Excess of intracellular mucin : Signet ring cells.

Excess mucin inside the cell pushes the nucleus to the periphery and gives appearance of Signet ring cells.

Tumour markers :

- CEA / Carcino embryonic antigen.
- CA 19 - 9.

On Barium Scan : Apple core deformity.



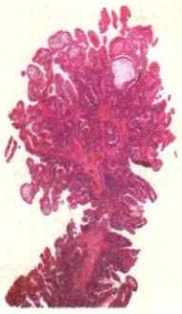
Right colon mass.

Tumor in left colon : Napkin ring constriction.

Q. A 17 year old boy presented with intussusception and was taken up for surgery. He was found to have multiple polyps. The resected section was sent for histopathology and the whole image of the specimen is given below. Identify the lesion.

Active space

A. Tubullovillous adenoma.
B. Hamartomatous polyp.
C. Adenocarcinoma.
D. Hyperplastic polyp.



Answer : B. Hamartomatous polyp.
Seen in Peutz jegher's syndrome.

Q. A 20 year old man is healthy, but has a family history of colon cancer with onset at a young age. There are no abnormal physical examination findings. He undergoes colonoscopy and there are over 200 tubular adenomas ranging in size from 0.2 to 1 cm on gross inspection and microscopic examination of biopsies. Which of the following genetic diseases is he most likely to have?
A. Hereditary non polyposis colon carcinoma syndrome.
B. PTEN associated syndrome.
C. Peutz jeghers syndrome.
D. Adenomatous polyposis coli.
E. Multiple endocrine neoplasia.
Answer : D. Adenomatous polyposis coli.

Q. A 51 year old man undergoes routine health examination by his nurse practitioner. There are no abnormal physical examination findings except for a stool sample positive for occult blood. Colonoscopy is performed and there is a 1 cm polyp on a narrow stalk located in the descending colon at 30 cm from the anal verge. The polyp is resected and on microscopic examination shows crowded, tubular, atypical colonic type glands. The stalk of the polyp is covered with normal colonic epithelium. Which of the following is the most likely diagnosis?
A. Adenomatous polyp.
B. Inflammatory fibroid polyp.
C. Peutz Jeghers polyp.
D. Ulcerative colitis pseudopolyp.
E. Hyperplastic polyp.
F. Crohn disease.
Answer : A. Adenomatous polyp

Active space

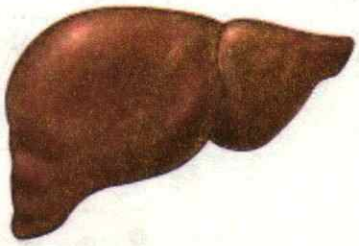
LIVER PATHOLOGY : PART 1

Anatomy of liver

00:01:24

Gross : Brownish smooth surface.

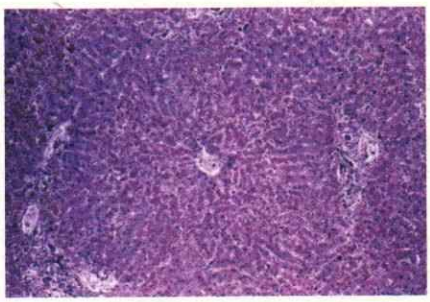
Normal weight : 1400–1600 g.



Light microscopic appearance :

- Cords of hepatocytes which have abundant eosinophilic cytoplasm (due to the presence of excess mitochondria).
- Central vein at the center.
- Portal tract/triad comprising of bile duct, portal vein and the hepatic artery.

Oncocytic/Hurtle cells also have got abundant eosinophilic cytoplasm.



Light microscopy of liver

Zones :

Zone 1/periportal zone : Zone of hepatocytes which are present near the portal triad.

Zone 3/centrilobular zone : Zone of hepatocytes which are present around the central vein.

Zone 2/midzonal : The small zone of hepatocytes which is present between the periportal and the centrilobular zones.

Hepatic lobule :

Liver consists of hexagonal plates.

The zone most susceptible to ischemic/hypoxic damage : Zone 3.

The zone more susceptible to toxin induced damage : Zone 1.

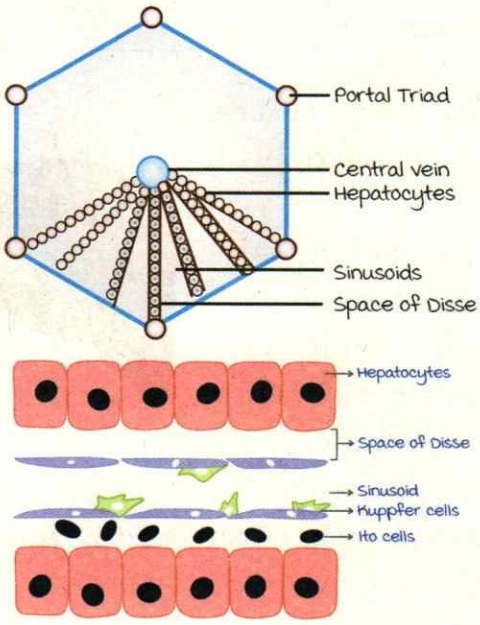
Zone 2 is affected in yellow fever.

Sinusoids : Space between the two layers of hepatocytes. Sinusoids are lined by Kupffer cells (tissue macrophages of

Active space

the liver).

Space of Disse : The small area between the hepatocytes and the sinusoidal lining.



Significance :

- Amyloidosis first affects the space of Disse.
- Contains Ito cells which store vitamin A.
- Ito cells, when stimulated get converted to stellate cells which cause :
  1. Fibrosis.
  2. Synthesis of type 1 and 3 collagen.
  3. Activation of myofibroblasts.

Hepatocytes are interconnected by canals of Hering.
Canals of Hering contain the oval cells which are the stem cells of liver.

Jaundice

00:13:43

Increase in bilirubin.

Unconjugated hyperbilirubinemia	Conjugated hyperbilirubinemia
Hemolytic anemia. Crigler-Najjar syndrome type 1 and 2. Gilbert syndrome.	Primary biliary sclerosis. Primary biliary cholangitis. Obstruction of bile duct due to stones/cancer/stricture. Dubin-Johnson syndrome. Rotar syndrome.

Active space

Hereditary hyperbilirubinemias 00:16:20

Unconjugated Hyperbilirubinemia :

Crigler-Najjar syndrome type I	Crigler-Najjar syndrome type 2	Gilbert syndrome
Autosomal recessive	Autosomal dominant	
Complete deficiency of UGTAI enzyme	Partial deficiency of UGTAI enzyme	Mild defect in UGTAI enzyme
Completely fatal	Not fatal	

Conjugated hyperbilirubinemia :

Dubin-Johnson syndrome	Rotor syndrome
Defect in canalicular MRP2 protein.	Defect in _____
There is accumulation of epinephrine leading to pigmented liver.	Non pigmented liver

Cirrhosis 00:19:32

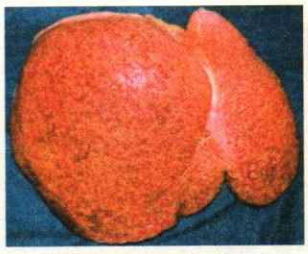
End-stage liver disease.

Characteristics :

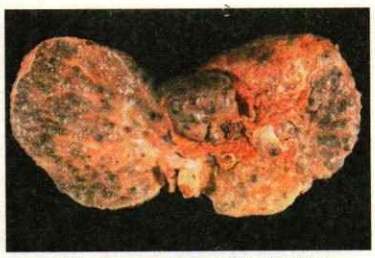
- Disruption of the entire lobular architecture of liver.
- Regenerating parenchymal nodules.
- Fibrosis.

Gross types :

- Micronodular cirrhosis (nodule size < 3mm).
- Macronodular cirrhosis (nodule size > 3mm).



Micronodular Cirrhosis



Macronodular Cirrhosis

Pathogenesis :

In the normal liver, type I and 3 collagen are present in the periportal and centrilobular area and type 4 collagen is present in the space of Disse.

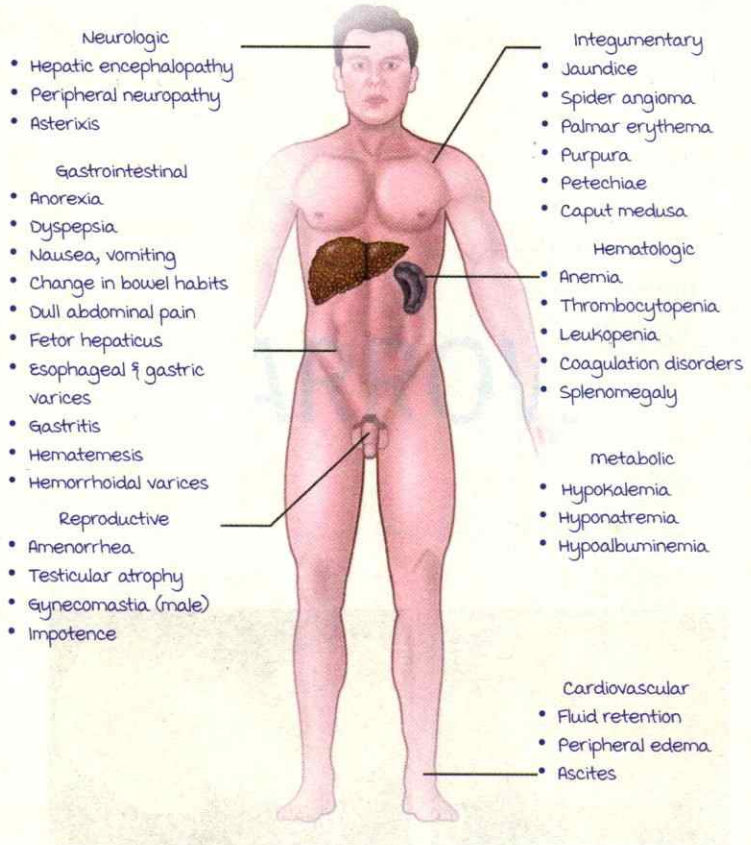
Active space

In cirrhotic liver, Ito cells are converted to stellate cells which secrete type I and 3 collagen in the space of Disse leading to the loss of fenestrations of the sinusoids (capillarization of the sinusoids).

Causes :

Micronodular cirrhosis (< 3mm)	Macronodular cirrhosis (> 3mm)
Early alcoholic liver disease (ALD). Hemochromatosis. PBC. Indian childhood cirrhosis.	Late stages of ALD. Wilson's disease. α-1 Antitrypsin deficiency. Drug induced hepatitis. Viral hepatitis.

Clinical features :



Stain used for fibrosis (collagen fibrosis) : Masson Trichrome (MT).

Collagen fibres appear blue in color on MT staining.

Masson Fontana is used to stain melanin pigment.

Active space

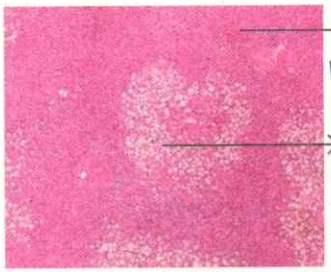
Alcoholic liver disease

00:30:34

Only 15% of the people who consume alcohol will develop ALD.
Intake of 60-80 ml of alcohol per day for 10 years can lead to ALD.
It is the common cause of liver cirrhosis in Western countries.
Gross specimen : Soft, yellow and greasy appearance due to excess of fat.

Microscopy :

- Steatosis.
- Hepatitis.
- Cirrhosis.



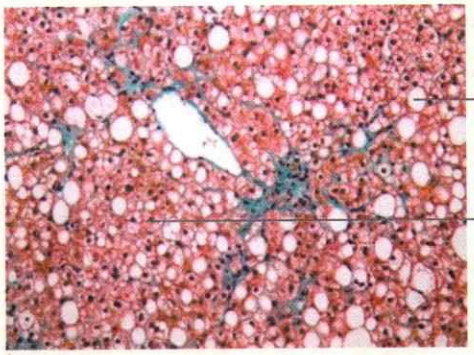
Stages of cirrhosis :

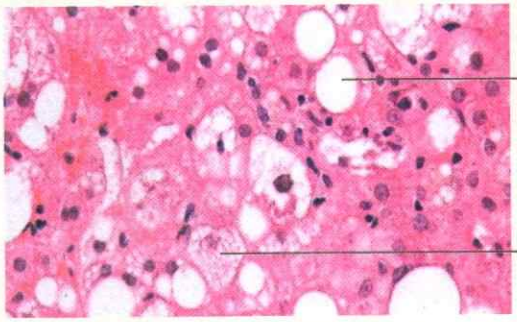
Stage I/steatosis :

- Fatty change.
- Earliest change in ALD.
- Reversible stage.

Types :

- Microvesicular steatosis : Small lipid droplets in hepatocytes, nucleus in the center.
- Macrovesicular steatosis : Large lipid droplets in hepatocytes, nucleus is pushed to the periphery.





Active space

Causes :

Microvesicular steatosis	Macrovesicular steatosis
Early ALD Fatty liver of pregnancy Reye's syndrome Chronic viral hepatitis	Late ALD Hemochromatosis Obesity Protein energy malnutrition Chronic hepatitis B NASH (non-alcoholic steatohepatitis)

Stain used for steatosis : Oil red O, Sudan black.

Stage 2/hepatitis stage :

Inflammation of the liver parenchyma.

Neutrophilic infiltration.

Mallory hyaline/dent bodies.

Chicken wire fibrosis.

Mallory hyaline/Mallory dent bodies :

Pinkish/dense eosinophilic inclusions inside the hepatocytes.

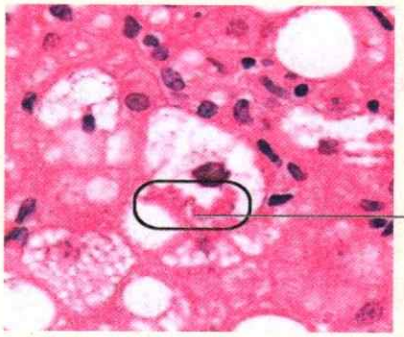
Composition : Intermediate filaments like CK-8 and CK-18.

Disorders in which they are seen (mnemonic : New Indian WATCH) :

- NASH.
- Indian childhood cirrhosis.
- Wilson's disease.
- α-1 Antitrypsin deficiency.
- Tumors : Hepatocellular carcinoma (HCC).
- Cirrhosis : PBC.
- Focal nodular Hyperplasia.

Conditions in which Mallory hyaline bodies are not seen :

- Hemochromatosis.
- Secondary biliary cirrhosis.



Mallory hyaline bodies

Active space

Chicken wire fibrosis : Perisinusoidal fibrosis.
Microscopy of oligodendroglioma shows fried egg appearance, chicken wire blood vessels (due to anastomosing vascular channels).

Cirrhosis stage :
Appears as micronodular cirrhosis which later advances to macronodular cirrhosis.
Lennac cirrhosis :
When the liver gets converted into a fibrous scar.

NASH/Non-alcoholic steatohepatitis 00:49:02

AKA Non-alcoholic fatty liver disease.
It is the MC cause of cirrhosis in Western countries.
It increases the risk of HCC.
Minimal/no history of alcoholic intake.
Risk factors :

- Obesity.
- Diabetes mellitus.
- Insulin resistance.
- metabolic syndrome.
- Hypercholesterolemia.

Alcoholic steatohepatitis/ASH	Non-alcoholic steato-hepatitis/NASH
H/o alcoholic intake	No H/o alcoholic intake
Obesity, DM, Hypercholesterolemia is absent	Obesity, DM, Hypercholesterolemia is present
mallory hyaline bodies are more prominent	mallory hyaline bodies are less prominent
Perisinusoidal inflammation is more	Periportal inflammation is more
Neutrophils are more prominent	monocytes are more prominent
Increased GGT enzyme	Less/no increase in the GGT enzyme
AST/ALT > 2	AST/ALT < 1

Active space

Reye's syndrome

00:55:51

History : Child who has got a viral infection treated with aspirin.

Child can develop features of hepatic encephalopathy/ hypoglycemia/vomiting.

Biopsy shows extensive micro vesicular steatosis.

Q. A 55 year old women had a leg swelling and pitting oedema over the knees, with prominent jugular venous distension and increasing levels of AST and ALT. A diagnosis of CHF was made. The gross appearance of liver is shown. What is the most likely condition?

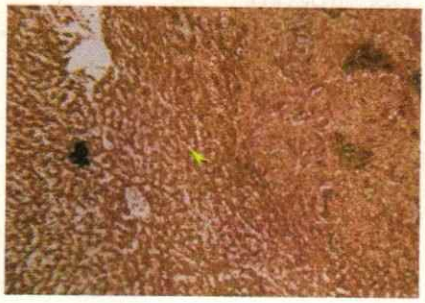
A. Cirrhosis.
B. Fatty change.
C. Chronic venous congestion.
D. Thrombosis.

Q. MRP 2 defect is associated with which of the following?

A. Dubin Johnson syndrome.
B. Rotor syndrome.
C. Gilbert syndrome.
D. Crigler-Najjar syndrome.

Q. Identify this special stain used in a liver biopsy:

A. Warthin starry silver stain.
B. Methanamine silver stain.
C. Sweets reticulin stain.
D. Steiner silver stain.



Warthin starry silver stain : Used in Helicobacter pylori.

Methanamine silver stain : To stain fungi.

Q. A 45 year old obese lady presented with diabetes mellitus, hypertriglyceridemia, right upper quadrant pain and recurrent jaundice. What will be seen in the liver pathology ?

Active space

A. Microvesicular steatosis.

B. Autoimmune hepatitis.

C. NASH.

D. Peliosis hepatitis.

Q. What is the name of the instrument shown below :

A. Jamshidi bone marrow aspiration needle.

B. Vim silverman liver biopsy needle.

C. FNAC needle.

D. Kidney biopsy needle.

Q. A 45 year old male alcoholic presented with pain abdomen. The USG of the patient showed fatty liver. Liver biopsy of the patient is shown below. What is the composition of structure marked with an arrow?

A. Vimentin.

B. Fibrillin.

C. Cytokeratin.

D. Desmin.

Active space

LIVER PATHOLOGY : PART 2

Metabolic liver diseases :

- Haemochromatosis.
- Wilson's disease.
- α 1 antitrypsin deficiency.

Haemochromatosis 00:01:03

Also called as bronze diabetes.

Excessive iron deposition in the body.

Autosomal recessive disorder.

Male = females.

m/c cause of cirrhosis due to a metabolic disorder.

Types :

Hereditary and acquired.

Heriditary	Acquired
Mutation of HFE gene on 6p chromosome	Repeated blood transfusions
HAMP gene mutation	Bantu siderosis (Bantu, an African tribe → Risk of hemochromatosis due to cooking in iron utensils).
HJV gene mutation (juvenile hemochromatosis)	

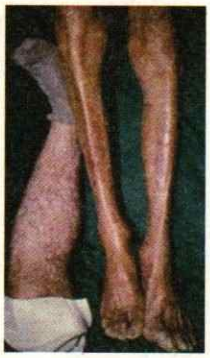
Gene for HLA is located on short arm of chromosome 6p.

Pathogenesis :

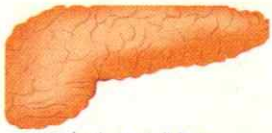
HFE gene mutation on chromosome 6p → Decreased level of hepcidin → Increased iron overload → Haemochromatosis.

Hepcidin : Negative iron regulator.

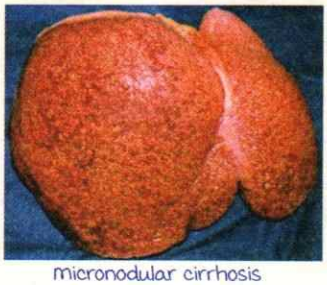
C/F :



Bronze pigmentation of skin



Diabetes mellitus



Micronodular cirrhosis

Active space

- Triad of :
  1. Bronze pigmentation of skin (due to melanin > haemosiderin).
  2. Diabetes mellitus.
  3. Micronodular cirrhosis.
- Joints : Pseudogout.
- Testis/gonads : Atrophy.
- Heart : Both dilated cardiomyopathy (m/c) and restrictive cardiomyopathy.
- Adrenal glands can also be affected.

Diagnosis :

Iron profile :

Sr. iron : Increased.

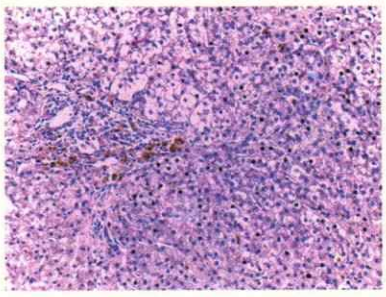
Sr. ferritin : Increased.

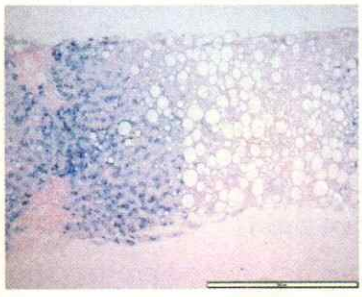
Sr TIBC : Decreased.

Sr. transferrin saturation : Increased (good screening test).

Liver biopsy : Golden yellow or brown pigment in hepatocytes.

Special stain : Prussian blue or pearl's stain.





Haemosiderin in Prussian blue stain appears as blue granular pigment.

Treatment :

DOC : Iron chelators like desferoxamine.

Treatment of choice : Phlebotomy.

Wilson's disease 00:14:47

Excessive copper deposition in the body.

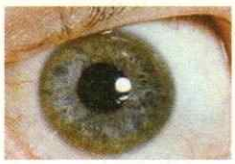
AKA hepatolenticular degeneration.

Pathogenesis : ATP 7B gene mutation on chromosome 13q.

Active space

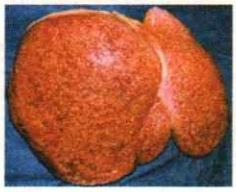
Leading to impaired copper incorporation into ceruloplasmin (ceruloplasmin : Copper transporting protein) ⟶ Increased copper in body ⟶ Wilson's disease.
Other mechanism : Impaired copper excretion in bile.

C/F : Triad of



1. Ocular :
   Kayser-Fleischer ring in Descemet's membrane of cornea (KF ring).
   Sunflower cataract.

2. Brain :
   Putamen and basal ganglia are affected.
   Neuropsychiatric manifestations.
   Features of psychosis.
   Parkinson's like disease.



3. Liver : Cirrhosis.

Diagnosis :
Liver biopsy :

- Acute and chronic inflammation.
- Steatosis.
- Mallory hyaline bodies can be present.

Special stain : Rhodamine and rubeanic acid.
Copper associated protein staining : Orcein stain (can also stain elastin fibres, HBsAg).
Sr. copper levels : Increased.
Sr. ceruloplasmin level : Decreased (as excessive Cu binding leads to exhaustion of ceruloplasmin in blood)
Most specific test : Increased urinary excretion of copper.

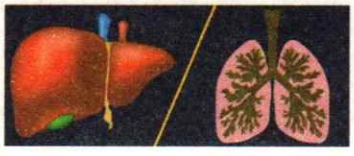
Treatment :
Copper chelator : Penicillamine.

Active space

α1 Antitrypsin deficiency

00:23:56

In lungs : Pan acinar emphysema.
In liver : Cirrhosis.



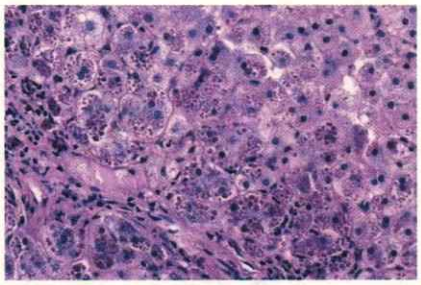
Pathogenesis : Deficiency of α 1 antitrypsin (type of neutrophil antiprotease) → Increased neutrophil elastase activity → Damage to lungs and liver.

Gene for α 1 antitrypsin is located on chromosome 14.

Pimm form of α 1 antitrypsin : Normal.

PiMZ form : Carrier state.

PiZZ form : Diseased.



Liver biopsy :

PAS + Diastase resistant inclusions in hepatocytes.

Mallory hyaline bodies may be seen.

	Hemochromatosis	Wilson's disease	α 1 antitrypsin deficiency
Pathogenesis	HPE gene mutation on Chromosome 6p	ATP 7B gene mutation on chromosome 13	Deficiency of α1 anti trypsin on chromosome 14
	Excessive iron depletion	Impaired incorporation of copper into bile, excess copper depletion.	Increased neutrophil elastase activity
C/F	Skin pigmentation, DM, micronodular cirrhosis, arthritis and hypogonadism	KF rings, cirhossis and brain manifestations	Pan acinar emphysema and liver diseases
Investigations	Increased Iron and ferritin. Reduced TIBC.	Decreased ceruloplasmin. Increased urinary excretion of copper.	
HPE	Hemosiderin deposition prussian blue stain.	Steatosis, hepatitis. Rhodamine and orecin stain	PAS positive diastase resistance globules

Active space

Hepatitis

00:31:06

2 types :

- Viral hepatitis.
- Autoimmune hepatitis.

Viral hepatitis :

5 types of hepatitis virus : A,B,C,D and E.

Hepatitis A and E : Feco oral route.

Hepatitis B, C and D : Sexual, vertical (mother to child) and parenteral.

M/C cause of acute liver disease in children : Hepatitis A.

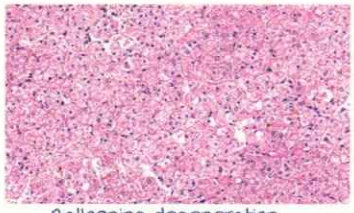
M/C cause of mortality in pregnancy : Hepatitis E.

All are RNA virus except hepatitis B (Hepadna virus) DNA virus.

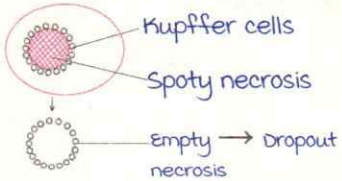
Acute hepatitis :

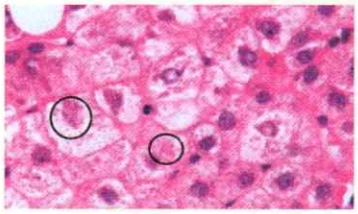
Liver biopsy shows :

- Ballooning degeneration (swollen up balloon like appearance).
- Councilman bodies : Apoptotic bodies (densely eosinophilic).
- Lymphoplasmacytic/mononuclear infiltrate.
- Spotty necrosis (necrosis in specific sites).
- Drop out hepatocytes (empty space lined by Kupffer cells) Empty space occurs after clearing of necrosed areas by Kupffer cells.
- Absent portal inflammation (seen in chronic hepatitis).

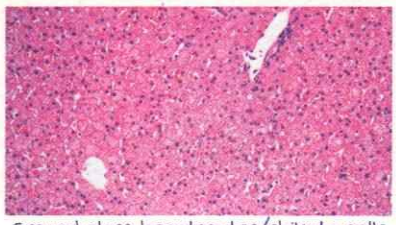


Ballooning degeneration





Councilman bodies

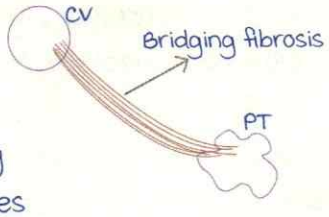


Ground glass hepatocytes/shikata cells

Active space

Chronic hepatitis :

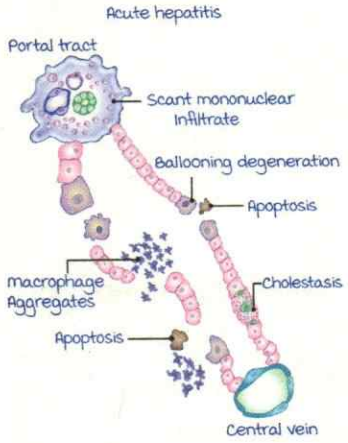
Liver biopsy :

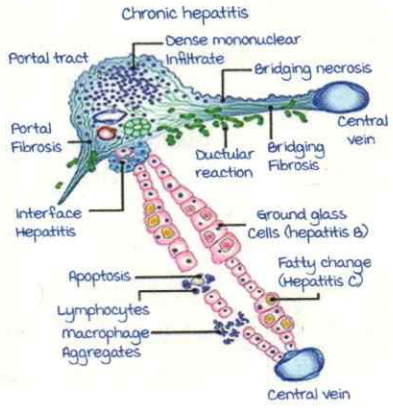


- Lymphoplasmacytic infiltrates.
- Bridging fibrosis.
- Interface hepatitis (inflammatory cells present between hepatocytes & portal triad).
- Portal inflammation (extensive).
- Ground glass hepatocytes (seen in chronic hepatitis B infection : Densely eosinophilic cells with glassy cytoplasm).
  Composed of HBsAg which makes the cells glassy.
  Ground glass hepatocyte aka shikata cell.
  Special stain : Orcein stain.

Chronic hepatitis C :

- Lymphoid aggregates.
- Fatty change or steatosis.
- Bile duct damage & bile duct proliferation (simultaneously).





Autoimmune hepatitis

00:46:09

Females > males.

3 types :

Type I autoimmune hepatitis :

m/c type.

Women are usually affected.

ANA antibodies, anti mitochondrial antibodies and anti smooth muscle antibodies (anti SMA).

Active space

Type 2 autoimmune hepatitis :

Affects children and young adolescents.

Anti LKM 1 (Hepatitis C), LKM 2 (drug induced) and LKM 3 (Hepatitis D).

LKM : Liver Kidney Microsome.

Type 3 autoimmune hepatitis : Rare.

Anti SLA (soluble liver antigen) positive.

HPE :

- Tense lymphoplasmacytic infiltrate.
- Interface hepatitis (lymphoplasmacytic infiltrates at the junction).
- Hepatic rosettes.
- Emperipolesis (cell within cell appearance).

Hepatic tumors

00:51:14

Divided into benign and malignant tumors.

Benign :

- Hepatic adenoma.
- Cavernous hemangioma.

Malignant :

- Hepatocellular carcinoma.
- Angiosarcoma.

m/c tumor or malignancy of liver : Metastasis or secondaries.

m/c primary malignancy of liver : _____

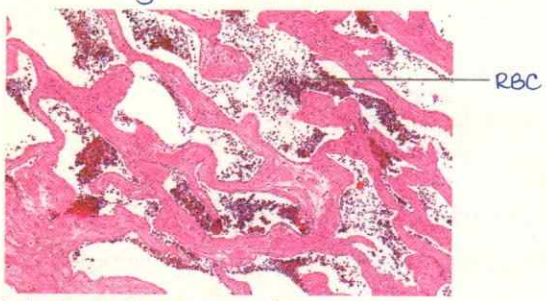
m/c Ca which metastises to liver : Colon carcinoma.

m/c hepatic tumor in children : Hepatoblastoma.

m/c sarcoma of liver : Angiosarcoma.

m/c benign hepatic tumor of liver : Cavernous hemangioma.

Associated with VHL gene mutation on chromosome 3.



Large dilated vascular spaces due to cavernous hemangioma.

Active space

Cavernous hemangioma affects organs like liver unlike capillary hemangioma which affects superficial tissues and small blood vessels.

Hepatic adenoma :
Female > male.
Middle aged.
20-30 years.
In females : H/O OCP use.
In males : H/O anabolic steroid intake.

Gross appearance : Well circumscribed and well encapsulated tumor usually in right lobe of liver.

HPE :
- well differentiated hepatocytes.
- No central vein and portal tract.
- No vascular invasion (differentiate from HCC).

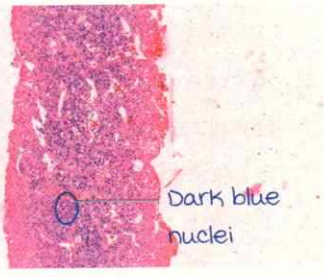
Hepatocellular carcinoma 00:58:54

Males > females.
Age : 60-70 years.

Risk factors :
- Alcohol.
- NASH.
- Hemochromatosis.
- Chronic hepatitis B.
- Chronic hepatitis C.
- Aflatoxin.
- Tyrosinemia.

Gross appearance :
multiple nodules or multiple foci.

HPE : Hepatocytes arranged in cords/sheets/trabeculae.



Active space

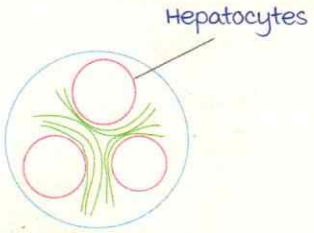
Mallory hyaline bodies +.

Vascular invasion is present.

AFP is also raised in yolk sac/ endodermal sinus tumor. Schiller duval bodies are present.s

Immunohistochemical markers :

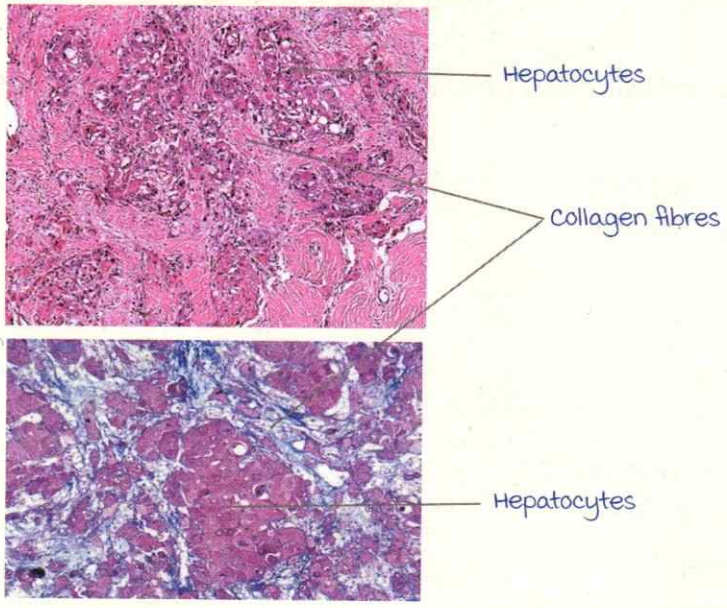
- α fetoprotein.
- Hep Par 1.
- Neurotensin.
- Glypican-3.



Fibrolamellar variant of HCC :

- Younger population.
- No increased AFP levels.
- No H/O hepatitis.
- Excellent prognosis.
- male = females.
- HPE : Fibrous septa separating nodules.

Immunohistochemistry : Neurotensin nodules.



Angiosarcoma

01:06:04

Risk factors :

- Polyvinyl chloride.
- Arsenic.
- Thorotrast.

Active space

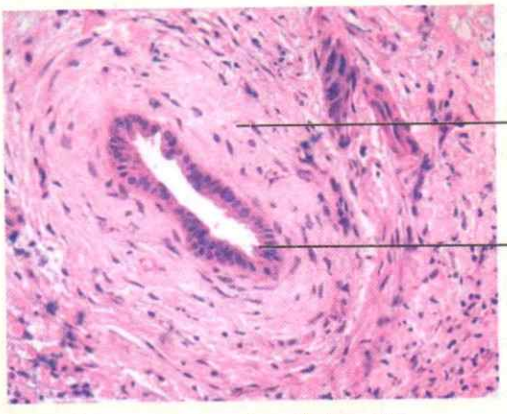
HPE : Anastomosing vascular channels lined by pleomorphic cells.

IHC : CD 13, VEGF, factor VIII and Von Willebrand factor.

Bile duct disorders

01:07:53

Primary biliary cirrhosis	Secondary biliary cirrhosis	Primary sclerosing cholangitis
F > M	M = F	M:F = 2:1
Destruction of intrahepatic bile ducts	Destruction of extrahepatic bile ducts	Both
AMA + and ANA +	Obstruction of bile duct by stones and carcinoma	p-ANCA positive
Associated with Sjogren's syndrome	None	Associated with ulcerative colitis > Crohn's disease
HPE : Lymphocytic infiltrate, granuloma formation and ductular atrophy.	Bile duct proliferation/ stasis	Concentric periductal fibrosis/onion skin fibrosis



Primary sclerosing cholangitis

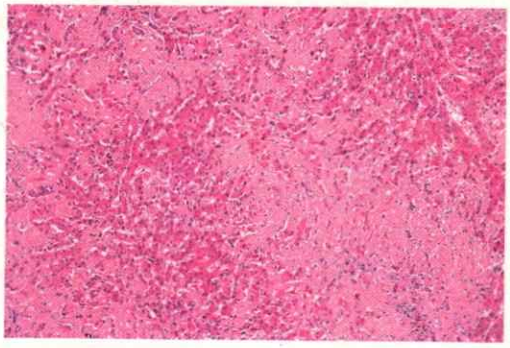
Onion skin appearance :

- Biopsy of malignant hypertension
- CIDP : Nerve biopsy.
- Primary sclerosing cholangitis : Biopsy.
- SLE, spleen – Gross.
- Ewing's sarcoma : X ray.
- Tay sach's disease : Electron micropsy.

Active space

Nutmeg liver seen in chronic venous congestion

Hydatid cyst



Amyloidosis of liver. Amyloid deposited first in space of disse. Congo red stain used.
Congo red stain

Q. A 53 year old non smoker woman with increasing dyspnoea for months. On examination : Liver edge is firm. Usg : abdomen shows liver damage. Spirometry suggestive of obstructive lung disease.
What is the diagnosis and biopsy finding ?
Ans : α 1 antitrypsin deficiency.
Biopsy : PAS + Diastase resistant inclusions in hepatocytes.

Q. A 44 year old man, an emergency medical technician, has felt fatigued for the past 4 months. He experienced an episode of jaundice 10 years ago, but that resolved and he has been healthy since. On physical examination there are no remarkable findings. Laboratory studies show his hemoglobin is 14 g/dL and serum electrolytes normal, but he has a total protein of 5.4 g/dL, albumin 2.9 g/dL, ALT 132 U/L and AST 113 U/L with total bilirubin 1.3 mg/dL and direct bilirubin 0.8 mg/dL. A liver biopsy is performed, and microscopic examination shows interface inflammation with extension of inflammation into the lobules from the triads. There is focal ballooning degeneration of hepatocytes. Which of the following laboratory test findings is most characteristic for his disease?

Active space

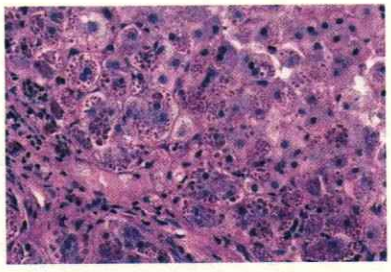
A. Decreased serum alpha-1-antitrypsin.
B. Positive hepatitis B surface antigen.
C. Increased serum ferritin.
D. Decreased serum ceruloplasmin.
E. Positive antimitochondrial antibody.

Q. A 22 year old woman has had progressive malaise for the past year. She has become increasingly obtunded over the past week. On physical examination she is afebrile. Laboratory studies show a plasma ammonia of 55 micromol/L along with serum total bilirubin of 5.8 mg/dL, direct bilirubin 4.6 mg/dL, AST 110 U/L, and ALT 135 U/L. Her serum ceruloplasmin is 14 mg/dL. The antimitochondrial antibody test is negative. A liver biopsy is performed and microscopic examination reveals increased copper deposition. Which of the following ocular findings is most likely to be present in this woman?

A. Bilateral papilledema.
B. Macular degeneration.
C. Proliferative retinopathy.
D. Crystalline lens cataract formation.
E. Corneal Kayser-Fleischer rings.
F. Canal of Schlemm occlusion.

Q. A 6 year old boy has shortness of breath with reduced breath sounds in both fields.
There is a family history of liver disease and he had marked icterus when he was a neonate.
His liver biopsy is shown below. The patient is at high risk of developing which of the following?

A. Bronchiectasis.
B. Emphysema.
C. SLE.
D. Fulminant hepatitis.



Active space

Q. A 15 year old boy from Ghana has the acute onset of right upper quadrant abdominal pain. Abdominal ultrasound reveals a dilated gallbladder with thickened wall and filled with calculi. A laparoscopic cholecystectomy is performed. The gall bladder is opened to reveal ten multifaceted 0.5 to 1 cm diameter dark, greenish-black gallstones. Which of the following underlying conditions does this boy most likely have?

A. Sickle cell anaemia.

B. Crohn disease.

C. Hypercholesterolemia.

D. Hyperparathyroidism.

E. Primary biliary cholangitis.

F. Schistosomiasis.

Hemolytic anaemia can increase the risk of gallstones.

Q. A 41 year old man has experienced progressive fatigue, pruritus, and icterus for the past 4 months. He had a total colectomy performed five years ago. On physical examination he is afebrile. Scleral icterus is present. His stool from a Koch pouch is negative for occult blood. Cholangiography reveals the widespread obliteration of intrahepatic bile ducts. A liver biopsy is performed and on microscopic examination shows periductular 'onion skin' fibrosis with a moderate lymphocytic infiltrate. Some intrahepatic bile ducts are obliterated, but there is no interface hepatitis. Which of the following underlying diseases is he most likely to have ?

A. Ulcerative colitis.

B. Systemic lupus erythematosus.

C. Wilson disease.

D. Hepatitis B viral infection.

E. Primary biliary cholangitis.

F. Alpha-1-antitrypsin deficiency.

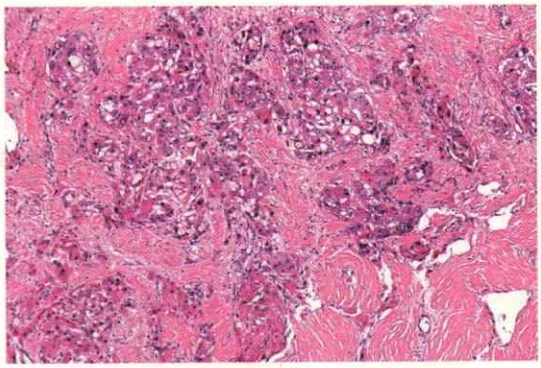
Active space

Q. A 54 year old Asian man has had malaise with a 6 Kg weight loss over the past 7 months. On physical examination he has a firm, nodular liver edge. His stool is negative for occult blood. Laboratory studies show a positive serology for hepatitis B surface antigen, but negative serologies for

hepatitis B surface antibody, hepatitis A IgM antibody, and hepatitis C antibody. His serum alpha-fetoprotein is 109 ng/mL. Which of the following neoplasms is he most likely to have?

A. Hemangioma.
B. Hepatic adenoma.
C. Hepatic angiosarcoma.
D. Bile duct adenocarcinoma.
E. Cholangiocarcinoma.
F. Hepatocellular carcinoma.
G. Non-Hodgkin lymphoma.

Q. Which of the following statements are true for the tumour shown below :



A. Better prognosis than primary HCC.
B. More common in elderly.
C. Raised AFP seen.
D. Underlying cirrhosis is not a risk factor.
E. Neurotensin is a biomarker.

Ans : A, D and E.

Active space

KIDNEY - BASICS

Urine examination

00:02:18

Microscopy (3Cs) :

- Cells : RBC, WBC & inflammatory cells.
- Casts.
- Crystals.

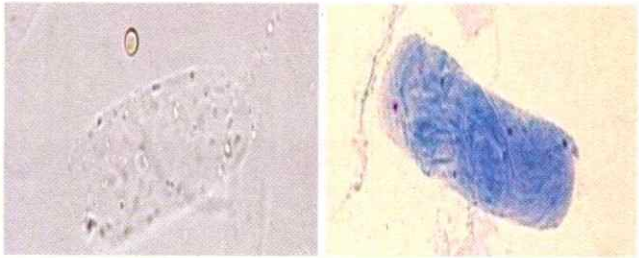
(3Cs in sputum microscopy of bronchial asthma : Curschmann spirals, charcot leyden crystals & creola bodies)

Casts :

All casts are composed of Tamm-Horsfall protein (produced in the thick ascending limb of loop of Henle).

Various casts seen on urine examination :

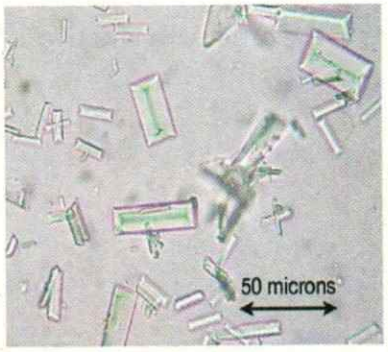
Casts	Conditions
Hyaline cast (physiological cast)	Can be seen in normal individuals, pregnancy, stress, fever.
RBC casts	Glomerulonephritis
WBC casts	Pyelonephritis
Broad/waxy cast	Chronic renal disease
Muddy brown granular cast	ATN (Acute Tubular Necrosis)
Lipid/fatty cast	Nephrotic syndrome



Hyaline cast with rounded ends

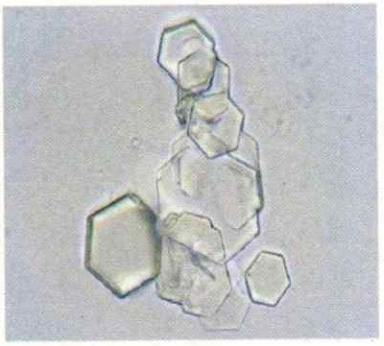
Active space

Microscopic appearances of various stones/crystals :



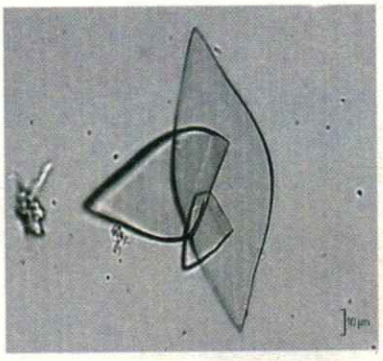
Struvite/staghorn stones :

- Radiopaque.
- Seen in alkaline urine.
- Rectangular/coffin lid appearance.
- Associated with urea splitting organisms.



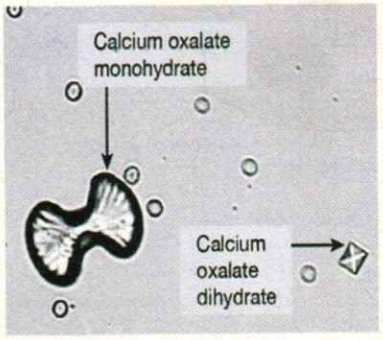
Cystine stones :

- Radiopaque.
- Seen in acidic urine.
- Hexagonal shaped.
- Very hard stones.



Uric acid crystals :

- Radiolucent.
- Seen in acidic urine.
- Varying shapes (rhomboids or parallellograms).



Calcium oxalate mono/dihydrate stones :

- Radiopaque.
- Seen in acidic urine.
- Dumbell shaped/envelope shaped.
- Most common type of renal calculi.

Active space

Ammonium urate stones :

- Radiolucent.
- Associated with laxative abuse.

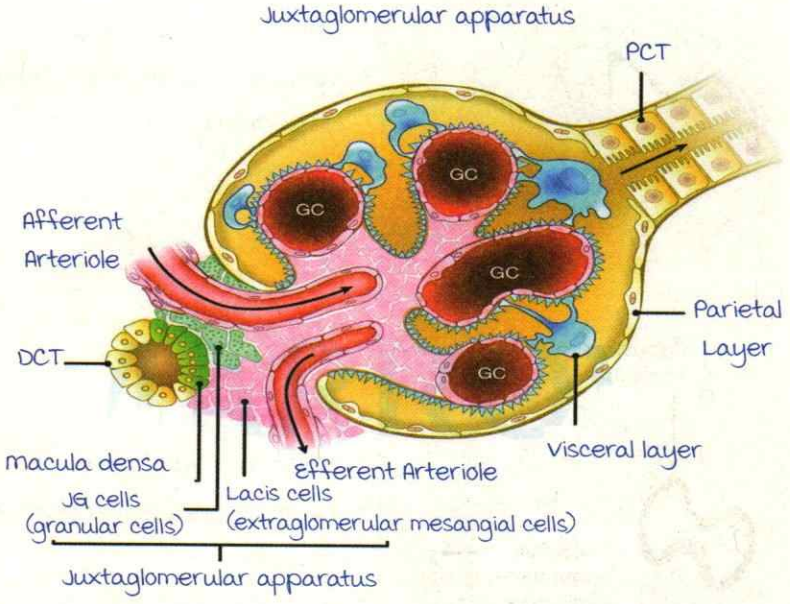
Kidney biopsy

00:11:40

Structures seen in Kidney biopsy :

- Glomerulus.
- Tubules.
- Interstitium.
- Renal blood vessels.

Structure of glomerulus :



Glomerulus is comprised of a tuft of capillaries, an afferent arteriole and an efferent arteriole.

Bowman's space : The space between parietal and visceral layers.

Active space

Glomerulus has two epithelial cell layer :

- Outer parietal epithelial cell layer.
- Inner visceral epithelial cell layer : Contain podocytes/foot processes.

Glomerular capillaries are lined by endothelial cells.

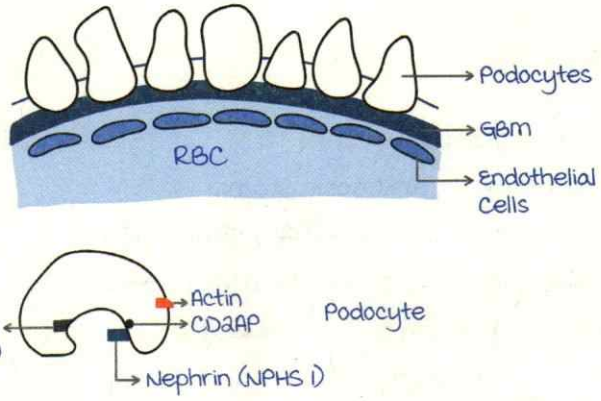
Glomerular basement membrane (GBM) is present between the endothelial cell layer and the visceral epithelial cell layer.

GBM is composed of :

- Type 4 collagen.
- Laminin.
- Proteoglycans.
- Heparan sulfate.

Endothelial cell layer has fenestrations (70-100nm in diameter) to allow the passage of solutes through it.

Filtration membrane



Glomerular filteration membrane is comprised of :

- Podocytes.
- GBM.
- Endothelial cells.

Podocyte has four different kinds of proteins :

- Nephrin : Encoded by NPHS 1 gene.
- Podocin : Encoded by NPHS 2 gene.
- CD2AP.
- Actin fibres.

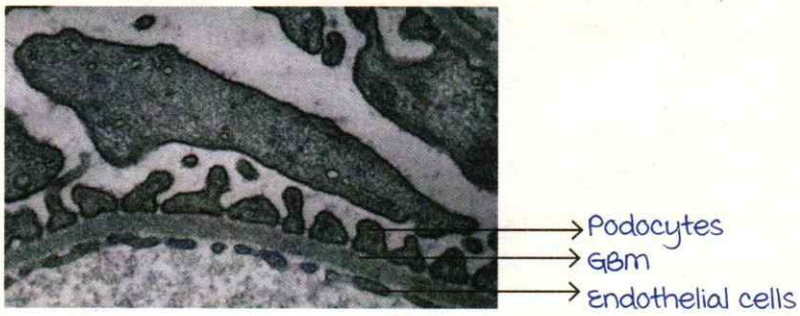
Stain for GBM : PAS stain (magenta colored GBM).

Active space

Filteration process :

It depends on the following factors :

- Size of the particles : >3.6 nm radius particles cannot be filtered.
- Charge of particles : Filteration membrane is negatively charged and thus, it prevents the filteration of protiens (negatively charged) from the body.



Electron microscopy of Glomerular filteration membrane

Kidney biopsy

00:23:27

- Light microscopy :
  1. Hematoxylin and eosin stain.
  2. Periodic acid-Schiff (PAS) stain : GBM.
  3. Silver stain : Reticulin deposition, GBM.
  4. Congo red : In renal amyloidosis.
- Electron microscopy (EM).
- Immunofluorescence (IF).

Kidney is the most common organ which is affected in amyloidosis.

Amyloid deposits are first seen in :

- Kidney : Mesangium.
- Liver : Space of Disse.
- Heart : Subendocardium.

Diagnosis of Glomerulonephritis from the Kidney biopsy :

- Count the number of glomeruli : Optimal number of glomeruli which should be present for apt interpretation of glomerulonephritis : 10–15 glomeruli.

Active space

Terms :

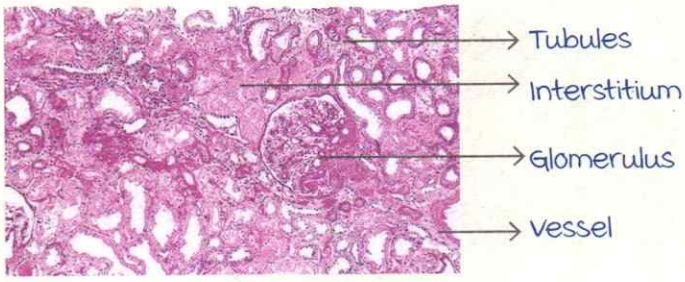
- Proliferative : Increased cellularity of either epithelial cells mesangial cells/inflammatory cells.
  Example : Focal proliferative glomerulonephritis, diffuse proliferative glomerulonephritis.
- Focal : < 50% of glomeruli are affected.
- Diffuse : > 50% of glomeruli are affected.
- Segmental : Involvement of a portion of a glomerulus.
- Global : Entire glomerulus is affected.

Example :

FSGS (Focal Segmental Glomerulo Sclerosis) means < 50% of the glomeruli are showing sclerosis in only a portion of each glomerulus.

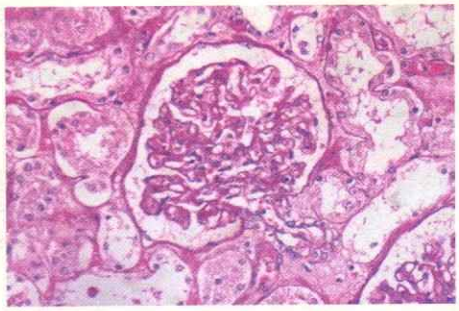
DPGN (Diffuse Proliferative GlomeruloNephritis) means > 50% of the glomeruli in that particular biopsy are showing increased cellularity.

Normal kidney biopsy :

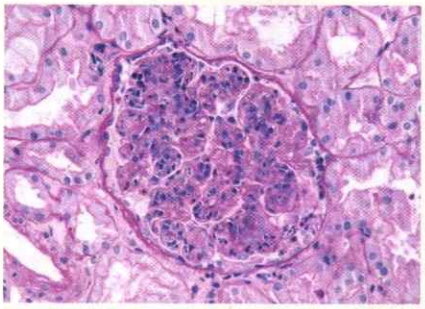


Normal glomerulus on PAS stain :

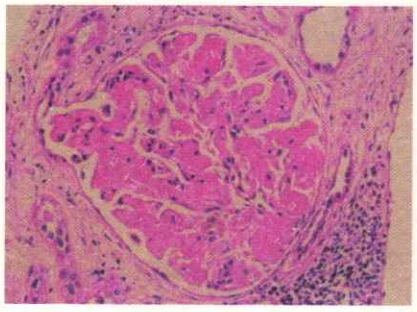
- Capillary lumens are open.
- 1 or 2 cells per capillary tuft.
- Mesangial cells in the center.
- Thickness of the GBM is compared to the tubular wall thickness.

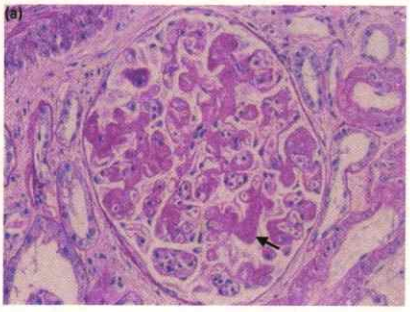


Active space

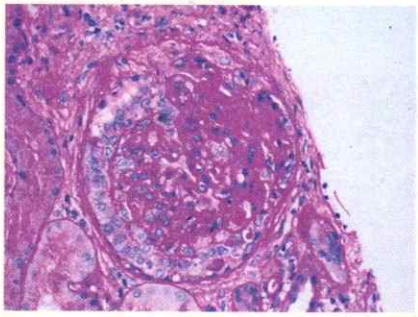


Increased size of the glomerulus.
Increased cellularity by neutrophils.
Closed capillary lumen.
Normal GBM.
Proliferative disease





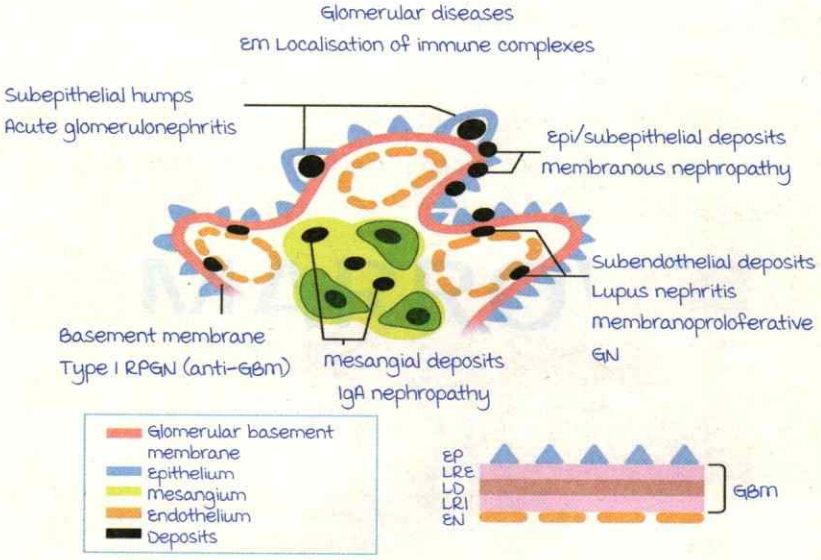
Closed capillary lumen.
Pink colored deposition in the glomerulus which can be due to sclerosis (DM) or amyloidosis.



PAS stain :
Pink deposit (sclerosis)
Crescent formation
↓
RPGN (rapidly progressive glomerulonephritis)

Electron microscopy

00:36:37

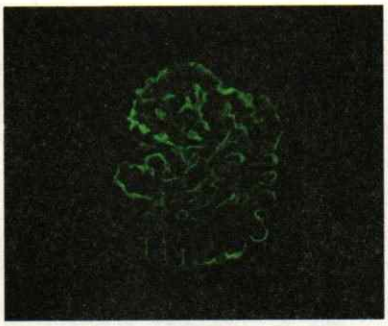
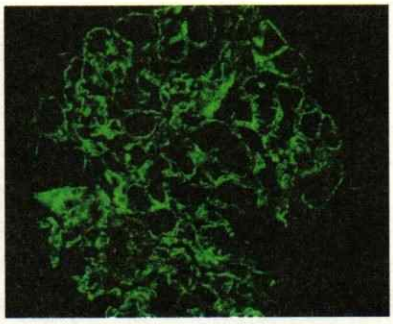


Active space

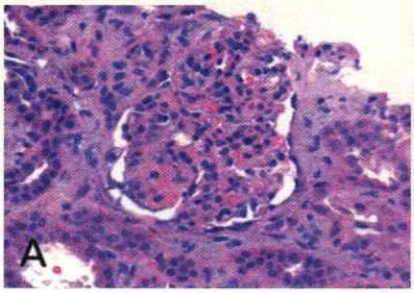
EM deposits	Conditions
Subepithelial humps (below the visceral epithelium)	Acute glomerulonephritis like PSGN (Post-Streptococcal glomerulonephritis). RPGN (Rapidly progressive glomerulonephritis). membranous glomerulonephritis.
Intramembranous deposits (inside the GBM)	MPGN 2 (membranoproliferative glomerulonephritis)
Subendothelial deposits (below the endothelium)	Lupus nephritis. MPGN 1 (membranoproliferative glomerulonephritis).
Mesangial deposits	HSP (Henoch-Schonlein purpura). IgA nephropathy.

Immunofluorescence

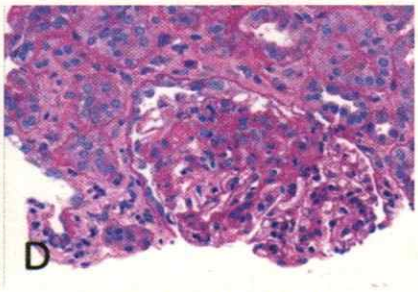
00:40:03

Linear pattern	Granular pattern
GBM diseases	Due to immune complex/ complement deposition
Good Pasteur's syndrome (anti-GBM antibodies)	PSGN (lumpy bumpy appearance)
	

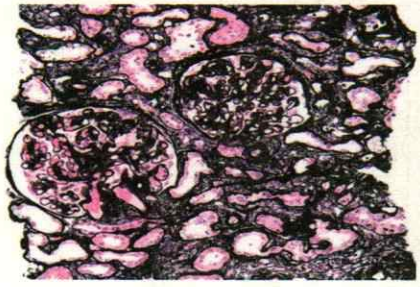
Active space



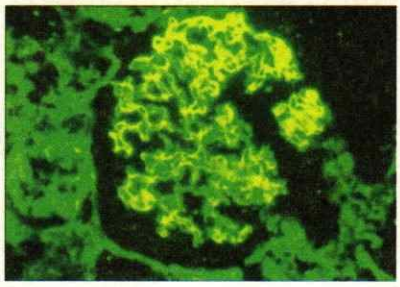
Increased cellularity.
Pink colored deposit.



Segmental sclerosis



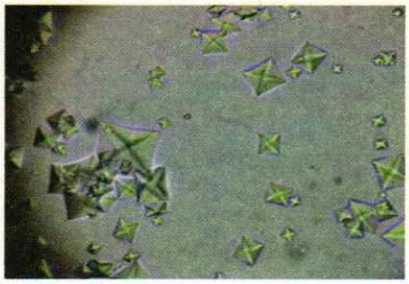
Silver stain (black)



Linear pattern on IF

Q. Identify the urinary crystals seen on urinary examination in a patient with renal stones?

A. Uric acid.
B. Cystine.
C. Triple phosphate.
D. Calcium oxalate.



Active space

NEPHRITIC SYNDROME

Clinical presentation :

Proteinuria (not in nephrotic range) <3.5gm /24hours.

Edema present.

Hematuria → Cola coloured urine.

Hypertension.

Azotemia → Ammonia in the blood.

Post streptococcal glomerulonephritis (PSGN) 00:01:56

Type III hypersensitivity reaction → immune complex mediated.

Age : 5- 15years.

Occurs 2- 3 weeks after an infection with → β - hemolytic streptococci → 12, 4, 1 strains.

Presents with cola coloured urine.

Morphology of the Kidney :

Light microscopy shows :

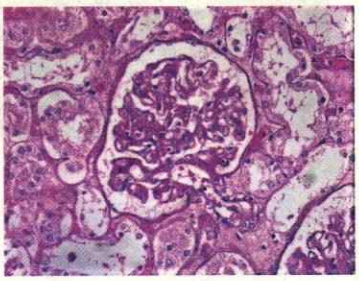
- Enlarged hypercellular glomeruli with neutrophils → also known as acute proliferative glomerulonephritis.
- Endo/exo capillary proliferation.

Electron microscopy shows :

- Sub-epithelial humps.

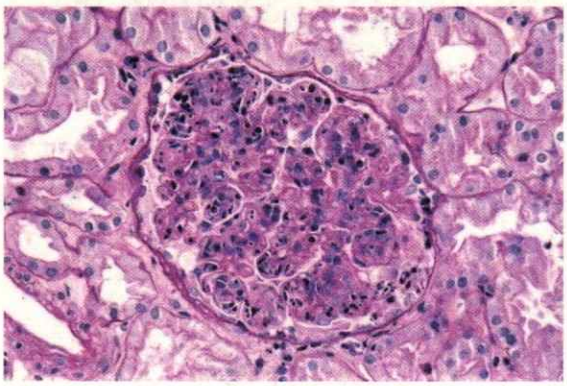
Immunofluorescence :

Granular pattern, also called lumpy bumpy pattern or starry sky pattern.

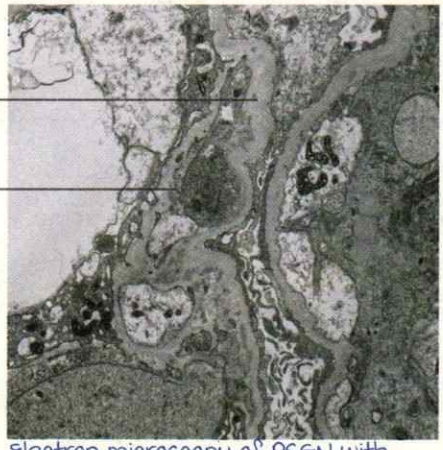


Normal glomerulus with open lumen and 1 or 2 cells per capillary tuft

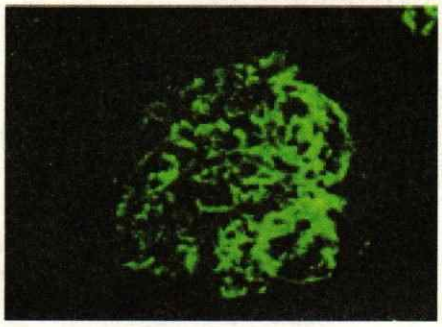
Active space



PSGN with enlarged glomeruli, closed lumen and increased cellularity with neutrophils



Electron microscopy of PSGN with sub-epithelial humps



Immunofluorescence showing granular pattern/ lumpy bumpy pattern/ starry sky pattern

Active space

Starry sky in pathology :

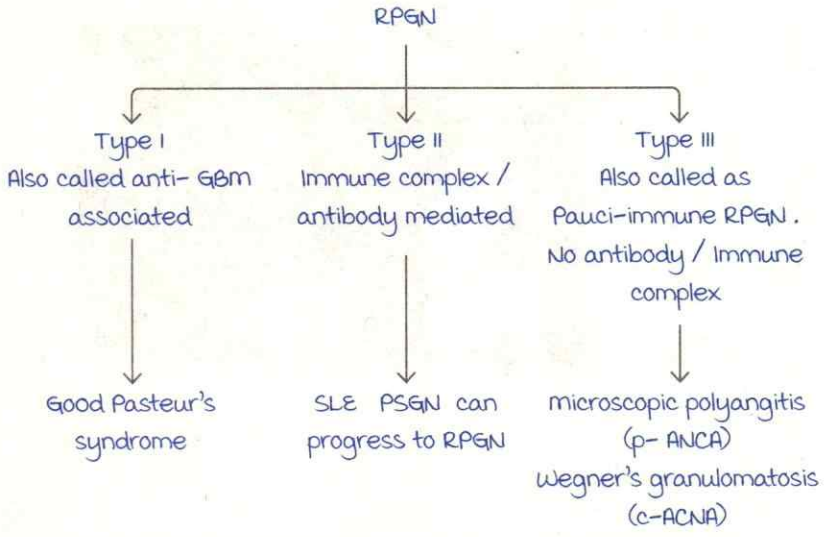
- Acute proliferative glomerulonephritis immunofluorescence.
- Burkitt's lymphoma.

No treatment required, as it is a self-limiting condition.
ASO titer can be assessed → streptococcal sore throat infection.

Rapidly progressive glomerulonephritis (RPGN) 00:10:43

medical emergency.
Also known as crescentic glomerulonephritis → >50% of glomeruli in biopsy show crescents.

Types :



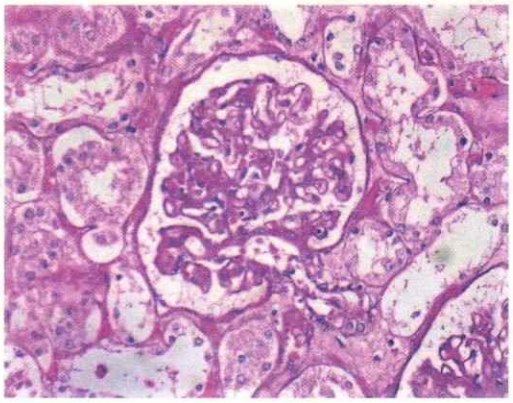
Morphology of RPGN :
Light microscopy :

- Presence of crescents in > 50% glomeruli → crescentic glomerulonephritis.
- Crescents are formed by the proliferation of parietal epithelial cells, fibrin (imparts pink colour) and leucocytes.

Active space

Electron microscopy :

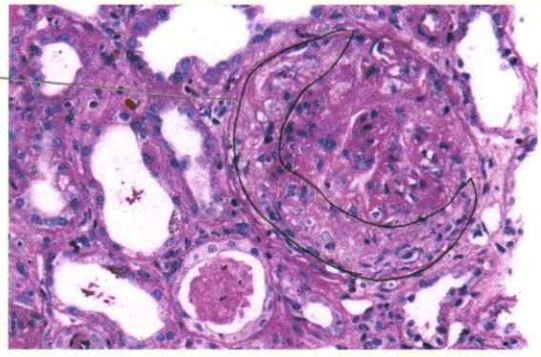
- Rupture or wrinkling of basement membrane.

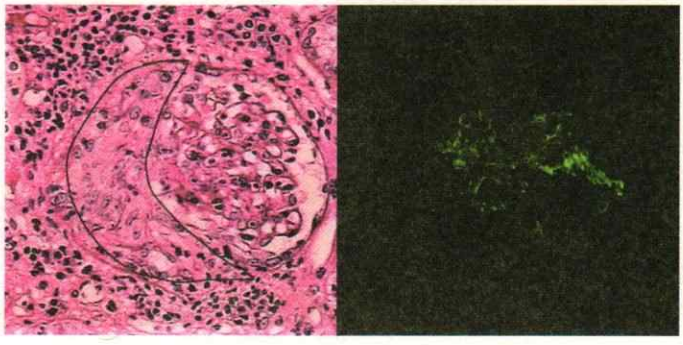


Normal glomerulus

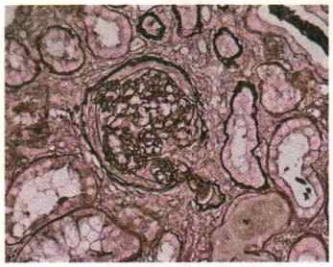
Immunofluorescence :

- Type I RPGN : Linear pattern.
- Type II RPGN : Granular pattern.
- Type III RPGN : No deposits visualized.



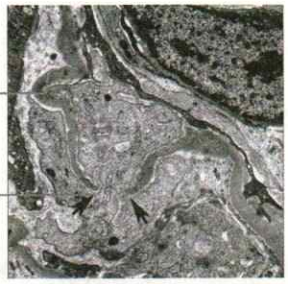


Active space

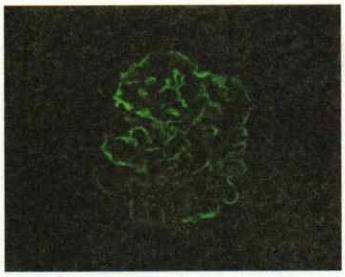


Glomeruli with a crescent in silver stain

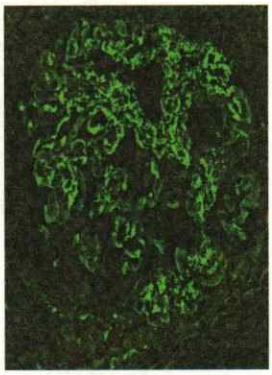
The more the number of crescents, the poorer is the prognosis.



Electron microscopy showing break in the basement membrane



Linear pattern in Type I



Granular pattern in Type II

Good Pasteur syndrome 00:20:31

Mnemonic : 1234.

Type 1 RPGN.

Type 2 hypersensitivity reaction.

α 3 chain.

Type 4 collagen.

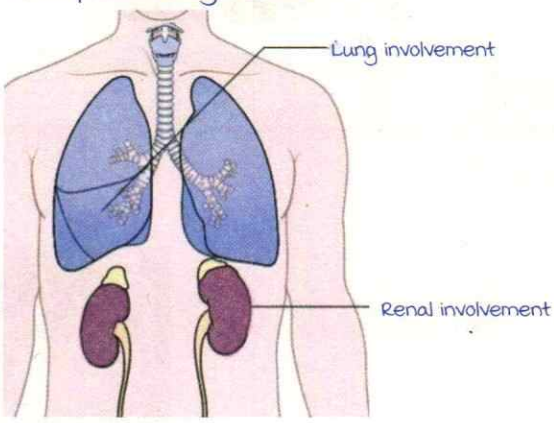
Pathogenesis : defect in α 3 chain of type 4 collagen.

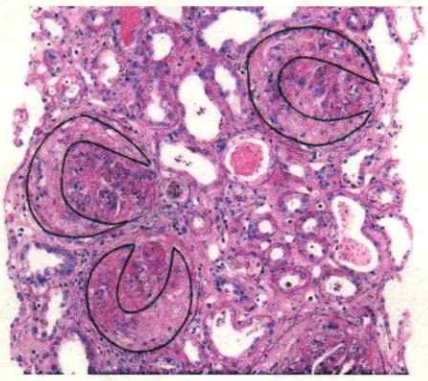
Active space

Organs affected : lung and kidney.

- Lung → Pulmonary alveolar hemorrhages → Hemoptysis.
- Type I RPGN → Hematuria.

Goodpasture syndrome





Glomeruli with a crescent

Light microscopy shows crescents.
Electron microscopy shows break in glomerular membrane.
Immunofluorescence shows linear pattern.

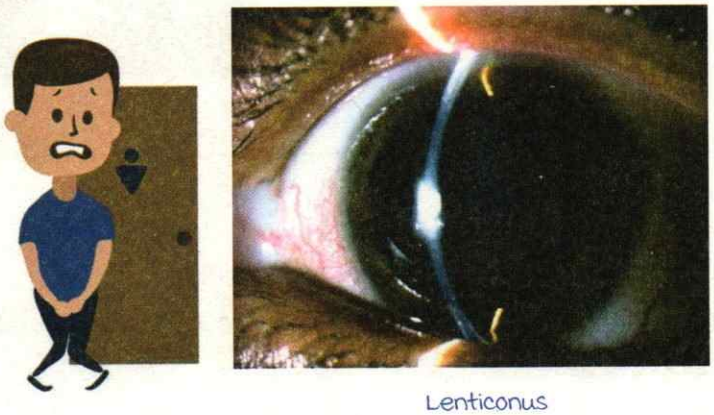
Thin basement membrane disease :
Also known as benign familial hematuria.
Pathology in α 4 chain of type 4 collagen.
Normal thickness of basement membrane : 250–400nm.
Thin basement membrane disease : <200nm.

Active space

Alport syndrome

00:26:15

Defect in α 5 chain of type 4 collagen.
One of the causes of hereditary nephritis.
It follows all mendelian modes of inheritance → AR, AD, X-linked recessive or dominant pattern.
Most common inheritance is X-linked dominant disorder.



Lenticonus

Clinical presentation :
"The patient can't see, can't pee and can't hear a buzzing bee."
Eye : anterior lenticonus.
Kidney : hematuria.
Ear : sensorineural deafness.

Most common and earliest organ affected is Kidney > ear.

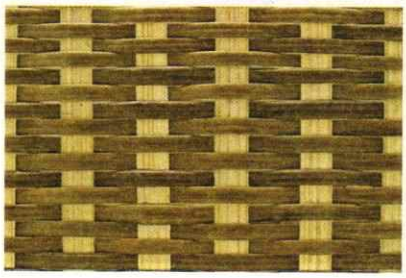
Morphology :
Light microscopy : cannot be diagnosed in light microscopy.

Electron microscopy : Diagnostic investigation of choice.

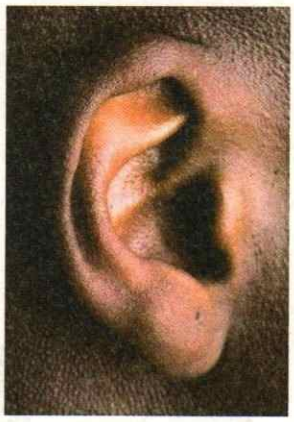
- Shows _____
  No deposits in immuno fluorescence.

Active space

Basket Weave appearance



Hearing Loss



IgA nephropathy

00:32:00

Also known as Berger's disease.
most common glomerulonephritis worldwide.
most common cause of gross and microscopic hematuria.
Due to deposition of IgA.
Pathology : increased mucosal secretion of IgA → IgA deposition in the mesangium.

Morphology :
Shows mesangial widening and IgA deposition.

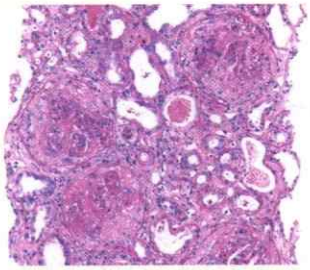
PSGN	IgA nephropathy
Children of 5- 15years of age	Adult patient
2- 4 weeks after streptococcal infection	Occurs 2-3days after a streptococcal infection

Q. The pathogenesis of acute proliferative glomerulonephritis :
A. Cytotoxic T cell mediated.
B. Immune complex mediated.
C. Antibody mediated.
D. Cell mediated.

Q. A 42 year old man comes to the physician because of fatigue and decreased urination for the past 3 days. His creatinine is 2.5 mg/dL. A photomicrograph of a biopsy specimen of the right kidney is shown. Which of the following

Active space

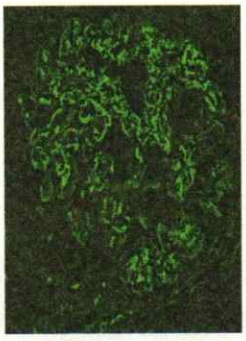
mechanisms most likely contributed to this patient's biopsy findings?



A. Effacement of podocyte foot processes.
B. Expansion of mesangial matrix.
C. Deposition of immunoglobulin light chain.
D. Fibrin formation in Bowman's space.

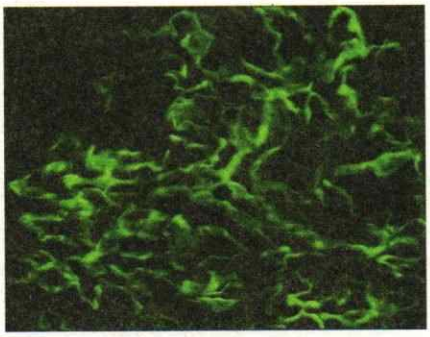
A → nephrotic syndrome.
B → IgA nephropathy.

Q. An 11 year old girl comes to the physician with her mother because of a 2 day history of passing "cola-coloured" urine. During the past week, her mother noticed episodes of facial swelling. The patient had a rash on her face about 4 weeks ago. A renal biopsy after immunofluorescence is shown. Which of the following is the most likely diagnosis?



A. Alport's syndrome.
B. MCD.
C. IgA nephropathy.
D. Lupus nephritis.
E. RPGN.
F. PSGN.

Q. Immunofluorescence microscopy of renal biopsy is shown below. The patient complaints of hematuria. What is the most likely diagnosis:



A. Membranous GN.
B. IgA nephropathy.
C. Good Pasteur's syndrome.
D. PSGN.

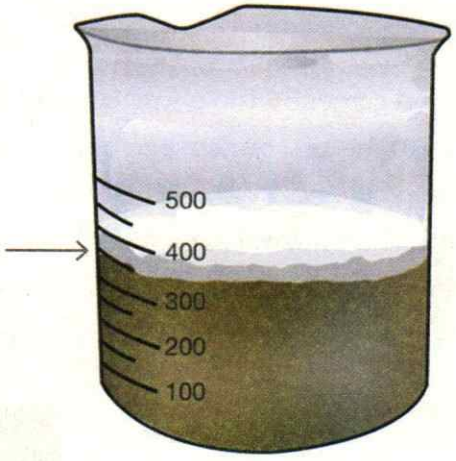
Active space

NEPHROTIC SYNDROME

Patients with nephrotic syndrome have massive proteinuria.

- Excretion of > 3.5 gm protein/24 hours.
- Edema : Periorbital edema is common.

Patient can also have hypercholesterolemia and dilution coagulopathies.



Urine examination :

Frothy urine.

Lipid/fatty casts seen in urine microscopy.

Most common cause of nephrotic syndrome :

In children : Minimal change disease.

In adults : Focal Segmental Glomerulosclerosis (FSGS).

In elderly : Membranous nephropathy.

Most common cause of glomerulonephritis worldwide : IgA nephropathy.

Most common nephritic syndrome in children : PSGN.

Minimal Change Disease (MCD) 00:03:22

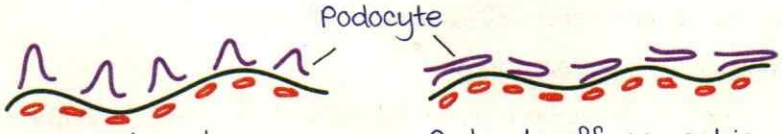
Most common cause of nephrotic syndrome in children.

Age : 2–6 years.

Also known as nil deposit disease/lipoid nephrosis.

Etiology unknown.

Active space



Normal

Podocyte effacement in minimal change disease

Morphology :

Light microscopy :

Glomeruli appears normal.

Lipid deposition in tubules, so called lipoid nephrosis.

Electron microscopy : Effacement of podocyte foot processes, so called podocytopathy.

In Alport's syndrome → no light microscopy findings. Only finding in electron microscopy, basket weave appearance.

Immunofluorescence : No deposits → called nil deposit disease.

Responds well to steroids.

Causes selective proteinuria.

Focal Segmental Glomerulosclerosis (FSGS) 00:08:26

Most common cause of nephrotic syndrome in adults.

Causes :

Primary cause : Idiopathic.

Secondary causes : Mnemonic → 3H2RIS.

Hypertension.

HIV.

Heroin abuse.

Reflux nephropathy.

Renal ablation surgery → nephrectomy.

Sickle cell anemia.

IgA nephropathy.

Obesity.

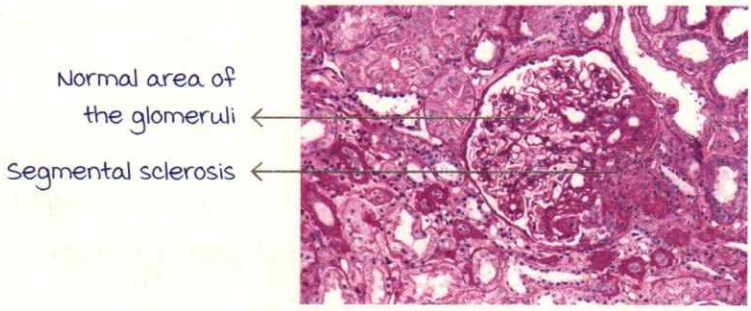
Morphology :

Light microscopy : <50% glomeruli show segmental sclerosis → so called focal.

Active space

Electron microscopy : Effacement of podocyte foot processes → podocytopathy.

Immunofluorescence : Some deposits of IgG and C3 in the sclerotic area.



Variants :

FSGS not otherwise specified.

Glomerular tip variant : Affects the glomerular tip → best prognosis.

Peri-hilar variant.

Cellular variant.

Collapsing variant : Usually seen in HIV positive patients → worst prognosis.

Genetic basis of nephrotic syndrome 00:16:17

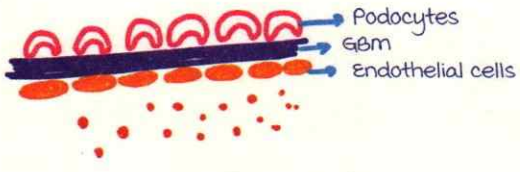
Mutations of NPHS1, NPHS2 and actin can produce genetic type of nephrotic syndrome.

NPHS-1 gene :

Located in chromosome 19.

Encodes for nephrin.

Leads to congenital nephrotic syndrome of Finnish type.



Active space

NPHS-2 :

Located in chromosome 1.

Encodes for podocin.

Causes steroid resistant nephrotic syndrome.

Can also cause autosomal recessive FSGS.

α actinin-4 :

Encodes for podocin actin binding protein.

Causes adult onset FSGS.

Membranous nephropathy 00:20:07

Most common cause of nephrotic syndrome in elderly.

Causes :

Malignancy of colon, pancreas, lung.

Infections like malaria, syphilis, hepatitis, schistosomiasis.

(Schistosomiasis can also cause bladder cancer)

Drugs like gold, Penicillamine.

Autoimmune disorders like SLE.

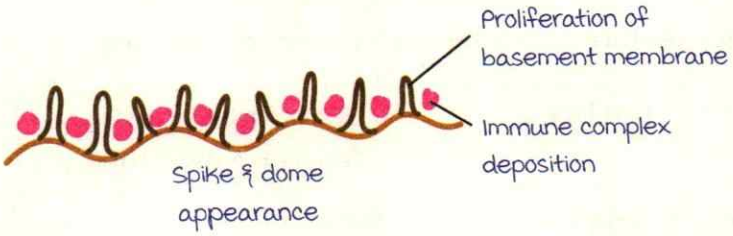
Renal vein thrombosis.

Pathogenesis :

Immune complex mediated.

Phospholipase A2 (PLA2) defect.

Morphology :



Light microscopy :

Deposition of immune complex in basement membrane → thickening of basement membrane.

Silver stain : Spike and dome appearance.

Spikes → basement membrane.

Dome → immune complexes.

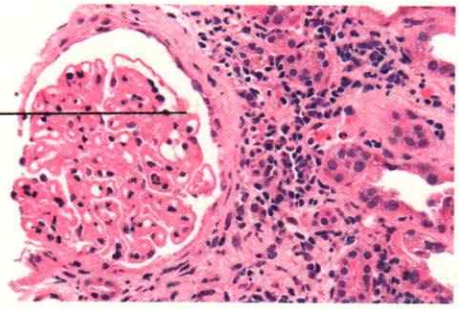
Active space

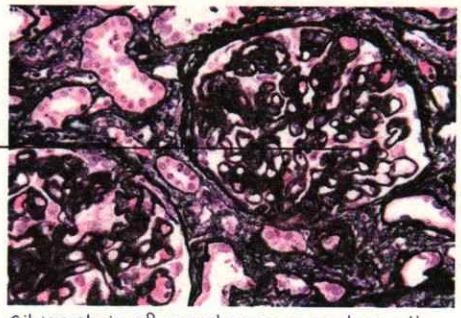
Electron microscopy :

Sub-epithelial deposits.

Effacement of podocyte foot processes → podocytopathy.

Immunofluorescence : Granular deposits.





Silver stain of membranous nephropathy

Membranoproliferative glomerulonephritis (MPGN)

00:26:55

Also called mesangiocapillary glomerulonephritis.

Shows features of nephrotic > nephritic syndrome.

Type I MPGN	Dense deposit disease (earlier called type II)
Immune complex deposition. Complement is sometimes deposited.	Activation of complement pathway (alternate pathway) → C3 glomerulopathy.

Light microscopy :

Tram track appearance → immune complexes and complements deposited splits the basement membrane into two.

Active space

Enlarged hypercellular glomeruli.

Endocapillary proliferation → lobular architecture.

Electron microscopy :

Type I : Subendothelial deposits.

Type II : Dense deposits may be seen.

Immunofluorescence :

Type I : Granular pattern.

Type II : Ribbon- like/linear pattern.

Persistent hypocomplementemia :

- Continuous activation of complements (via the alternate pathway) → decreased levels of complements.

PSGN shows transient hypocomplementemia.

Q. A 6 year old girl is brought to the physician because of increasing swelling around her eyes for the past 3 days. Her vital signs are within normal limits. Physical examination shows periorbital edema and abdominal distention with shifting dullness. Laboratory studies show a serum albumin of 2 g/dL and a serum cholesterol concentration of 290 mg/dL. Urinalysis shows 4+ proteinuria and fatty casts. Histological examination of a kidney biopsy specimen is most likely to show which of the following findings?

A. Mesangial proliferation on LM.

B. Effacement of podocyte foot processes.

C. Normal glomeruli on LM.

D. Subepithelial humps on EM.

Q. Membranous glomerulonephritis is found at autopsy in a 25 year old woman who died of renal failure. Other autopsy findings include pleuritis, diffuse interstitial fibrosis of lungs, concentric rings of collagen surrounding splenic arterioles and warty vegetations of mitral and tricuspid valves affecting the surfaces behind the cusps as well as surfaces exposed to forward blood flow. Which of the following is an expected laboratory finding ?

Active space

A. Increased ASO titer.

B. Lymphocytosis.

C. Peripheral rim pattern of antinuclear antibody fluorescence.

D. Positive blood culture for streptococcus viridians.

Q. Colon cancer is associated with which type of glomerulonephritis :

A. MGN.

B. MCD.

C. MPGN.

D. FSGS.

Q. A 62 year old man has had back pain for the past 8 months. He has had a productive cough for the past 2 days. On physical examination his temperature is 39°C and there is dullness to percussion at the right lung base.
Laboratory studies show 4+ gram positive diplococci in the sputum. A chest radiograph shows right lower lobe consolidation. An abdominal CT scan shows multiple lytic lesions of the vertebrae. On the day prior to death his serum urea nitrogen was 63 mg/dL with creatinine 7.1 mg/dL. A dipstick urinalysis was normal. At autopsy, his kidneys are firm and pale. Microscopically, there is abundant pink hyaline material in glomeruli and around small vessels. This material stains positively with Congo red. Which of the following laboratory findings was most likely to have been present in this patient in the week prior to death ?

A. Positive antinuclear antibody test.

B. Serum glucose of 210 mg/dL.

C. CD4 lymphocyte count of 110/microliter.

D. Total serum protein of 9.2 g/dL.

E. Serum prostate specific antigen of 11.8 ng/mL.

Active space

Q. A 21 year old man comes to the emergency department because of a 2 week history of progressive shortness of breath and intermittent cough with blood tinged sputum. During this time, he has also noticed blood in his urine. He

has no history of serious illness and does not take any medications. His temperature is 37°C (98.6°F), pulse is 92/min, respirations are 28/min, and blood pressure is 152/90 mm Hg. Cardiopulmonary examination shows crackles at both lung bases. Urinalysis is positive for blood and results of a direct enzyme-linked immunoassay are positive for anti-GBM antibodies. The pathogenesis of this patient's disease is most similar to which of the following?

A. Henoch Schonlein purpura.

B. Post streptococcal glomerulonephritis.

C. Polyarteritis nodosa.

D. Autoimmune hemolytic anaemia.

Type II hypersensitivity reaction.

Active space

RENAL INVOLVEMENT IN SYSTEMIC DISEASES

Diabetic nephropathy 00:00:53

Kidney is more affected in type I > type II diabetes mellitus.
Development of diabetic nephropathy depends on the duration of the disease.

- The more the duration, the more is the chance of developing diabetic nephropathy.

Morphological features :
Gross features → renal papillary necrosis.
Causes of renal papillary necrosis : Mnemonic : SODA.
Sickle cell anemia.
Obstructive uropathy.
Diabetes mellitus → most common cause.
Analgesic use.

HPE :

Thickening of the capillary walls or glomerular basement membrane → earliest finding.
Diffuse glomerulosclerosis → most common finding.
Nodular glomerulosclerosis → Kimmelstiel Wilson lesion.

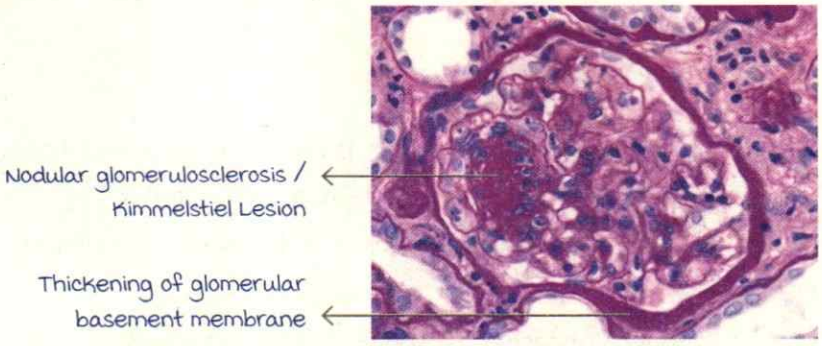
- PAS positive nodular glomerulosclerosis.
- most characteristic/specific feature of diabetic nephropathy.

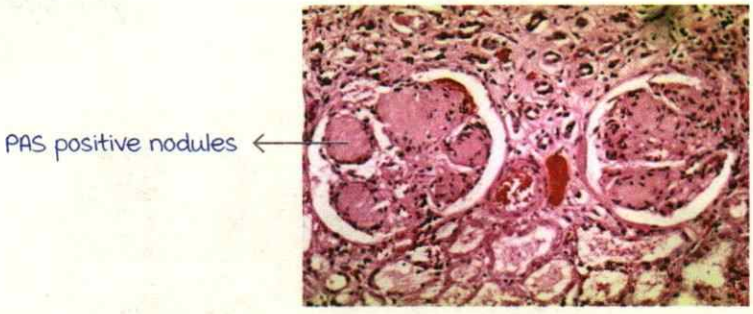
Fibrin caps and capsular drops :

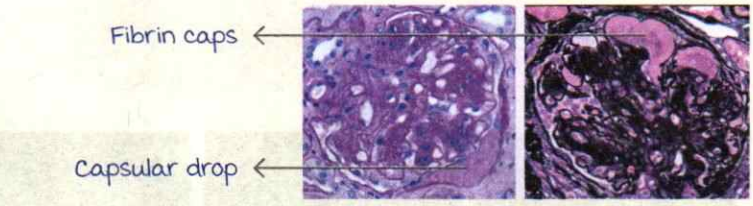
- Capsular drop → Excess hyaline in Bowman's capsule.
- Fibrin cap → Excess hyaline in the glomerular capillary wall.

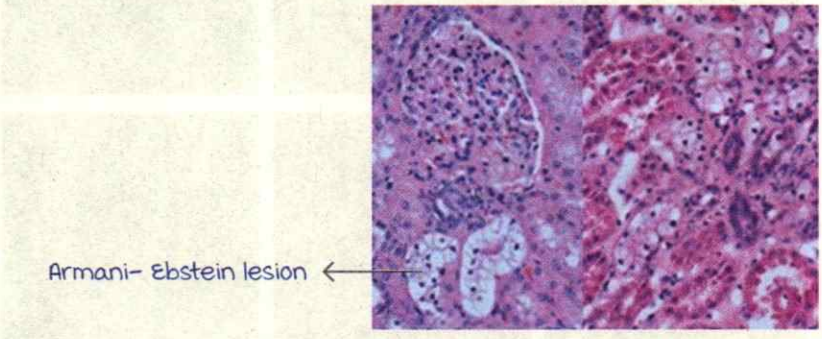
In long standing, severe diabetes mellitus, cells of PCT becomes clear due to glycogen → Armani-Ebstein lesion.

Active space









Kidney involvement in SLE / lupus nephritis 00:10:13

Grades of lupus nephritis according to WHO :

Grade I : Minimal mesangial.

Grade II : Mesangio-proliferative.

Grade III : Focal proliferative.

Grade IV : Diffuse proliferative.

Active space

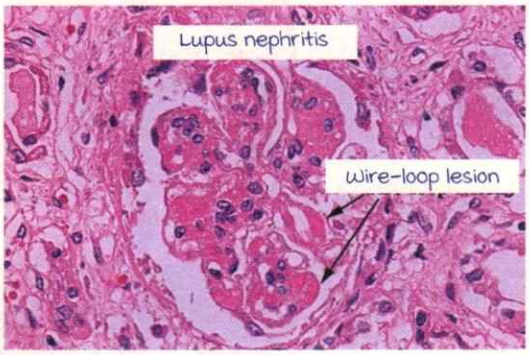
Grade V : Membranous.

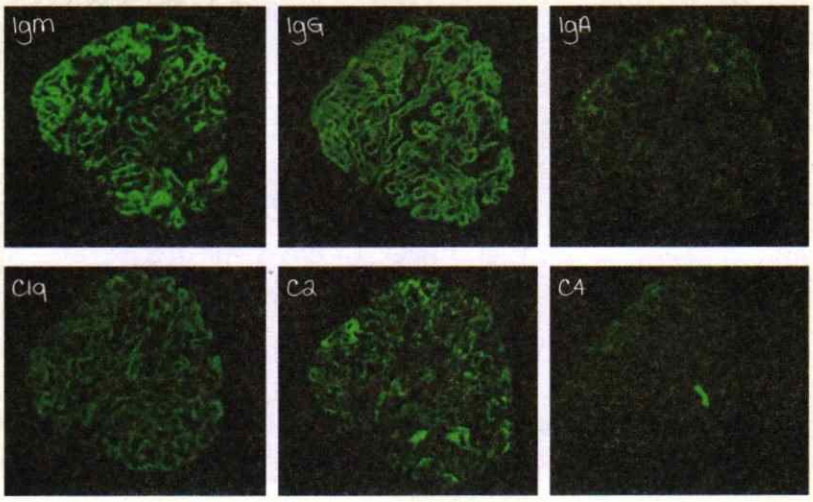
Grade VI : Dense sclerosing.

Most common type is grade IV → Diffuse proliferative type.
Wire loop lesions → seen in grade II, III, IV → most prominent in grade IV, occurs due to thickened glomerular capillary walls.

SLE on immunofluorescence shows full house effect.

- Immunofluorescence with all immunoglobulins and complements.





Full house effect

SLE has both type 2 and type 3 hypersensitivity reactions.

- Hematological lesions are type 2 hypersensitivity reaction.
- Visceral lesions are type 3 hypersensitivity reaction.

Simple best answer : Type 3 hypersensitivity reaction.

Active space

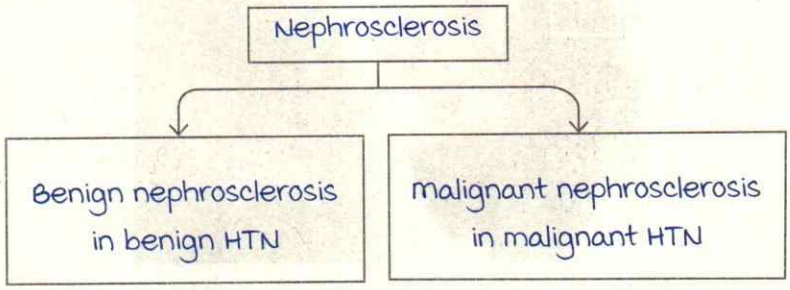
SLE causes Libman-Sacks endocarditis → vegetations on both sides of the valve surface and endocardium.

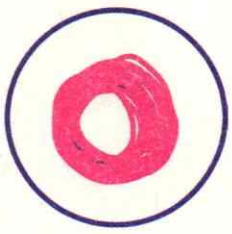
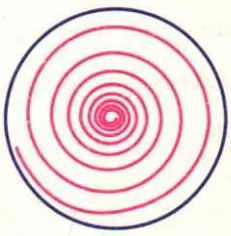
- Rheumatic heart disease, infective endocarditis and marantic endocarditis shows vegetations on only one side, along the line of closure of valve leaflet.

Nephrosclerosis

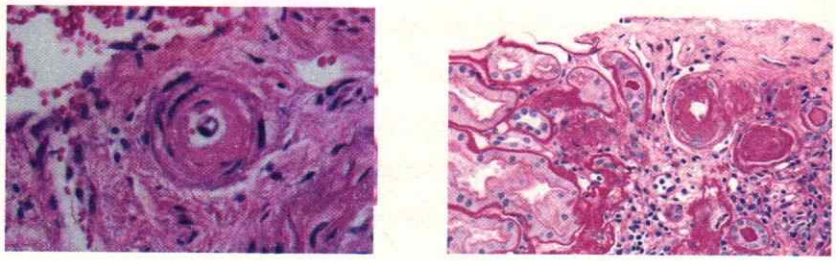
00:15:57

Kidney disease in hypertension.
Vessels will become hardened /sclerosed.

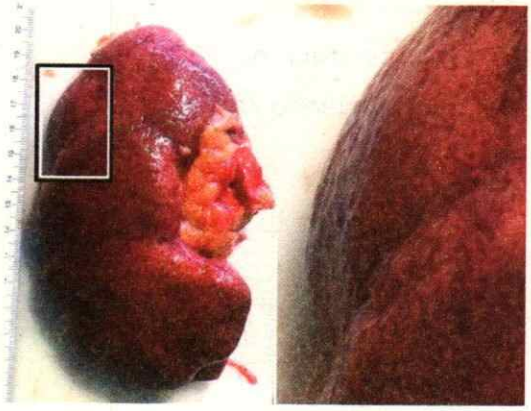


	Benign nephrosclerosis	malignant nephrosclerosis
Gross specimen	Leather grain appearance	Flea bitten appearance due to petechial hemorrhages.
HPE	Hyaline arteriosclerosis. Deposition of pink homogenous hyaline → luminal wall narrowing. 	Hyperplastic arteriosclerosis. Laminated thickening of the vessel wall → onion skin appearance. 

Active space

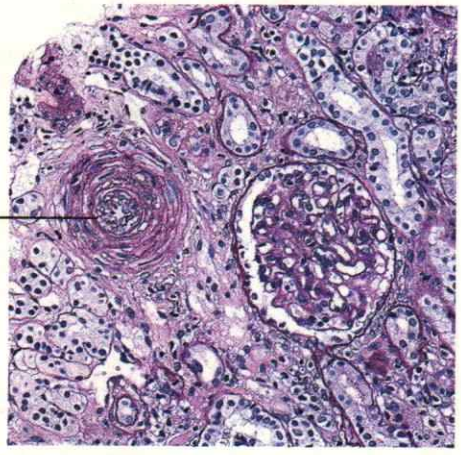


Hyaline arteriosclerosis in H&E and PAS stain



Leather grain appearance in benign nephrosclerosis

Onion skin appearance in malignant nephrosclerosis



Causes of flea bitten kidney :

Malignant hypertension.

Subacute bacterial endocarditis.

Henoch-Schönlein purpura.

Polyarteritis nodosa.

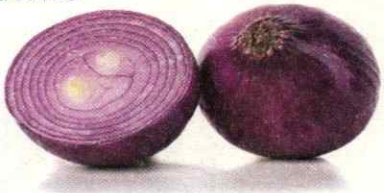
RPGN.

SLE.

Flea bitten kidney in malignant nephrosclerosis

Active space

Onion skin appearance :



- Malignant hypertension on biopsy.
- Nerve biopsy of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).
- Primary sclerosing cholangitis on biopsy shows onion skin fibrosis of bile duct.
- Spleen in SLE on gross specimen.
- X-ray of Ewing's sarcoma.
- Electron microscopic examination of Tay Sach's disease.

Chronic pyelonephritis

00:22:57

Morphology of Kidney :

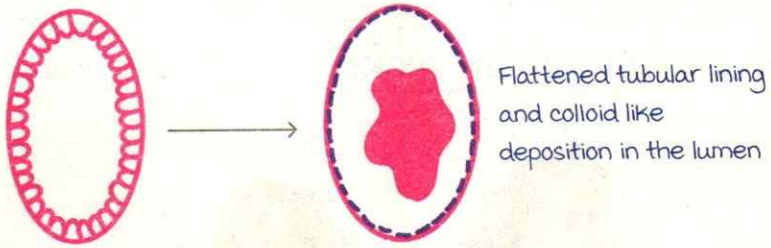
Gross specimen : Asymmetrically shrunken Kidney and irregular scars.

Symmetrically shrunken Kidney is seen in chronic glomerulonephritis.

HPE :

Tubular atrophy.

Lining of the tubule becomes atrophic and flattened.



Thyroidization of the renal tubules → Deposition of pink colloid like material within the tubules → Resembles thyroid gland.

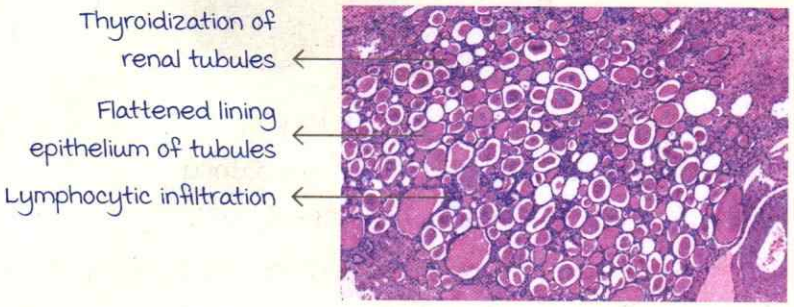
Lymphocytic infiltrate.

Peri-glomerular fibrosis.

Active space

Urine microscopy :

WBC casts (RBC casts in glomerular disease).



Malakoplakia :

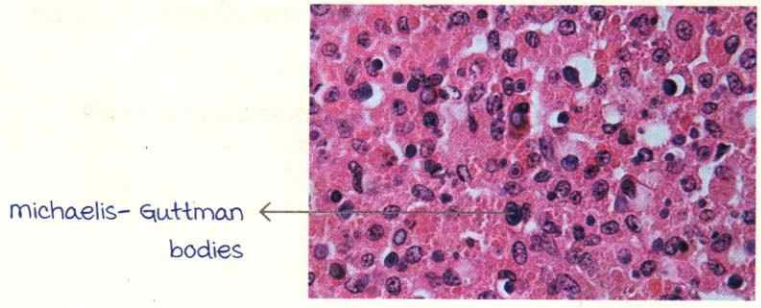
Rare disorder.

Michaelis-Guttman bodies are seen → Concrete basophilic calcifications around the microorganism.

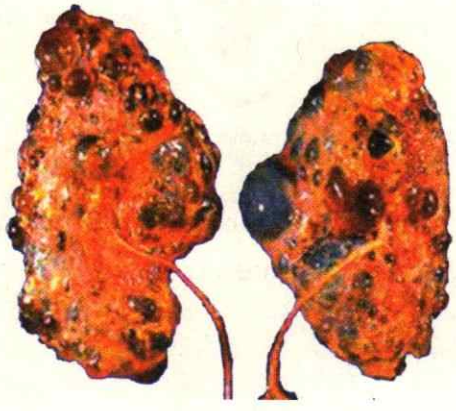
Defect of macrophage function.

Caused by E.coli infection.

Gross appearance : Yellow plaque lesions.



Polycystic kidney disease (PCKD) 00:28:34

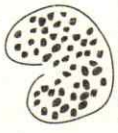


Active space

Based on the onset of the disease :

Adult	Infantile
Autosomal dominant	Autosomal recessive
Chromosome 16. PKD 1, 2, 3 gene → Encodes polycystin.	Chromosome 6. PKHD gene → Encodes fibrocystin.
Larger cysts, seen outside as well.	Smaller cysts, usually present inside.
Complications : Mitral valve prolapse. Aortic dissection. Berry aneurysm of Circle of Willis. Increased risk for developing colonic diverticula. Cysts in other organs like pancreas, spleen.	Association : Congenital hepatic fibrosis.

Gene for HLA : Chromosome 6p.

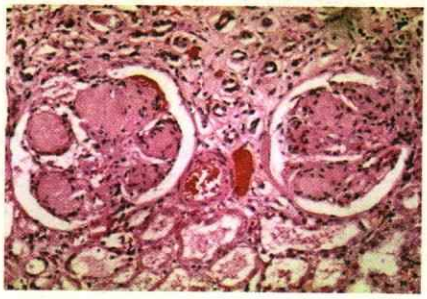
Disease	Inheri-tance	Pathologic Features	Clinical Features / Complications	Typical Outcome	Diagram
Adult polycystic kidney disease	AD	Large multi cystic kidneys, liver cysts berry aneurysm	Hematuria, flank plan urinary tract infection renal stones, hypertension	Chronic renal failure beginning at 40-60 years of age	
Childhood polycystic kidney disease	AR	Enlarged, cystic kidneys at birth	Hepatic fibrosis	Variable, death in infancy or childhood	

Active space

Medullary sponge Kidney	None	Medullary cysts on excretory urography	Hematuria. UTI, recurrent renal stones	Benign	
Familial juvenile nephro-nophthisis	AR	Cortico-medullary cysts, shrunken Kidneys	Salt wasting, polyuria, growth retardation anemia	Progres-sive renal failure be-ginning in childhood	
Multicys-tic renal dysplasia	None	Irregular Kidneys with cysts of variable size	Association with other renal anomalies	Renal failure if bilateral, surgically curable if unilateral	
Acquired renal cystic disease	None	Cystic degen-eration in ESRD	Hemorhage, erythrocytosis, neoplasia	Depen-dence on dialysis	
Simple cysts	None	Single or multiple cysts in normal sized Kid-neys	Microscopic hematuria	Benign	

Q. A 45 year old women presents with blurring of vision and massive proteinuria. Fundus examination of eye revealed microaneurysms, cotton wool spots. The patient is also found to have microalbuminuria. Renal biopsy is shown below. Most likely diagnosis is :

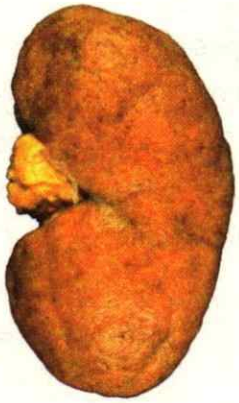
A. Amyloidosis.
B. Wire loop lesions.
C. Crescentic glomerulonephritis.
D. Kimmelstiel Wilson lesion.



Active space

Q. The morphological image of the kidney is shown below. This appearance is associated with which condition?

A. Renal amyloidosis.
B. Chronic glomerulonephritis.
C. Chronic pyelonephritis.
D. Malignant hypertension.



Flea bitten kidney seen in malignant nephrosclerosis.
Renal amyloidosis : Waxy appearance.

Chronic glomerulonephritis : Symmetrically shrunken kidney.
Chronic pyelonephritis : Asymmetrically shrunken kidney.

Q. A 70 year old woman has had a fever for the past 3 days. She has burning dysuria. On physical examination her temperature is 37.8°C and there is dull pain on palpation of her left lower back. Laboratory studies show Hgb 13.3 g/dL, Hct 40.2%, and WBC count 12,300/microliter with differential count 72 segs, 9 bands, 13 lymphs, 5 monos, and 1 eosinophil. A urine dipstick analysis shows sp gr. 1.017, pH 6, leukocyte esterase positive, nitrite positive, protein negative, glucose negative, and blood negative. Which of the following microscopic urinalysis findings would be most diagnostic for her renal disease?

A. Dysmorphic red blood cells.
B. Oval fat bodies.
C. Renal tubular epithelial cells.
D. White blood cell casts.

Dysmorphic red blood cells → Glomerulonephritis.
Oval fat bodies → Nephrotic syndrome.

Active space

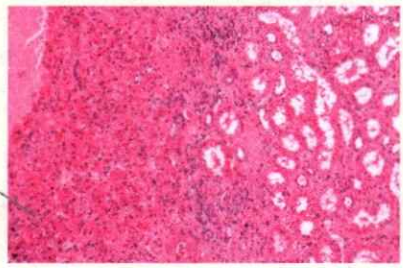
KIDNEY TUMORS

Types of kidney tumors

00:00:12

Types :
Benign :
Angiomyolipoma.
Oncocytoma.
Malignant :
In child : Wilm's tumor.
In adult : Renal cell carcinoma.

Renal oncocytoma :
Arises from intercalated cells of collecting duct.
Gross appearance : Tan, mahogany brown.
Microscopy : Cells with abundant eosinophilic granular cytoplam (excess of mitochondria).
Electron microscopy : Excess of mitochondria.
Other disease with oncocytic cells : Hashimoto's thyroiditis.



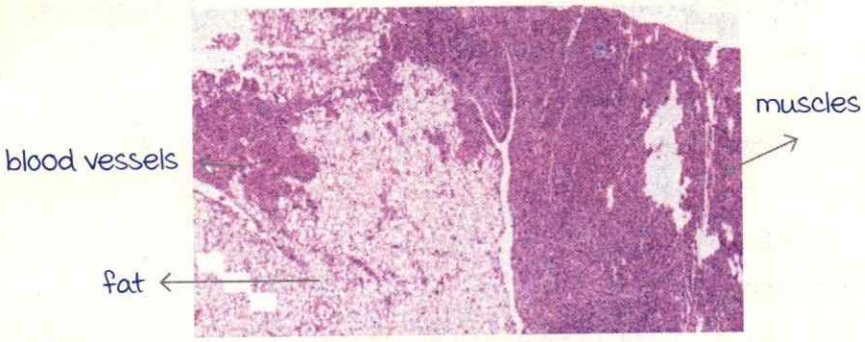
Angiomyolipoma

0:04:10

Syndrome associated : Tuberous sclerosis.
Other tumor associated with tuberous sclerosis : Cardiac rhabdomyoma.

Cardiac rhabdomyoma :
Spider cell in microscopy.
In 50% associated with tuberous sclerosis.
Skin lesions : Shagreen patch, ash leaf macule.
In microscopy of angiomyolipoma : Vessel + muscle + fat.

Active space



Wilm's tumor

0:06:55

Malignancy of childhood.
Also known as nephroblastoma.
Seen in 2 to 5 years of age.
Presents as abdominal mass.
(Neuroblastoma also presents as abdominal mass).

Genetics :

WT1 on chromosome 11p 13.
WT2 on chromosome 11p 15.

These are tumor suppressor genes, hence loss of function mutation.

Precursor lesion : Nephrogenic cell rest.

Syndromes associated with wilm's tumor :

- WAGR syndrome : Wilm's tumor, Aniridia, Genital abnormalities, mental Retardation.
- Deny Drash syndrome :
  Mutation on WT1 gene on chromosome 11 p 13.
  Contain :
  Wilm's tumor.
  Gonadal dysgenesis.
  Diffuse mesangial sclerosis.
- Beckwith Weidman syndrome :
  Defect in WT2 on chromosome 11 p 15.
  Symptoms :
  Hemihypotrophy (organs in one half of body enlarges).
  Macroglossia
  (In amyloidosis : Tongue biopsy done.

Active space

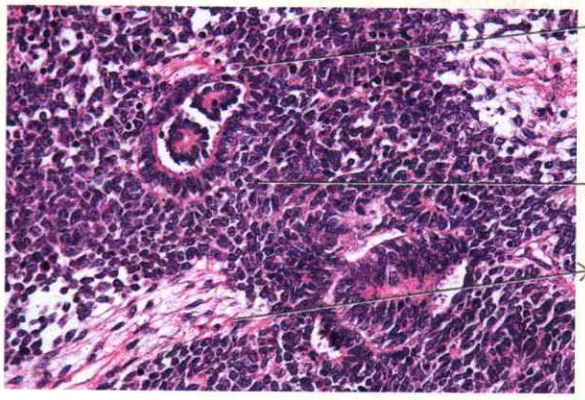
Best biopsy site in amyloidosis : Abdominal fine fat aspirate.
Second best : Rectal biopsy.
Third : Tongue biopsy.)

Heptoblastoma.
Adrenocortical neoplasms.
Wilm's tumor.

Microscopy :

Triphasic tumor (3 element/foci seen) :

Epithelial : As gland/tubules/rosettes formation.
Mesenchymal : As spindle shaped cells.
Blastemal (primitive element).



Due to presence of blastemal component, it is an example of small round blue cell tumor of childhood.

Prognostic factor : Histologic anaplasia.

If present :

Poor prognosis.
p53 mutation.
Chemoresistant.

Nephrogenic cell rests :

Possibility of tumor in contralateral kidney.
Precursor lesion.

Renal Cell Carcinoma (RCC) 0:17:10

Average age of presentation : 60 to 70 years.
Males >> females.
Also known as :

Active space

Renal adenocarcinoma.

Hypernephroma.

Grawitz tumor.

Risk factor :

- Smoking (most important).
- Obesity.
- Petroleum products.
- Chronic kidney disease/dialysis.
- Asbestos.

Clinically :

Triad :

Flank pain.

Hematuria.

Abdominal mass.

Paraneoplastic syndrome :

Hypercalcemia.

Polycythemia.

Increased ESR.

Stauffer syndrome : RCC + hepatic dysfunction.

Histological types :

- Clear cell RCC.
- Papillary RCC.
- Chromophobe RCC.
- Collecting duct/Bellini duct RCC.

Clear cell carcinoma 00:21:50

most common type of RCC.

Solitary & Unilateral .

Genetics :

VHL (Von Hippel–Lindau) gene mutation on chromosome 3.

Arises from PCT.

Microscopy :

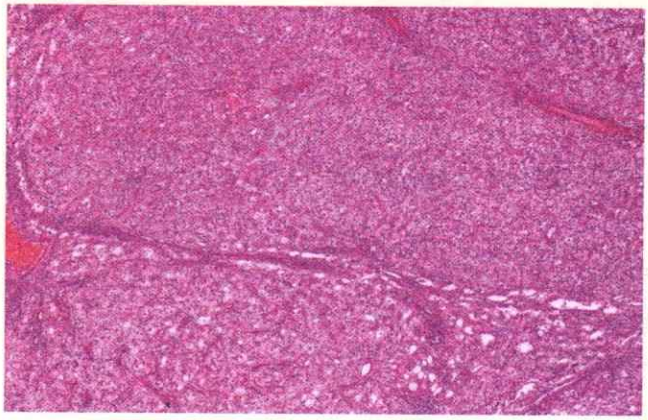
Sheets of cells with clearing due to fat & glycogen.

PAS positive : Due to glycogen.

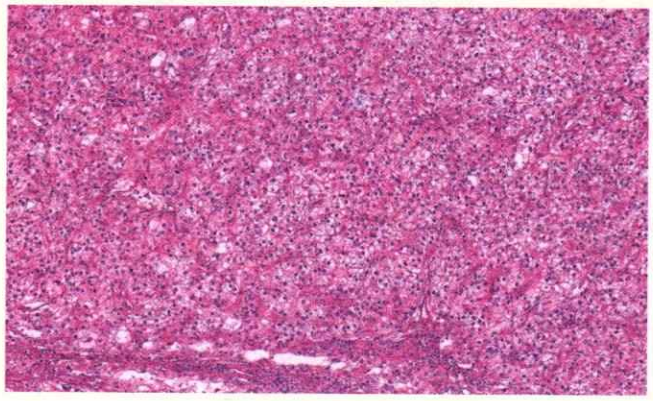
Oil Red O positive : Due to fat.

Active space

Low power focus :



High power focus : Clear cell seen.



Papillary renal cell carcinoma

00:24:24

2nd most common RCC .

Arises from PCT or DCT.

Usually bilateral (multicentric).

Seen in dialysis patient (long term).

A beta 2 microglobulin amyloid is seen in patient on dialysis.
(as it cannot be filtered by dialysis membrane).

Types :

- Hereditary papillary RCC (HP-RCC).
- Hereditary Leiomyomatosis papillary RCC (HL-PRCC) :
  Due to fumarate hydrotase deficiency.

Genetics :

Loss of Y chromosome.

Trisomy of chromosome 7 & 17.

Active space

Microscopy :

Papillae : Finger like projections with fibrovascular core.

Presence of foamy macrophages/foamy histiocytes lined papillae (no typical fibrovascular core).

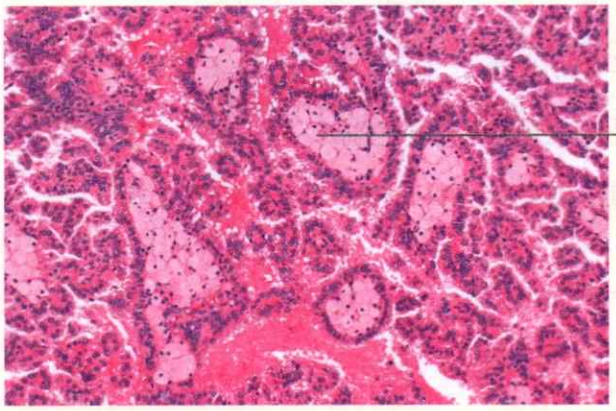
Psammoma bodies :

Foci of dystrophic calcification.

Is also seen in :

- Papillary carcinoma thyroid.
- Meningioma.
- Prolactinoma.
- Papillary serous cystadenocarcinoma of ovary.
- Mesothelioma.

Calcium : Densely basophilic.



Chromophobe RCC 0:28:38

Best prognosis.

Arises from intercalated cells of collecting duct .

Associated with Birt Hogg Dube Syndrome (due to BHD gene mutation).

Genetics : Hypodiploidy.

Loss of chromosomes.

Microscopy :

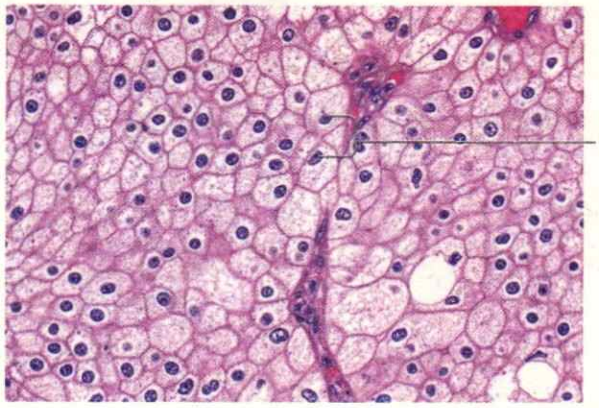
Polygonal cells with well defined boundaries.

Resinoid nucleus : Also seen in Koilocytes

Perinuclear halo.

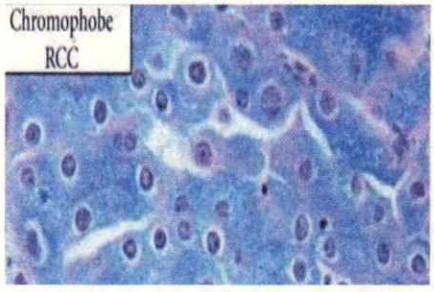
Active space

Plant like appearance.



Resinoid nucleus.

Special stain used : Hale's colloidal iron stain.



Collecting duct carcinoma

0:32:31

Arises from collecting/Bellini duct.

Least common.

Worst prognosis.

Microscopy :

- Hobnail cells.
- Desmoplasia (extreme fibrous, very hard).

Medullary RCC

0:33:45

Associated with sickle cell trait.

Due to :

- SMARC B gene deficiency.

Translocation Xp11.2 RCC :

- Can be due to TFE3 gene mutation.
- Associated with childhood RCC.

Active space

MCQs :

Q. Hobnail pattern is seen in which type of RCC ?

A. Clear cell.

B. Papillary.

C. Chromophobe.

D. Collecting duct cancer.

Q. A 45 year old man presented with painless hematuria. Bimanual examination revealed a mass over the right flank. Right nephrectomy was done and the mass was seen to be composed of cells with clear cytoplasm. Areas of hemorrhage and necrosis are seen. Cytogenetic analysis of the mass reveals the following abnormality :

A. Chromosome 1

B. Chromosome 3 (VHL gene)

C. Ch 11

D. Ch 17

Diagnosis : Clear cell RCC.

Q. A 3 year old child has become more irritable over the past two months and does not want to eat much at meals. On physical examination the pediatrician notes an enlarged abdomen and can palpate a mass on the right. An abdominal CT scan reveals a 10 cm solid mass involving the right kidney. The resected mass has a microscopic appearance with sheets of small blue cells along with primitive tubular structures. The child receives chemotherapy and radiation therapy, and there is no recurrence. Which of the following neoplasms is this child most likely to have had ?

A. Angiomyolipoma.

B. Renal cell carcinoma.

C. Urothelial carcinoma.

D. Wilms tumor.

E. Medullary fibroma.

Active space

MALE GENITAL - PENIS AND PROSTATE

Penis

00:00:40

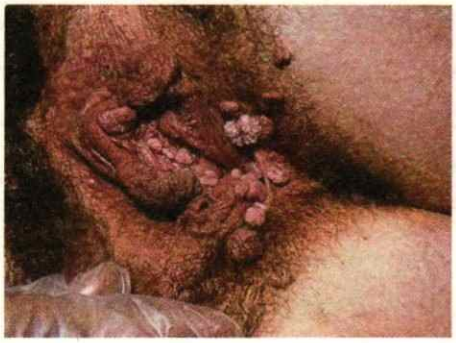
Neoplastic lesions :

Genital warts :
AKA condyloma acuminatum.

Cauliflower like growth.

Causative factors :
HPV 6 & 11 (low risk).

Condyloma acuminatum



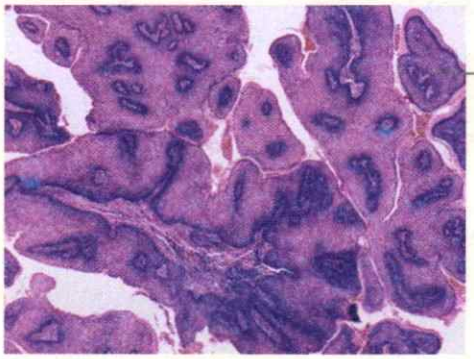
Pathogenesis :
HPV produces 2 proteins E6 & E, that will bind to tumor suppressor genes p53 and Rb respectively, suppressing both of themleading to formation of neoplasm.

Clinical features :
Red, velvety excrescences on the glans or inner surface of prepuce.

HPE/Histopathological examination :

- Koilocytic change → Large cells with thick membrane, raisin like nucleus and perinuclear halo.
- Branching villus pattern.
- Acanthosis, hyperkeratosis.

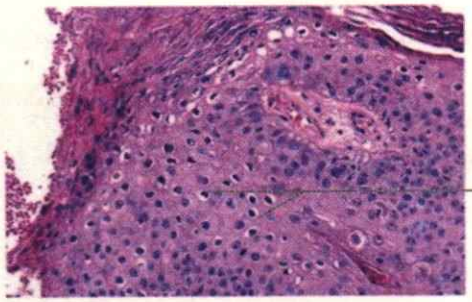
Genital warts



→ Thickening of epithelium

Active space

Genital warts



Koilocytes with perinuclear clearing.

Pre-malignant lesions of penis 00:07:07

They are namely :

- Bowen's disease.
- Bowenoid papulosis.
- Erythroplasia queyrat → Presents with tiny red papules on the penis.

Bowen's disease	Bowenoid papulosis
Elderly.	~35 years/sexually active individuals.
Solitary.	multiple papules.
Approximately, 10% changing into cancer.	Regresses spontaneously or low risk.

Squamous cell carcinoma/SCC of penis 00:09:09

Usually seen in people 40-50 years of age.

Risk factors :

- Poor genital hygiene.
- HPV 16, 18.

Site → Shaft of penis.

HPE :

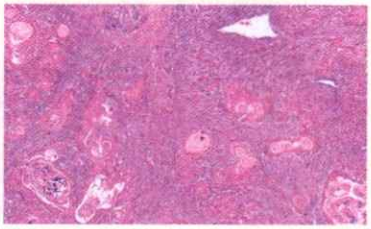
- Keratin pearls → Squamous cells secrete excess of keratin which sometimes take up a pearl like

Active space

configuration.

- Desmosomes : Are the inter-digitating bridges between 2 squamous cells (seen on high power).

Well differentiated SCC



Well differentiated SCC will have well defined Keratin pearls along with desmosomes.

If the patient has moderately differentiated SCC the pearls will be very less there will individual cell Keratinization.

If it is poorly differentiated SCC no pearls or Keratin is seen, therefore Cytokeratin (CK) an IHC marker is used.

Verrucous carcinoma of penis :

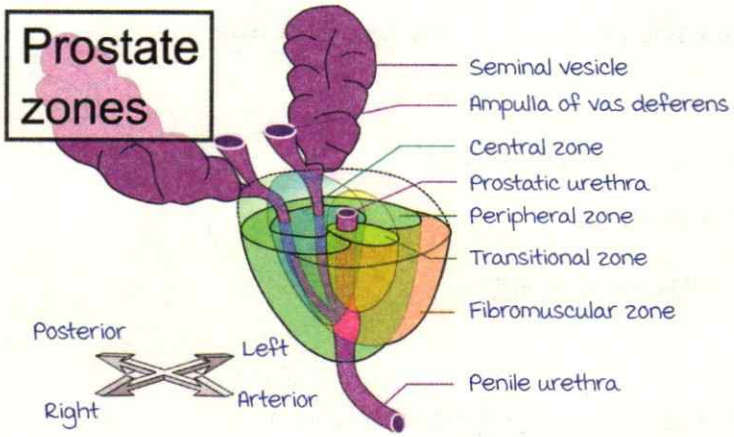
Is a variant of SCC.
It is very superficial and not infiltrative.

∴ Has a good prognosis.

Prostate

00:13:12

Normal weight = 20 gm.
most carcinomas arise in the peripheral zone.
most BPH arise in the transitional zone.



Active space

As carcinomas arise from the peripheral zone and it is far from the urethra, urinary symptoms like dysuria, urinary frequency etc. does not happen early, it presents with very late symptoms in prostatic adenocarcinoma : Late diagnosis.

On the contrary, the transitional zone is very near to prostatic urethra and the patient often presents with urinary symptoms like urinary frequency, urinary urgency or nocturia quite early : Early diagnosis.

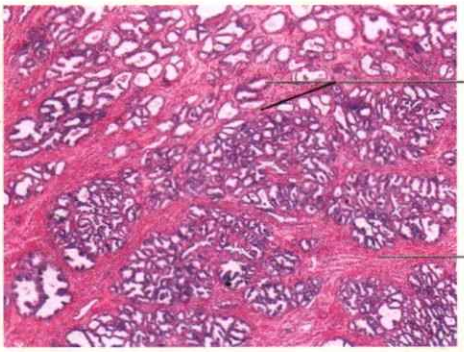
Normal microscopy of prostate :

Prostate gland is made up of fibromuscular stroma interspersed with glands lined with 2 layers of cells : Epithelial lining & below that the myoepithelial layer/basal layer.

If the myoepithelial layer or basal layer is absent : Indicative of prostatic cancer.

The myoepithelial layer is P-63 positive, and hence can be used to visualize the layer. In prostatic adenocarcinoma as this layer is absent it will be P-63 negative.

Prostate



Benign prostatic hyperplasia/BPH 00:18:35

Now called as the nodular hyperplasia of prostate.

Most common prostatic disease.

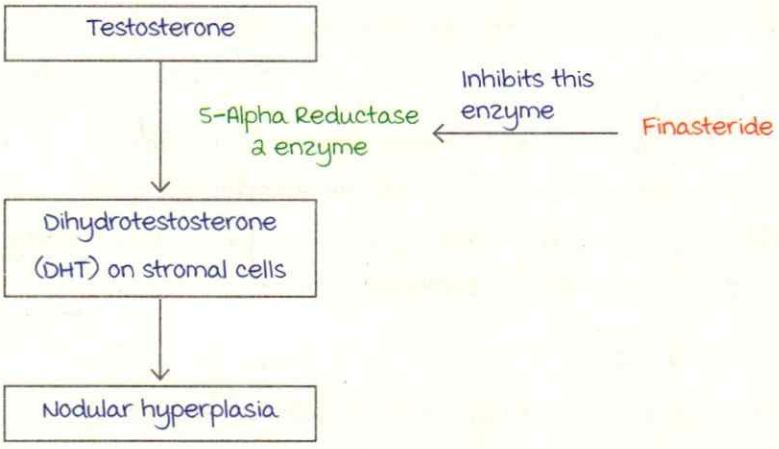
Mostly affects the elderly.

Clinical features : Dysuria, increased frequency of urine, nocturia.

Not a pre-malignant condition.

Active space

Pathogenesis :



Finasteride is the drug used in medical therapy of BPH as it inhibits the enzyme 5-Alpha Reductase 2.

Gross examination of BPH specimen :

Weight = 60-80gms.

White and nodular.

HPE :

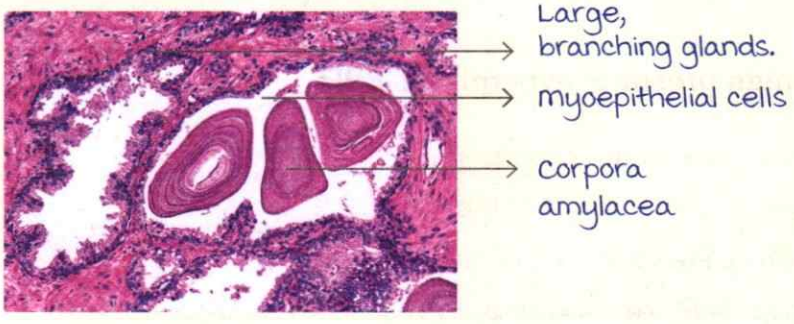
There is an increase in glands and stroma.

Myoepithelial layer is present.

Hyperplasia causes the glands to undergo papillary infoldings.

Corpora amylacea : Pink colored prostatic secretions/ pigments are secreted. They increase the risk of calcium phosphate stones.

BPH



The glands are large, branching. Some with papillary configuration.

Active space

Prostate adenocarcinoma 00:25:13

Risk factors are :

- Age → more common as the patient ages.
- High fat diet.
- Racial preponderance in blacks > whites.

Genetic factors :

- BRCA 2 gene mutation.
- Loss of E-cadherin.
- Hypermethylation of glutathione S transferase.
- Chromosome rearrangement that juxtaposes the TMPRSS 2 gene (androgen receptor gene) with ETS fusion gene.

Protective factors :

- Vitamin D.
- Selenium.
- Lycopene.
- Soy products.

Usually affects the peripheral zone and does not compress the urethra and therefore has no urinary complaints early.

The patient usually presents with bone pain as this tumor usually metastasizes to the bone and produces osteoblastic secondaries.

Lumbar spine is most affected, and patient presents with back pain.

Any clinicopathological question, with history of elderly male patient, complaining of back pain with osteoblastic secondaries, one differential diagnosis is prostatic adenocarcinoma.

Gross morphology :
It is a grey-white tumor.

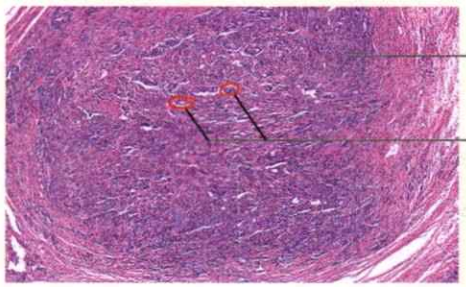
HPE :

- Small back to back glands.
- Less stroma.

Active space

- myoepithelial/ basal layer is absent.
- Perineural invasion : Poor prognosis.
  Other cancers perineural invasion is important :
  Adenoid cystic carcinoma of the salivary gland and pancreatic cancer.

Prostate adenocarcinoma



If not able to appreciate the presence or absence of myoepithelial/basal layerunder high power, IHC markers are used.

They are as follows :

- P-63 negative.
- AMACR is positive in prostatic adenocarcinoma.

Tumor markers in case of prostate cancer :

- PSA/Prostate specific antigen : Important marker in diagnosis of prostatic adenocarcinoma.
- PAP/Prostate acid phosphatase.

New biomarkers used are : PCA 3, NKX 3.1.

PSA

00:33:15

It is organ specific, however not tumor specific.
∴ PSA can be raised in other prostatic diseases also like BPH, prostatic calculi or any instrumentation of the prostate.

Variants of PSA :

- Age specific PSA :
  Different normal ranges of PSA at different ages :
  1. 40-49 years → 2.5 ng/ml.
  2. 50-59 years → 3.5 ng/ml.

Active space

3. 60–69 years → 4.5 ng/ml.
4. 70–79 years → 6.5 ng/ml.

If levels are more than this, patient has to undergo further evaluation.

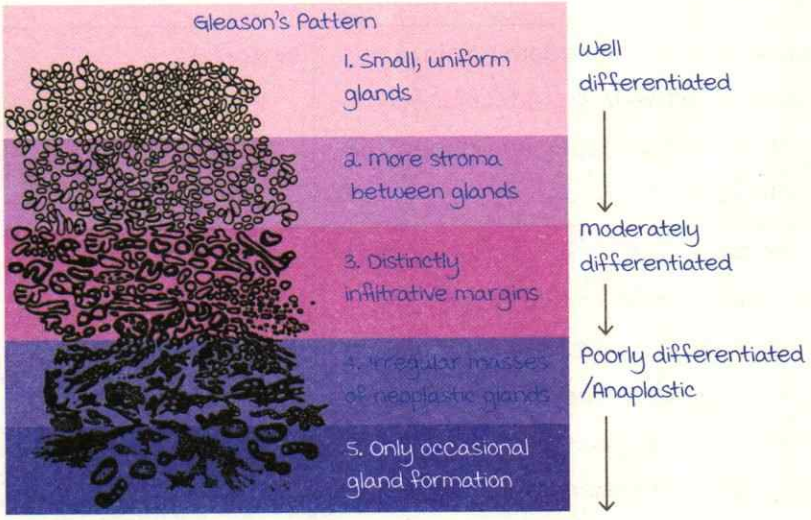
- PSA density = $\frac{\text{Serum PSA}}{\text{Volume of gland}}$
- PSA velocity : Rate of change of PSA per year
  <0.75 ng/mL/year implies no cancer.
- Rate of free PSA to bound PSA.

Gleason's score

00:37:43

Important prognostic factor for prostatic adenocarcinoma. 5 different patterns are given based on the architecture and morphology of the glands.

They are as follows :



Gleason's score = Primary dominant pattern + Secondary dominant pattern.

For example, on a slide if there are some glands with stroma in between, the Gleason's score will be 2. In the next foci, suppose there are few cells infiltrating with no gland formation, the Gleason's score will be 4.

∴ The patient's Gleason's score = 2+4 = 6.

Active space

If only one pattern is visible on the slide, the Gleason's score will be double that number.

Also, 2+3 has a better prognosis than 3+2. This is because, in 2+3 the lesser score is the dominant pattern whereas, in 3+2 the higher score is the dominant pattern.
∴ 2+3 better prognosis than 3+2.

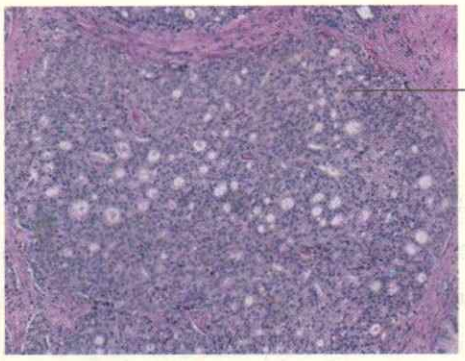
Latest guidelines for grading tumor based on these scores is as follows :

Traditional Gleason score	New grading system group I
Gleason 3+3=6. Only individual discrete well-formed glands.	Grade I
Gleason 3+4=7. Predominantly well-formed glands with a lesser component of poorly-formed/fused/cribiform glands.	Grade 2
Gleason 4+3=7. Predominantly poorly-formed/ fused/cribriform glands with a lesser component of well-formed glands.	Grade 3
Gleason 4+4=8. Only poorly formed/ fused/cribriform glands or Predominantly well-formed glands with a lesser component lacking or Predominantly lacking glands with a lesser component of well-formed glands.	Grade 4
Gleason 9-10. Lacks gland formation (or with necrosis) with or without poorly-formed/fused/ cribriform gland.	Grade 5

Active space

Q) The Gleason's score of the following slides :

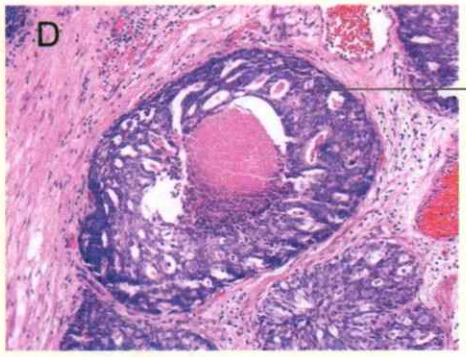
1)



→ Cribriform pattern with cookie cutter spaces.

It shows cribriform pattern with cookie cutter spaces, ∴ the score will be 4; since that is the only pattern visible the Gleason's score will be 4+4 = 8 i.e., Grade 4.

2)



→ Comedo pattern

It shows comedo pattern, which is Gleason's grade 5.
Any single cell infiltration without gland formation is grade 5.

Q. A 69 year old man presents to his primary care physician for annual examination. He reports new onset lower back pain. He also talks about unintentional weight loss and night sweats. He has tenderness on palpation of his lumbar spine. Digital rectal examination is notable for asymmetric and nodular prostate. Prostate specific antigen level is elevated at 40ng/ml. Radiography from his lumbar spine demonstrates lytic bone lesions. The biopsy from the prostate shows predominantly cribriform glands with a minor component of small well-formed glands. What Gleason grade does this tumour belong to?

Active space

A. Grade 2.

B. Grade 3.

C. Grade 4.

D. Grade 5.

Q. Prostate needle biopsy by a core needle biopsy shows adenocarcinoma with poorly formed glands in a cribriform pattern. Glands are crowded but separated and there is a minor 5% single cell infiltration. Which grade does it belong to?

A. Grade 2.

B. Grade 3.

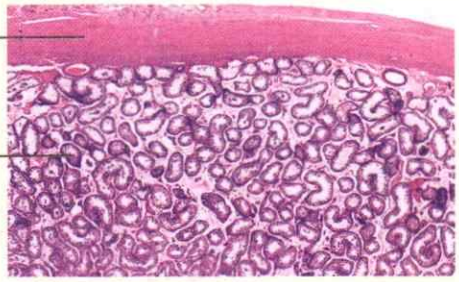
C. Grade 4.

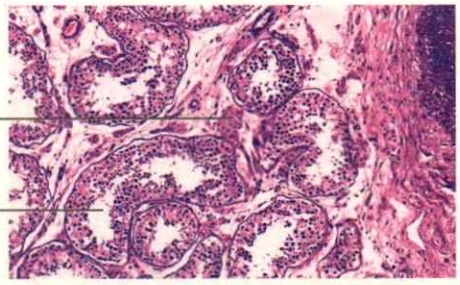
D. Grade 5.

Active space

TESTIS

Normal testicular histology :





Cryptorchidism 00:02:24

Undescended testis.

Failure of descend of intra-abdominal testis into the scrotal sack.

Most common site of arrest : _ _ _ _ _ _ _ _ _ _ _ _ _ _

Increases risk of testicular tumors.

Histopathology on testicular biopsy :

Testicular atrophy.

Thickening of basement membrane.

Sertoli cells present, but no spermatogenesis.

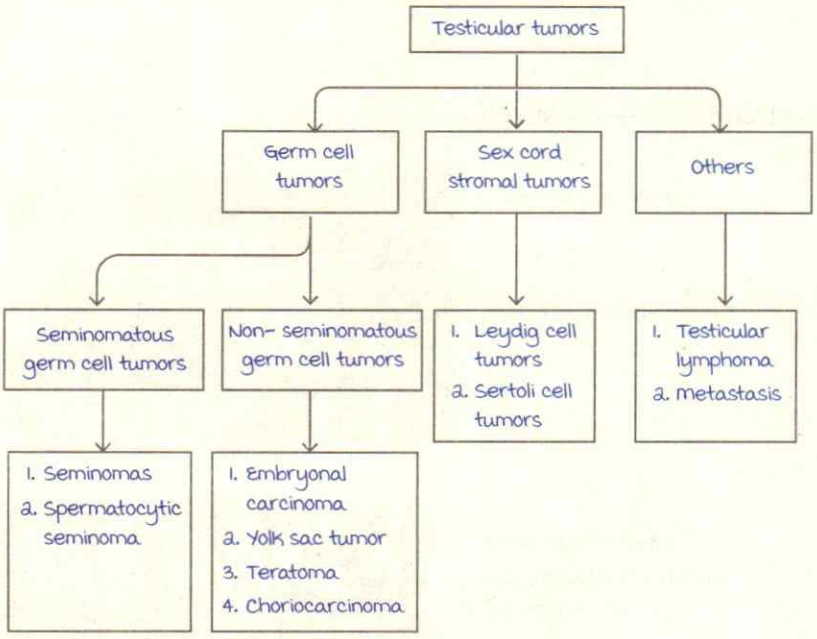
Leydig cell hyperplasia.

Infections that can affect testis : Syphilis and mumps.

Active space

Testicular tumors

00:04:50



Risk factors for testicular tumors :

1. Family history of testicular cancer.
2. Testicular dysgenesis syndromes.
   - Cryptorchidism.
   - Klinefelter syndrome.
3. Exposure to chemicals like pesticides.
4. Genetic factors like presence of isochromosome 12p (i 12p).

Precursor lesions for testicular tumor :

ITGCN : Intratubular germ cell neoplasm.

- Now called Germ Cell Neoplasia In Situ (GCNIS) : Identified using PAS staining to assess if basement membrane has been breached.
- Does not invade the stroma.
- Can lead to all testicular cancers except teratoma and spermatocytic seminoma.

Active space

Germ cell tumors

00:10:24

Seminomatous germ cell tumors	Non-seminomatous germ cell tumors
Age : 20 - 30years	Age : Usually elderly, can occur infants and children as well
Radiosensitive	Radioresistant, but chemo sensitive
Usually metastasize by lymphatic route	Usually metastasize by hematogenic route
Better prognosis	Poor prognosis

FNAC and testicular biopsy are contraindicated for testicular cancer : Increased chance for the tumor to spread to other sites.

Testicular cancers are minimally treated by high inguinal orchidectomy.

Indication for testicular biopsy : Infertility (to see for spermatogenesis).

Fixative used for testicular biopsy : Bouin's fluid contains picric acid.

- Sperms remain intact.
- 10% neutral buffered formalin is not used as the sperms would be destroyed.

Seminoma

00:16:01

Age : 20 to 30 years old.

Most common type of testicular cancer in adults.

Radiosensitive.

Usually metastasizes by lymphatics.

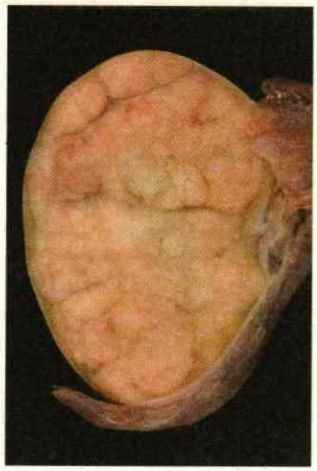
Clinically present with painless enlargement of testis.

Gross specimen : Bulky tumor.

Cut section is homogenous → Cut potato appearance.

- No areas of necrosis or hemorrhage.

Active space



Cut potato appearance

Histopathology :

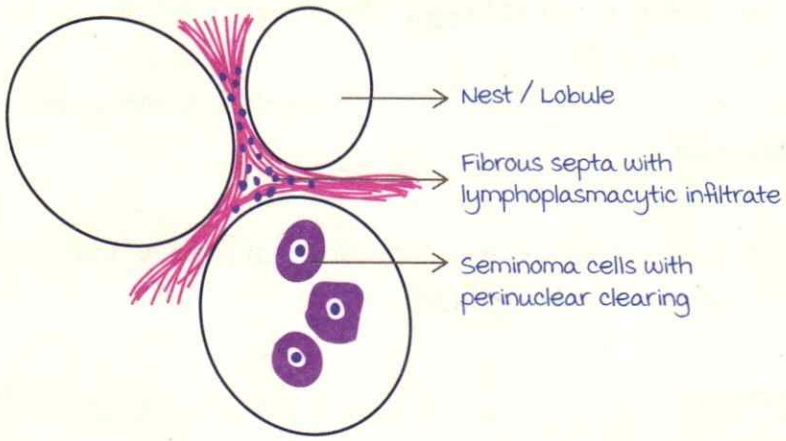
Cells are present in nests/lobules.

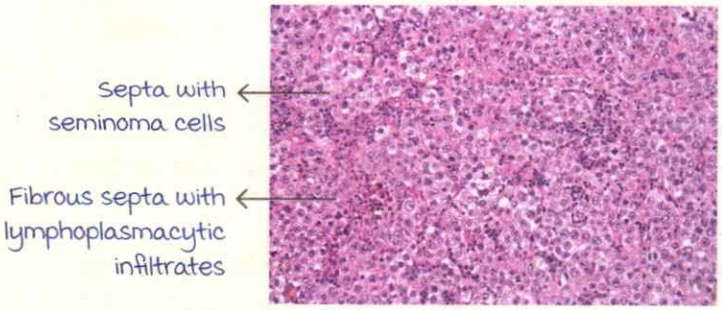
Nests are separated by fibrous septa.

Septa contains lymphoplasmacytic infiltrate.

Nests contain seminoma cells.

- Large polyhedral cells with central nuclei and perinuclear clearing.





Active space

Immunohistochemical (IHC) marker :

- Placental Alkaline Phosphatase (PLAP) +ve.
- 30% are HCG +ve : If syncytiotrophoblastic giant cells are present.
- Oct ¾
- Nanog.
- SALL4.
- AFP is never raised.

Spermatocytic seminoma :

Age > 60 years.

ITGCN is not a precursor.

Well differentiated tumor.

Good prognosis.

No metastasis.

HPE shows small cells, medium cells and giant cells.

Non- seminomatous germ cell tumors 00:25:28

Yolk sac tumors :

Age : Infants and children.

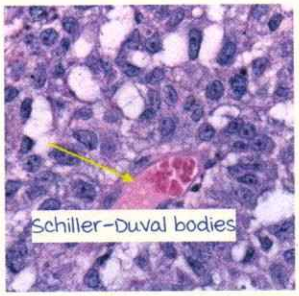
most common malignancy in children < 4 years of age.

Also called endodermal sinus tumor.

Gross appearance : Areas of hemorrhage, necrosis and cystic appearance (variegated appearance).

HPE :

- Cells arranged in cords/tubules/sheets.
- Schiller Duval bodies/ glomeruloid bodies.
- Eosinophilic hyaline globules.



Glomeruloid bodies are seen in :

1. Yolk sac tumor.
2. Glioblastoma multiforme.

IHC markers :

Active space

AFP.

AFP positive tumors :
1. Yolk sac tumors.
2. HCC.
3. Hepatoblastoma

Alpha 1 antitrypsin.

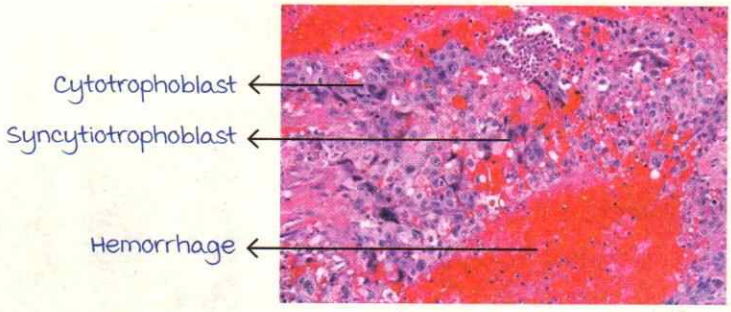
Choriocarcinoma

00:31:05

Age ~ 60 years, elderly.
Usually metastasizes by hematogenous route to lungs : cannon ball mets.
Aggressive germ cell tumor.
Not radiosensitive, but is chemosensitive.
Does not enlarge the testis as seminoma.

Gross appearance :
Huge areas of hemorrhage and necrosis.

HPE :
Cytotrophoblasts : Mononuclear cells.
Syncytiotrophoblasts : Giant cells.
IHC markers : HCG +ve.



Hemorrhagic appearance of choriocarcinoma

Embryonal carcinoma :
Age : 20–30 years.
Gross appearance : Cystic areas, mucinous areas.

Active space

HPE :

Primitive appearing cells.

- Arranged in cords or papillaroid configuration.

IHC markers : CD30 +ve.

- Also positive in Hodgkin's lymphoma.

Teratoma 00:36:53

Tumor with derivatives of ≥ 2 germ layers.

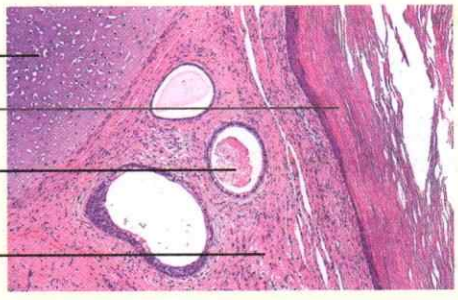
Dermoid cyst : When a teratoma becomes cystic.

Gross : Hair, bone, teeth, cartilage seen.

Rokitansky protuberance : Samples to be taken.

Dermoid cyst

HPE :



Types of testicular teratomas :

Prepubertal teratoma.

- Usually, benign.
- In females → Immature teratoma of the ovary.

Post pubertal teratoma.

- Usually, malignant.
- In females → Mature teratoma of the ovary.

Active space

- Malignancy detected by presence of immature, primitive or neural elements.
- Poor prognosis.

Sex cord stromal tumors

00:42:14

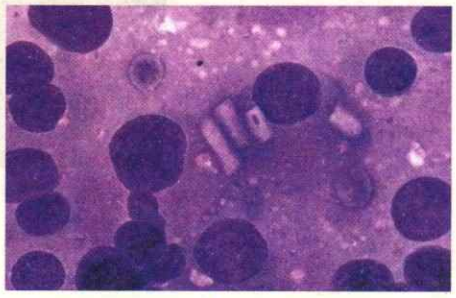
Leydig cell tumor :
Age : Middle age to elderly.
Secrete estrogen and androgens.
Clinical presentation :

- Feminization.
- Gynecomastia.
- Precocious pubery.

Gross specimen : Yellow brown in colour due to presence of lipofuscin.

HPE :

- Round cells with eosinophilic cytoplasm.
- Increased number of Reinke's crystals.



Reinke's crystals

Sertoli cell tumors :
Usually clinically silent.
IHC marker : _ _ _ _ _ _ _ _

Testicular lymphoma

00:45:18

Age > 60 years.
Most common testicular malignancy in elderly.
Diffuse large B-cell lymphoma.
Usually bilateral.
Poor prognosis.

Active space

Tumor	Histopathology	marker	Age
Seminoma	Cells in nodules, fibrous septae, lymphocytes	PLAP, oct3/4, Nanog, CD 117, HCG	20- 30 years
Yolk sac tumor	Schiller Duval bodies	AFP, Alpha 1 AT	< 4 years
Teratoma	Skin, bone, cartilage, teeth, hair		Any age
Chorio carcinoma	Cytotrophoblast, syncytiotrophoblast, no villi	HCG	> 60 years
Embryonal Ca	Primitive cells no villi	CD30+, CK+	Any age
Granulosa cell tumor	Call exner bodies Coffee bean nuclei		
Sertoli cell tumor		Inhibin	
Leydig cell tumor	Reinke's crystal		Any age
Lymphoma	DLBCL	Bcl-6	> 60 years

MCQs

Q. A 2-year-old boy is brought to the physician because his mother (a geometry teacher) has observed that his scrotum is no longer symmetrical. On physical examination the child has enlargement of the left testis. An ultrasound scan shows a 2 cm solid mass within the body of the testis. Laboratory studies show a serum alpha-fetoprotein of 226 ng/mL. Which of the following neoplasms is this child most likely to have?

A. Leydig cell tumor.
B. Neuroblastoma.
C. Rhabdomyosarcoma.
D. Teratoma.
E. Yolk sac tumor.

Active space

Q. A double blind study is conducted involving men who have been symptomatic from urinary frequency and hesitancy for 5 or more years. One group of men received a pharmacologic agent designed to reduce the synthesis of dihydrotestosterone in prostatic stromal cells. Another group received a placebo. The group receiving the drug has a statistically significant decrease in symptoms. Which of the following enzymes is this pharmacologic agent most likely to block?

A. 5-alpha-reductase.
B. Aromatase.
C. 17-alpha-hydroxylase.
D. Desmolase.
E. 11-beta-hydroxylase.

Q. Which of the following is not used as a tumor marker for germ cell testicular tumors?

A. AFP.
B. LDH.
C. HCG.
D. CEA.

AFP for yolk sac tumor.
LDH for seminoma.
HCG for choriocarcinoma.
CEA is a marker for colon or pancreatic cancer.

Q. A study is conducted to document testicular abnormalities in adult male patients with no major medical problems who had biopsies performed for infertility workups. In some of these cases, the patients have normal sized testes but microscopic examination showing a patchy pattern of atrophy of testicular tubules. Which of the following infections is most likely to produce the findings seen in these men?

A. Human papillomavirus.
B. Chlamydia trachomatis.
C. Neisseria gonorrheae.
D. Mumps virus.
E. Herpes simplex virus.

Active space

Q. A young man presented with a testicular mass and increased AFP levels. What is the likely diagnosis?

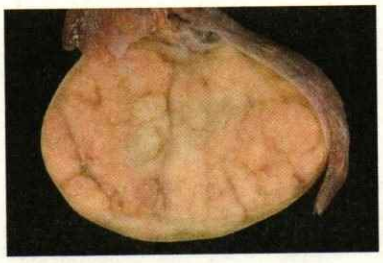
A. Choriocarcinoma.

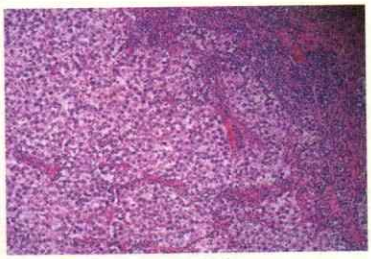
B. Teratoma.

C. Yolk sac tumor.

D. Seminoma.

Q. A 35 year old man presented with a painless testicular mass. Inguinal orchidectomywas done and the gross and histology is given below. What is the likely diagnosis?





A. Yolk sac tumor.

B. Seminoma.

C. Teratoma.

D. Testicular lymphoma.

Q. A 72-year-old man gets up several times during a football match to go to the restroom to urinate, even though he has had only one beer. This is a problem that has plagued him for 4 years. When he visits his physician for a checkup, on physical examination he has a diffusely enlarged prostate palpated on digital rectal examination. Laboratory studies show his serum prostate specific antigen is 6 ng/mL. Which of the following pathologic findings is most likely to be present in this man?

A. Adenocarcinoma.

B. Acute inflammation.

C. Multiple infarctions.

D. Nodular hyperplasia.

E. Granulomas.

Active space

FEMALE GENITAL TRACT : PART 1

Vulva

00:01:54

1. Paget's disease :

Also known as Extra mammary paget's disease.

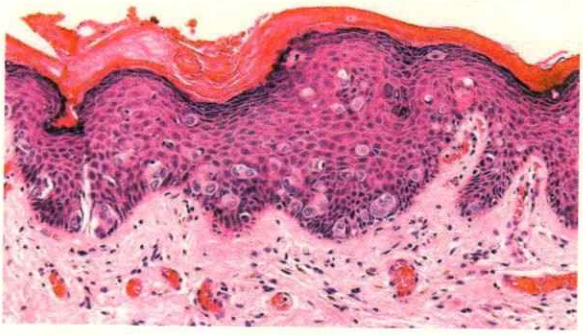
Microscopically : Presence of paget's cells.

- Central nuclei with perinuclear halo/ clearing.
- Halo/ clearing is due to glycogen/ fat : PAS & oil red O positive.
- Marker : CK7 positive.

Clinically presents as :

Erythematous ulcerated lesion on vulva, which is pruritic.

Not necessarily associated with malignancy.



Paget's disease of the vulva with Paget's cells

2. Condyloma acuminatum :

Cauliflower like growth.

Also called as genital warts.

Caused by HPV : low risk HPV 6, 11.

HPV in carcinogenesis :

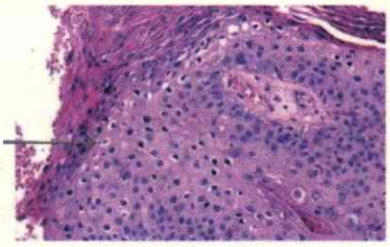
- HPV produces two proteins, E6 & E7.
- E6 combines with p53.
- E7 combines with Rb.
- This causes inactivation of these tumor suppressor genes.
- Causes cervical intraepithelial neoplasia, cancers.

Active space

Condyloma acuminatum

HPE : shows Koilocytes/ Koilocytic change.

- Thick membrane.
- Resinoid nucleus.
- Perinuclear halo.
- Produced due to ES.



Koilocytes

Cells with resinoid nucleus and perinuclear halo :

- Koilocytes.
- chromophobe RCC.

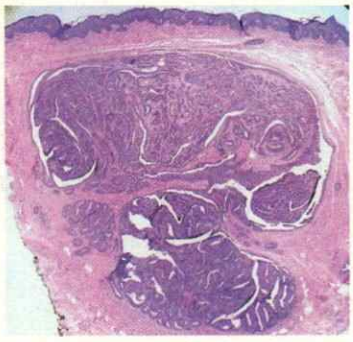
3. Intrapapillary hidradenoma :

Lesion with papillary configuration inside the epithelium.

Two layers of cells seen :

- myoepithelial layer seen, over which is the layer of tall columnar cells.

Looks similar to intraductal papilloma of the breast.



Intrapapillary hidradenoma

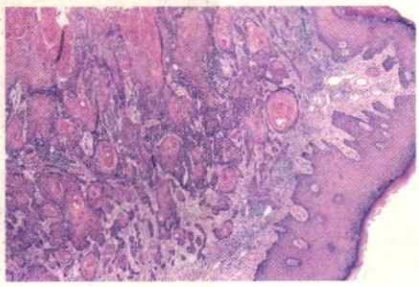
4. Squamous cell carcinoma (SCC) :

Presence of Keratin pearls.

Causative factors : HPV 16, 18.

Active space

IHC marker : cytokeratin (CK).



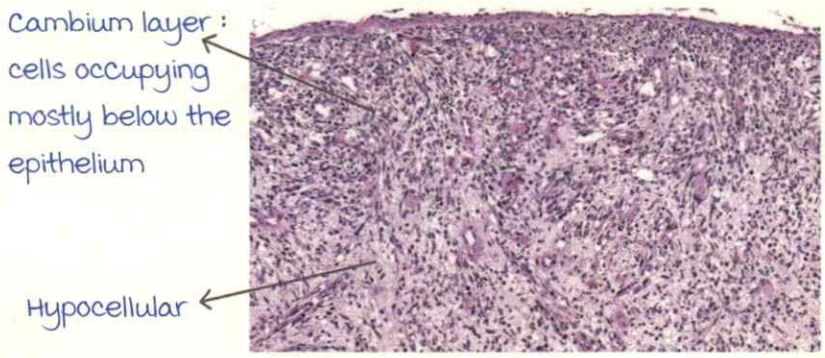
SCC

Lesions of the vagina

00:10:49

1. Embryonal rhabdomyosarcoma :
Also known as sarcoma botryoides.
Gross appearance shows grape like clusters.
Usually seen in children < 5years of age.

HPE :
Cambium layer : number of cells seen just below the epithelium.
The layers below are hypocellular.
Cells seen :
Strap cells/ tadpole cells/ tennis racket cells : small cells with eccentric nucleus & cytoplasmic protrusions.



Tennis racket in pathology :
- Embryonal rhabdomyosarcoma.
- Electron microscopy of Langerhans cell histiocytosis.

Special stain for embryonal rhabdomyosarcoma : PTAH.
IHC marker : Desmin / myo D1 / myogenin.

Active space

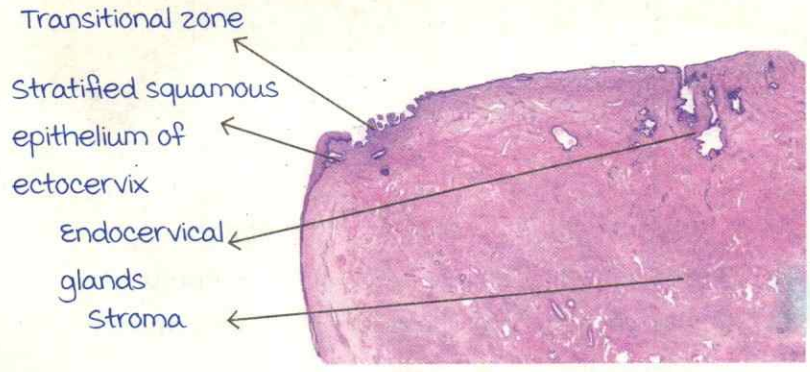
2. Clear cell carcinoma of vagina :

Diethyl stilbesterol exposure for mother during pregnancy can lead to clear cell carcinoma of vagina in daughter.

Lesions of cervix

00:16:29

Normal histology :



Ectocervix : Stratified squamous epithelium.

Endocervix : Glandular epithelium.

Transitional zone is also known as squamocolumnar junction.

1. Cervical intraepithelial neoplasia (CIN) :

Limited by the basement membrane.

PAS stain used to differentiate between CIN and invasive cancer.

- Intact pink coloured basement membrane ⟶ CIN.
- Breaks in the pink coloured basement membrane ⟶ Invasive cancer.

Caused by HPV.

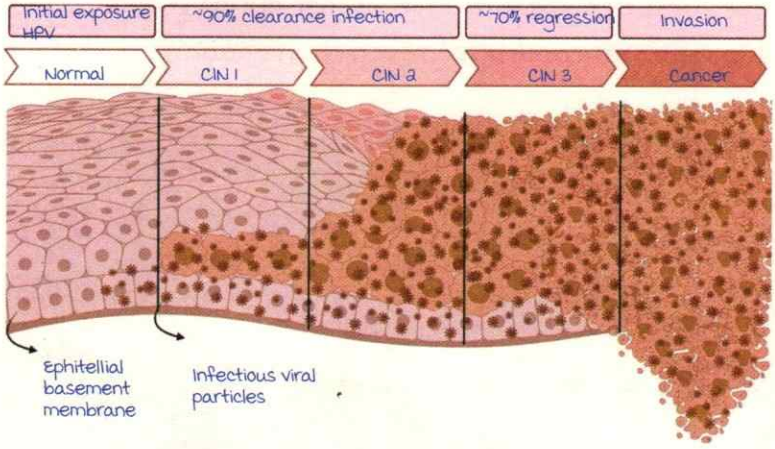
CIN I : Caused by HPV 6, 11.

CIN II & III : Can be also caused by HPV 16 & 18. ⟶ Higher risk for development into cervical cancer.

Shows koilocytic change in microscopy.

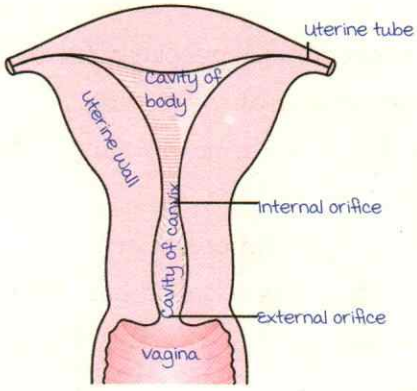
Active space

According to the older Bethesda classification :



- CIN I : Atypical cells in lower 1/3rd of the epithelium.
- CIN II : Atypical cells in lower 2/3rd of the epithelium.
- CIN III : Atypical cells involving entire thickness of the epithelium.
- Involvement of basement membrane: Invasive cancer.

Newer classification :



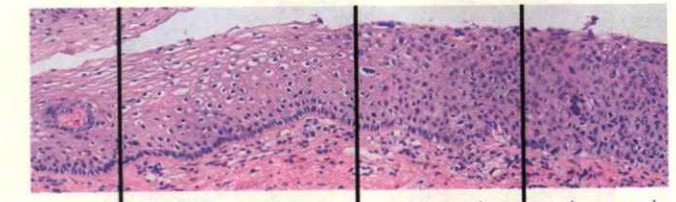
Based on the degree of atypia : LSIL & HSIL.

- Less pleiomorphic, not big in size, not that hyperchromatic nucleus, not prominent nucleus : Low grade squamous intraepithelial lesion (LSIL).
- Very pleiomorphic, large sized, hyperchromatic prominent nucleus : High grade squamous intraepithelial lesion (HSIL).

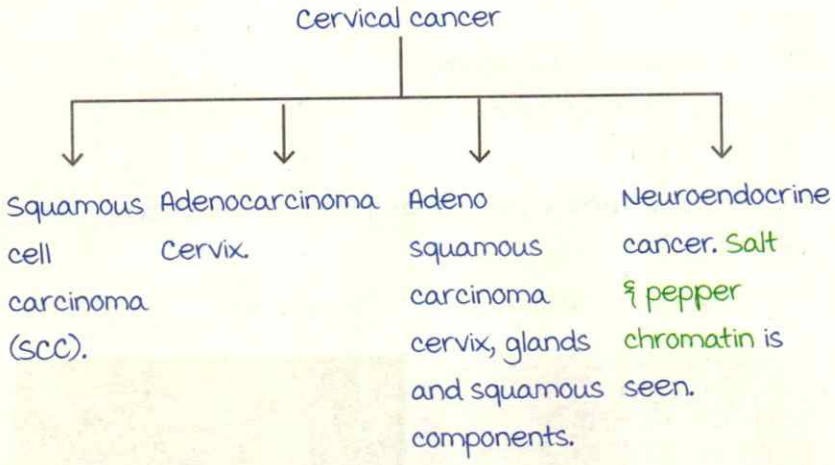
2. Cervical cancer :

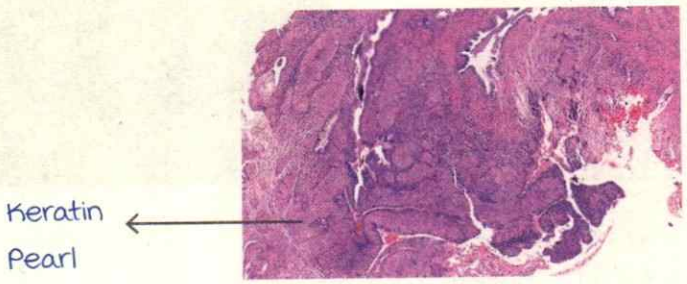
Most common is _____ adenocarcinoma of cervix.

Active space



Moderately differentiated SCC : Single cell keratinization.
Poorly differentiated SCC : Keratin pearls not seen.
Confirmed by IHC with cytokeratin.

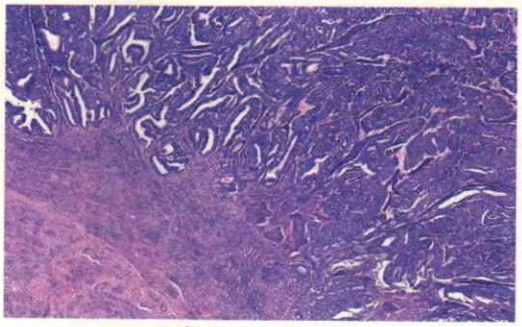




SCC

IHC markers for neuroendocrine tumors : NSE, chromogranin, synaptophysin.
IHC marker for cervical cancer : Ki67 (proliferative index), p16.
Vaccines for HPV for prevention of cervical cancer : Gardasil, Cervarix.

Active space

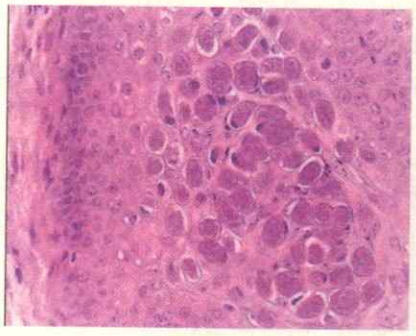


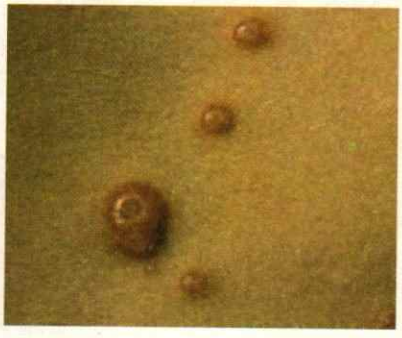
Adenocarcinoma

Q. A 15 year old girl shows the following. What is the most likely diagnosis?

A. Herpes simplex.
B. CMV.
C. Molluscum contagiosum.
D. Basal cell carcinoma.

Dimpled umbilicated lesions usually seen in molluscum contagiosum.
HPE : molluscum bodies in stratum granulosum.

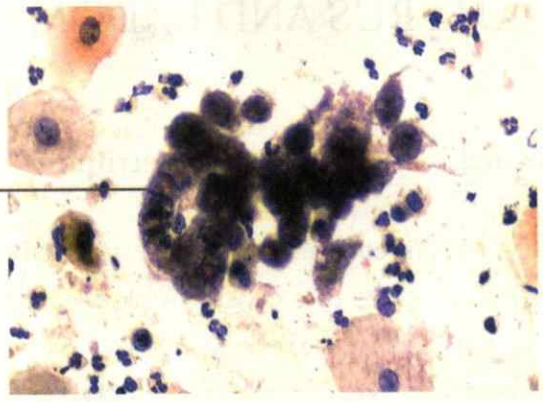




Herpes simplex :
Cowdry type A inclusions.
Genital herpes caused by HSV 2 shows these on microscopy :
3 M's.

- Margination of chromatin.
- Multinucleation.
- Molding.
- Ground glass cells.

Active space



Ground glasses in pathology :

1. HSV 2 infection.
2. Chronic hepatitis B infection shows ground glass hepatocytes.

CMV :

Shows owl's eye inclusion with basophilic nuclei.

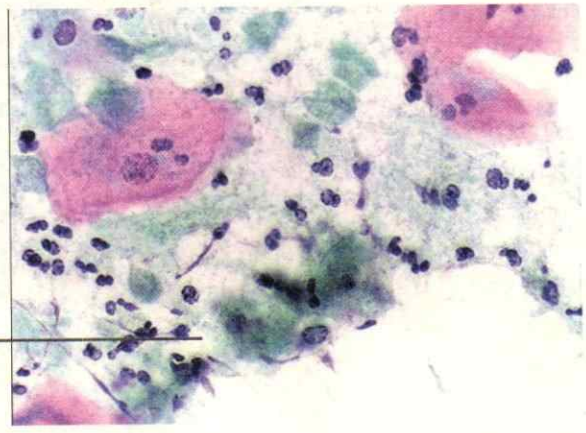
Basal cell carcinoma :

Nests of basaloid cells with peripheral pallisading and separation artifacts.

Q. A 33 year old female with foul smelling vaginal discharge. Pap smear shows the following.

Trichomonas vaginalis :

- Pear shaped or ovoid flagellate organism.
- Patient presents with foul smelling vaginal discharge and strawberry cervix.



Active space

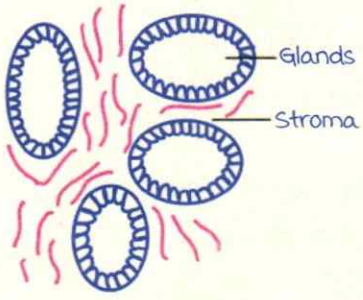
UTERUS AND ENDOMETRIUM

Normal histology of endometrium

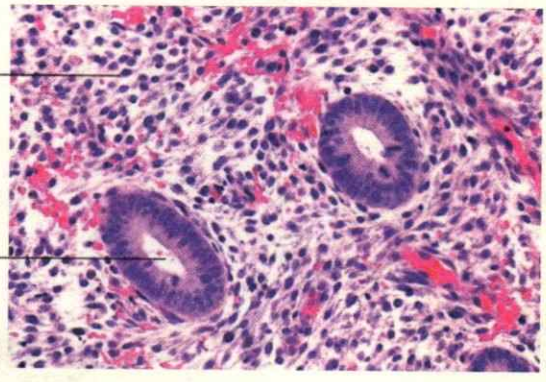
00:00:45

Endometrium consists of glands and stroma.
(Breast, prostate also consist of glands and stroma).
Endometrial glands are in 2 phases :
Proliferative phase and secretory phase.

- Proliferative phase : Compact stroma with small round uniform glands.
- Secretory phase : Tortuous coiled bigger glands with loose stroma.
  Early : Subnuclear vacuolation.
  Late : Serrated saw toothed glands with secretions in the lumen.

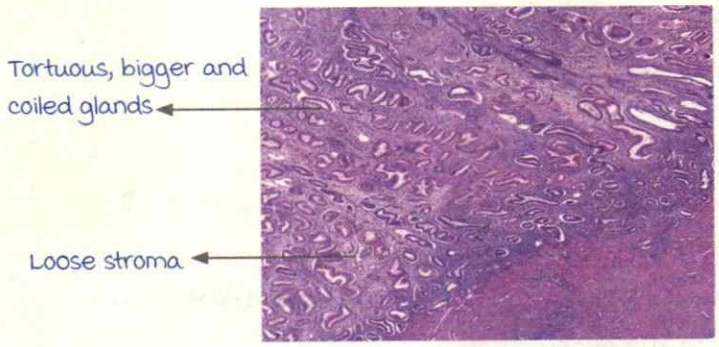


Endometrium

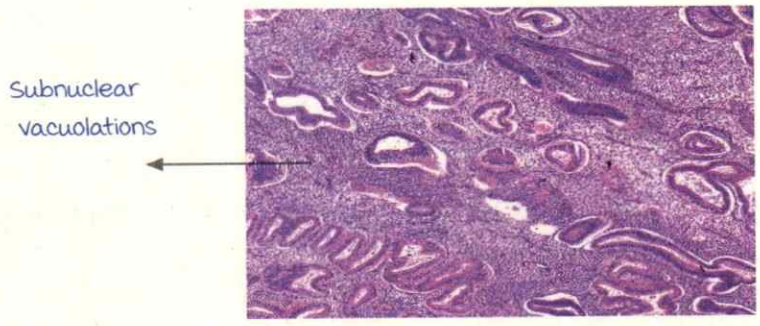


Proliferative endometrium
(endometrial biopsy)

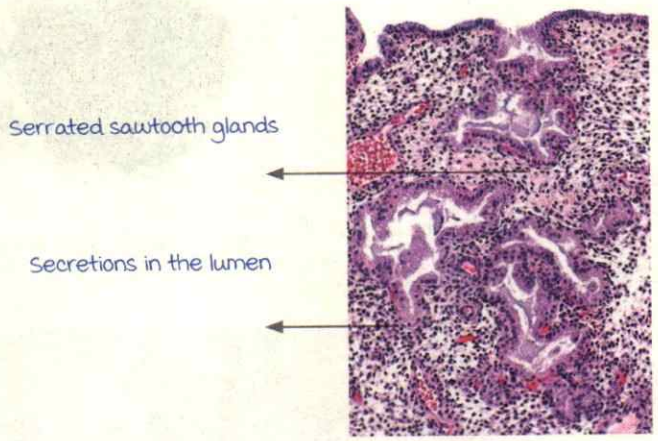
Active space



Secretory endometrium



Early secretory endometrium



Late secretory endometrium

Composition of myometrium : Composed entirely of smooth muscle cells.

Endometriosis

00:08:31

Presence of endometrial glands and stroma outside the uterine cavity.

Most common site : Ovary.

Other common sites are :

- Pouch of Douglas.

Active space

- Rectovaginal septum.
- Broad ligament.

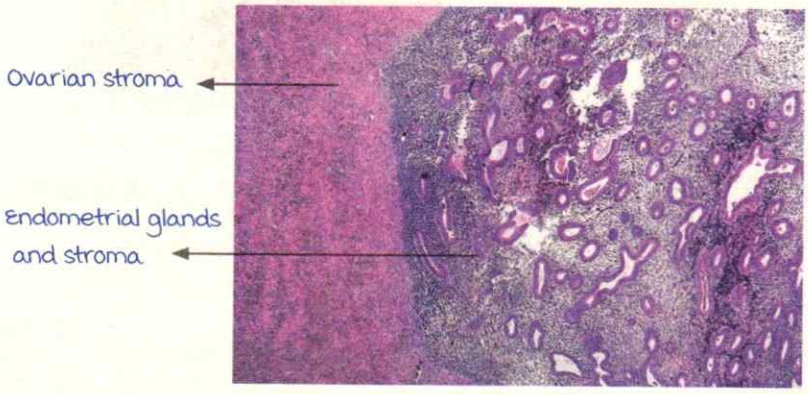
Retrograde menstruation theory :
Most widely accepted theory in the pathogenesis of endometriosis.
The menstrual blood goes in the opposite direction and impacts on the ovary.

Other theories are :
Stem cell theory.
metaplastic theory.

When the endometrial glands and tissue are in the ovary, it bleeds during menstruation.
This causes the ovary to become cystic.
Long standing hemorrhage causes the blood to turn brown → Chocolate cyst of ovary.

Chocolate cyst of ovary

HPE :
Endometrial glands and stroma, with hemosiderin laden macrophages in the ovary.



Endometriosis

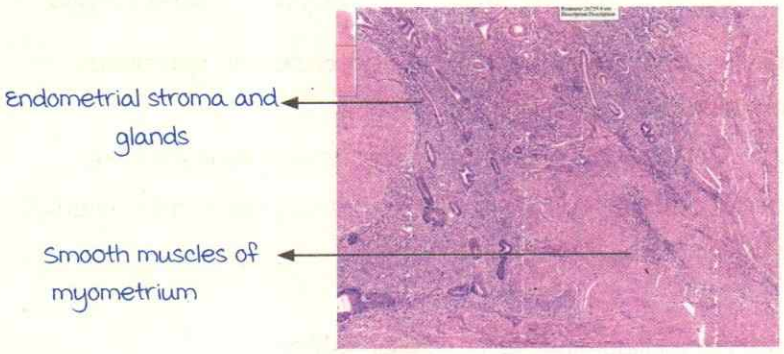
Clinical presentation :
Seen in females of reproductive age group.
Dyspareunia.
menorrhagia.
Infertility.

Active space

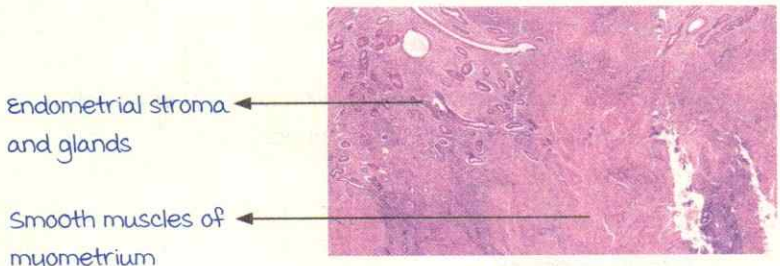
Adenomyosis 00:15:21

Presence of endometrial glands and stroma in the myometrium.

Glands and stroma should be present 2.5 mm from the endomyo-junction.



Adenomyosis



Adenomyosis

Endometrial hyperplasia 00:17:02

Increased proliferation of endometrial glands to stroma.

Increased glands : Stroma ratio.

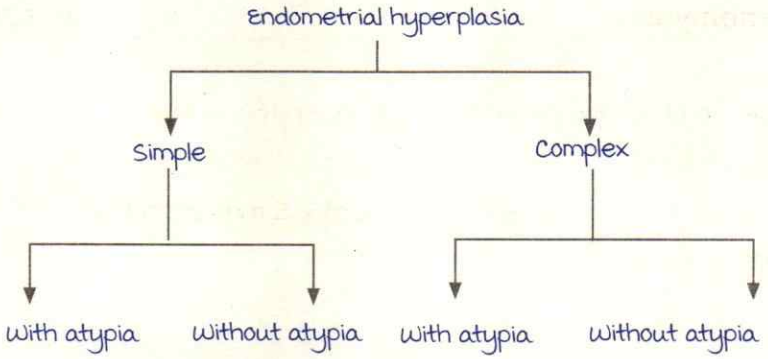
Cause : _____

Risk factor for endometrial carcinoma.

PTEN on chromosome 10 can lead to increased risk of endometrial hyperplasia, carcinoma & Cowden syndrome.

Endometrial hyperplasia was earlier classified as :

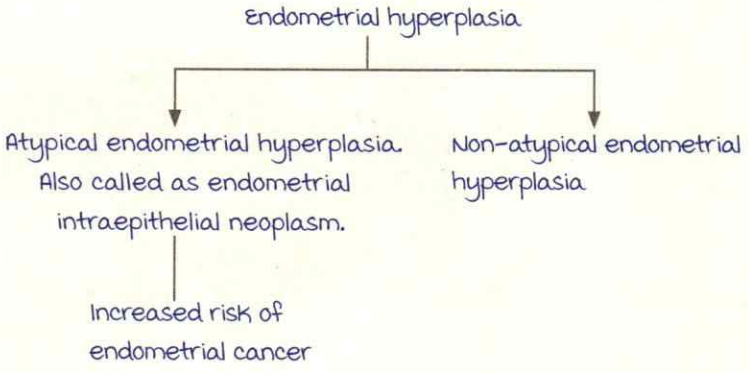
Active space



Simple and complex were classified based on glandular architecture.

Atypia was commented based on nuclear features like nuclear pleomorphism, hyperchromasia, prominent nucleoli, loss of polarity.

Endometrial hyperplasia is now classified as :



Endometrial carcinoma

00:15:21

Characteristics of type I and type II endometrial carcinoma.

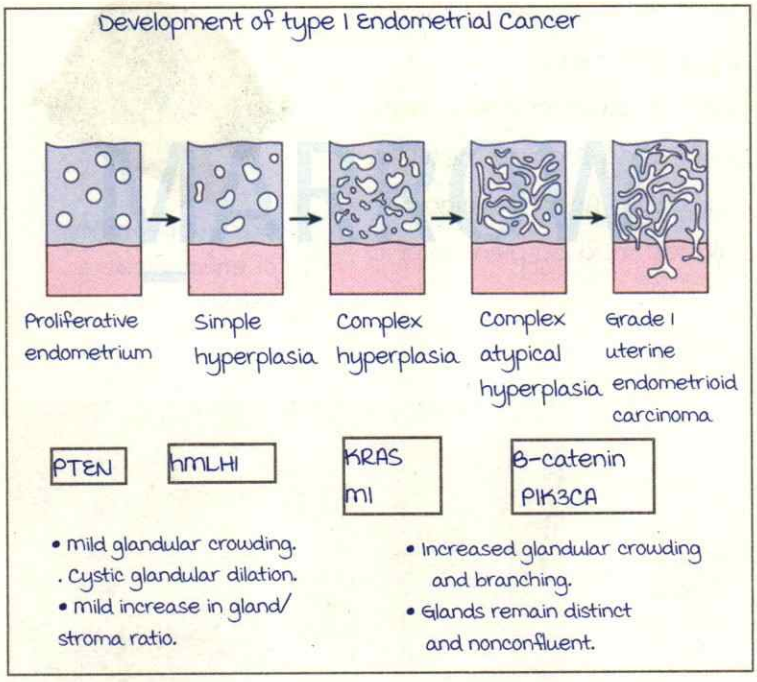
Characteristics	Type I	Type II
Age	55 to 65 years	65 to 75 years
Clinical setting	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin physique
Morphology	Endometrioid	Serous Clear cell Mixed mullerian tumor

Active space

Precursor	Hyperplasia	Serous endometrial intraepithelial carcinoma
mutated genes/genetic abnormalities	PTEN ARID1A (regulator of chromatin) PIK3CA (PI3K) KRAS FGF2 (growth factor) microsatellite instability CTNNB1 (Wnt signalling) POLE TP53 (progressed tumors)	TP53 Aneuploidy PIK3CA (PI3K) FBXW7 (regulator of MYC cyclin E) CCNE1 PPP2R1A (PPP2A)

Smoking is protective for endometrial cancer.

Pathogenesis of endometrial cancer :



PTEN : Tumor suppressor gene.

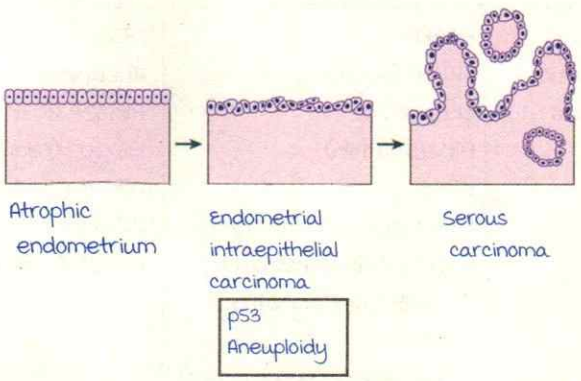
hMLH1 gene : Mismatched repair gene.

Also implicated in hereditary non-polyposis colorectal cancer.

KRAS : Oncogene.

Active space

Development of type II Endometrial Cancer



Serous adenocarcinoma tends to have deep myometrial invasion and extensive lymphatic invasion. Patients commonly present with extrauterine spread at the time of diagnosis

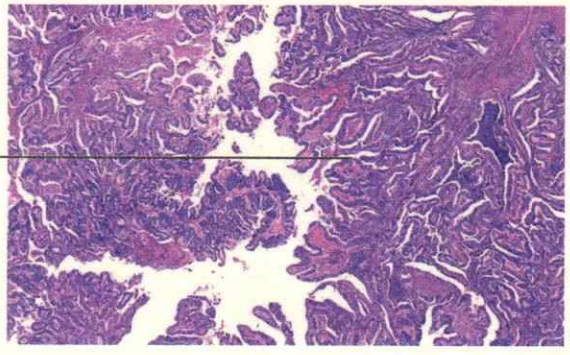
Morphology of endometrial cancer :

Gross appearance :

Polypoidal structure or grey-white mass, infiltrating the myometrium.

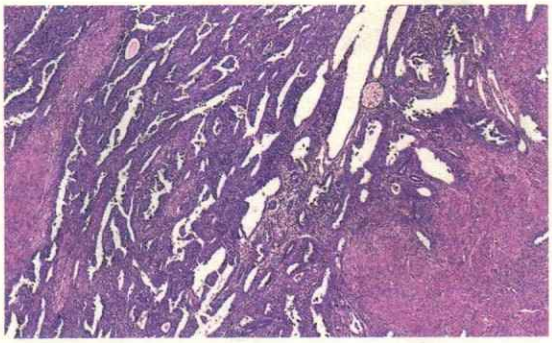
Microscopically : Adenocarcinoma → shows glands lined by pleomorphic cells.

Gross appearance of endometrial cancer



Type I endometroid cancer

Active space



Endometroid cancer

FIGO grading :

Grade I : <5% solid component is present → well differentiated.

Grade II : 5- 50% solid component is present → moderately differentiated.

Grade III : >50% solid component is present → poorly differentiated.

Lesions of myometrium 00:30:30

Myometrium consists of smooth muscle cells.

Leiomyoma :

Most common tumor in women.

Also known as fibroid uterus.

Benign tumor.

Pathogenesis :

Rearrangement in chromosomes 12q and 6p.

MED 12 gene rearrangement.

Gross appearance :

Cut section shows whorled pattern.

Grey-white, firm.

Well circumscribed, encapsulated tumor.

Active space

Leiomyoma

Types of fibroids :

Intramural : Within the myometrium.

Sub-mucosal : Beneath the mucosa.

Sub-serosal : Beneath the serosa.

a= Subserosal fibroids.

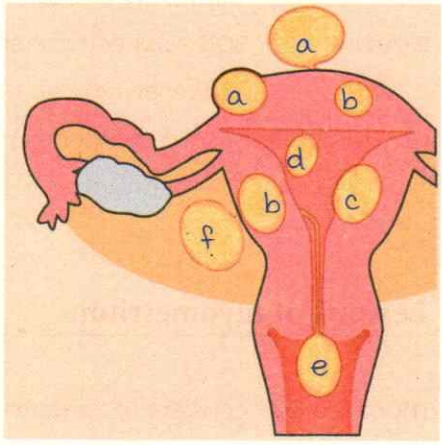
b= Intramural fibroids.

c= Submucosal fibroid.

d= Pedunculated submucosal fibroid.

e= Fibroid in statu nascendi.

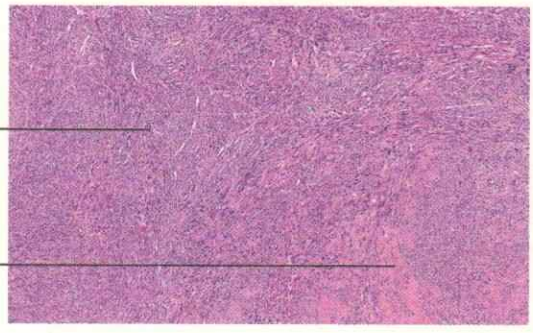
f= Intraligamental fibroid.



HPE :

Intersecting fascicles of smooth muscle.

Cells with cigar shaped nuclei.



HPE of leiomyoma

Degenerations in fibroid :

Hyaline degeneration.

Red degeneration → seen in pregnancy.

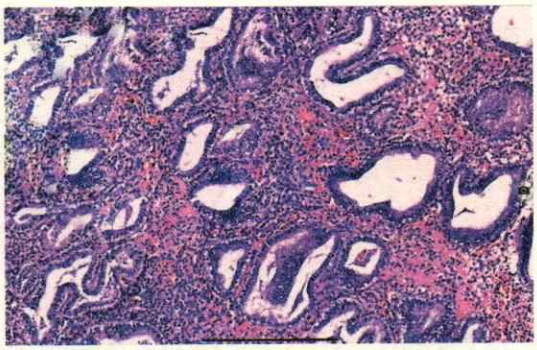
Calcific degeneration.

Active space

Symplastic leiomyoma :
Leiomyoma showing some atypia.

Leiomyosarcoma :
Mitosis >10/10 HPF.
Atypia/necrosis/increased cellularity.

Q. Identify the endometrium :

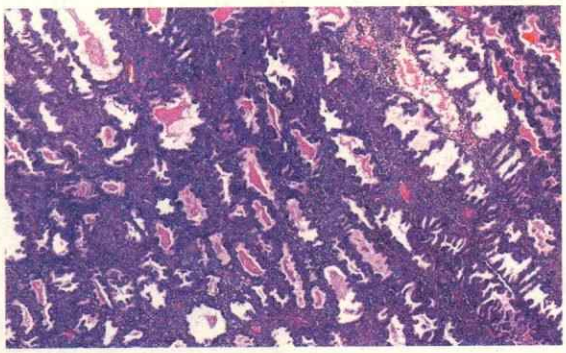


Early secretory endometrium showing subnuclear vacuolation.

Q. Which is not a risk factor for endometrial carcinoma ?

A. Obesity.
B. Smoking.
C. Infertility.
D. Tamoxifen.

Identify the endometrium ?



Late secretory endometrium with saw tooth and serrated glands with secretions in the lumen.

Active space

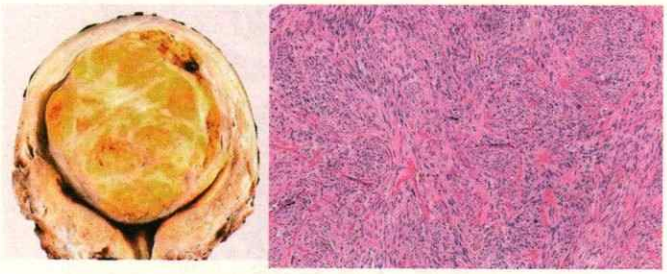
Q. Hysterectomy from a 35 year old female showed the following gross and histological features. What is your possible diagnosis ?

A. Carcinoma endometrium.

B. Leiomyoma.

C. MMMT.

D. Leiomyosarcoma.



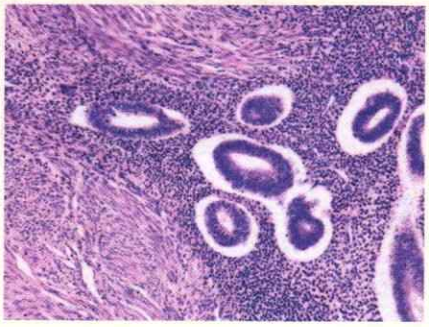
Q. A 44 year old female, G3P3, comes to her physician with complaints of heavy and painful menstrual bleeding. She has been experiencing these symptoms for the past 4 months. She explains that her last menstrual period was 20 days ago. Menarche was at age 11, and she has regular 29 day cycles. She is sexually active with her boyfriend, and denies any pain during intercourse. Her past history is notable for a bilateral tubal ligation 5 years ago. She does not take any medications and denies the usage of alcohol, tobacco, or any illicit substances. The patient's vital signs are unremarkable. During a physical exam the physician notes that her uterus is uniformly enlarged. A urine beta-hCG is performed and is negative. The patient undergoes an endometrial biopsy, which reveals the finding below. What is the most likely cause of this patient's symptoms ?

A. Endometriosis.

B. Adenomyosis.

C. Primary dysmenorrhea.

D. Endometrial cancer.

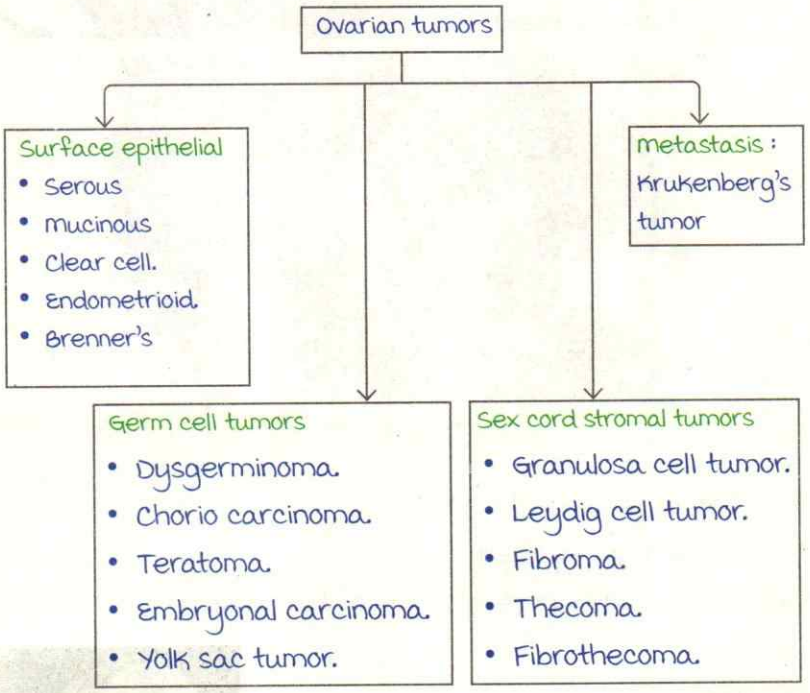


Active space

OVARIAN TUMORS

Ovarian tumors

00:01:04



Surface epithelial tumors

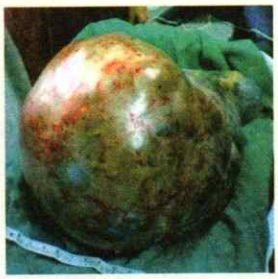
00:02:40

Arise from surface celomic epithelium.

MC tumors of ovary.

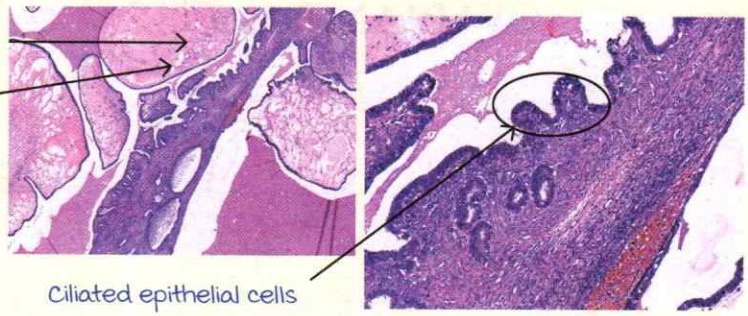
Divided into 3 categories :

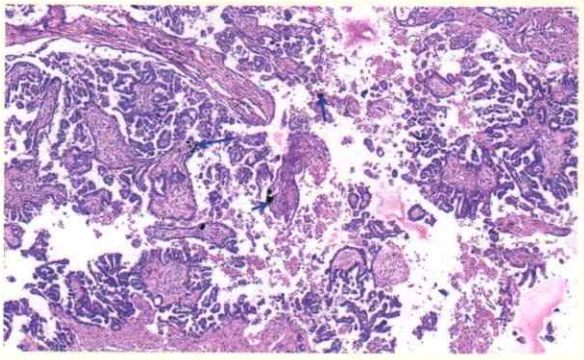
- Benign.
- Boderline.
- Malignant.



Serous epithelial tumors	Mucinous tumors
Most common	Least common.
Usually bilateral	Unilateral
R/F : Family history, multiparity	R/F : Smoking.
Genetics : BRCA 1, BRCA 2, p53.	K-RAS
Gross appearance : Uniloculated.	Gross appearance : Multiloculated.
HPE : Serous, ciliated coloumnar epithelial cells.	HPE : Tall, columnar, non ciliated cells with mucin
Psammoma bodies present	Psammoma bodies are absent

Active space



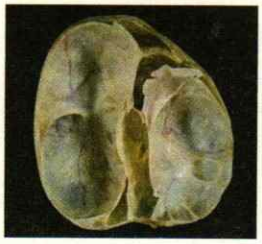


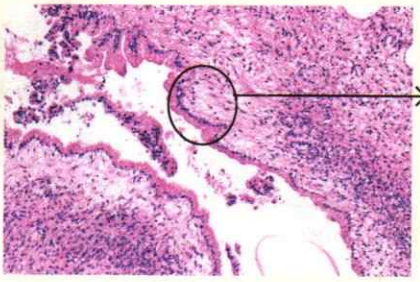
Psammoma bodies

HPE : Serous fluid filled cysts.
Ciliated columnar epithelium.
Psammoma bodies present with papillaroid arrangements.

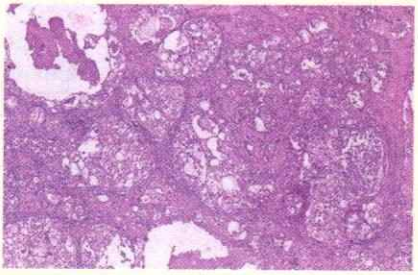
Mucinous :

- Multiloculated.
- Unilateral.
- Tall columnar cells with apical mucin.
- No psammoma bodies.





Clear cell carcinoma of ovary :
R/F :
Diethyl stillbesterol exposure of mother during pregnancy.



Clear cell carcinoma

Active space

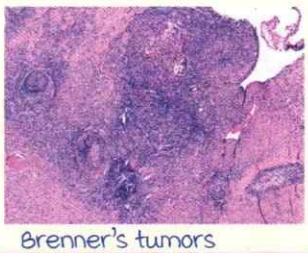
Endometroid cancer :

R/F :

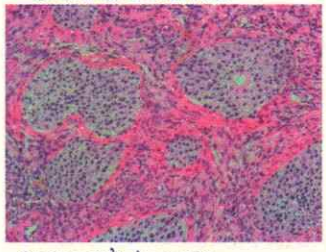
- Endometriosis.
- PTEN gene mutation.
- Arid 1A gene mutation.
- HPE : Cells resembles benign or malignant endometrium.

Brenner's tumor :

- Benign, Solid, Unilateral tumors.
- Shows presence of bladder like epithelium.
- AKA transitional cell tumor.
- Gross appearance : Yellow white firm tumor.



Brenner's tumors



Brenner's tumors

HPE :

Nests of cells which resembles bladder epithelium.

Dense fibrous stroma.

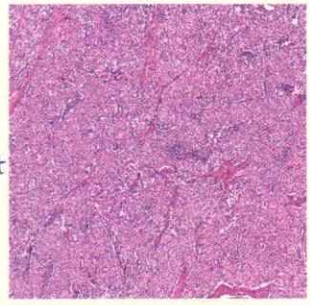
Coffee bean nuclei : Nuclear grooves.

Germ cell tumors

00:15:39

Dysgerminoma :

- Nests of cells seperated by fibrous septa.
- Contains lymphocytes.
- Round to polygonal with a central nuclei.
- Perinuclear clearing may or may not be present.



Dysgerminoma

IHC markers :

- Placental alkaline Phosphatase (PLAP) +
- HCG +
- Oct 3/ 4 +
- Nano g +
- C Kit +
- Never AFP +

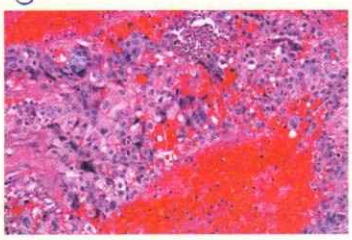
Active space

Choriocarcinoma :

- Age → Elderly.
- Rarely metastasize to lung as cannon ball mets.
- Gross→ Large areas of hemorrhage and necrosis.

HPE :

- Cytotrophoblast (mononuclear cells).
- Syncytiotrophoblast.
- No villi formation.
- Tumor marker → β hCg.



Choriocarcinoma

Yolk sac tumor :

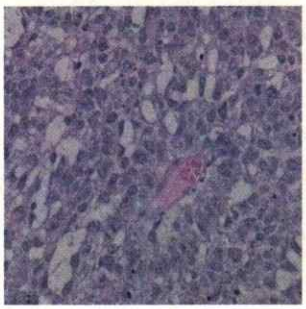
- AKA endodermal sinus tumor.
- Age → Younger age groups.

HPE :

- Schiller duval bodies.
- Hyaline globules (eosinophilic).

Markers :

- α feto protein (AFP).
- α 1 antitrypsin.



Yolk sac tumor

Teratoma :

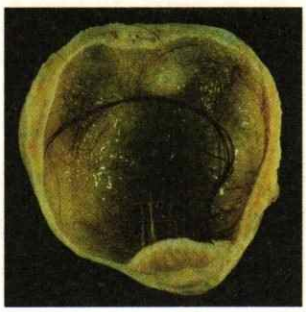
more than 2 germline derivatives.

(Bone, teeth, hair)

Gross :

Cystic mass : Dermoid cyst.

Protruberence :_____



Teratoma

3 types :

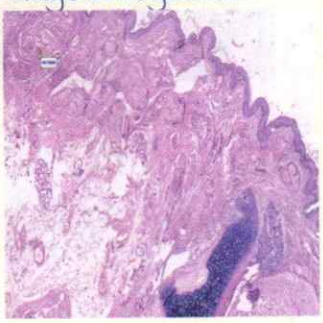
- Mature teratoma.
- Immature teratoma.
- monodermal teratoma.

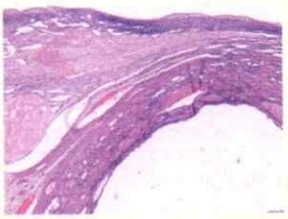
Mature	Immature	monodermal
Benign	Can be malignant	One germ layer
Absence of neural, blastemal and primitive component	Presence of neural, blastemal and primitive component	"Struma Ovarii" : Presence of thyroid tissue in ovary

Active space

HPE :

mixture of elements like neural cells, hair follicle, bone, cartilage and glands.





Struma Ovarii

Struma ovarii :

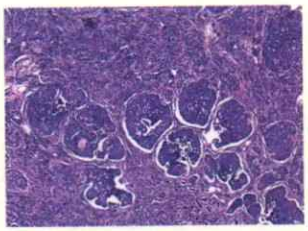
Thyroid follicles present along with ovarian cells.

Embryonal cell carcinoma : CD 30 +

Sex cord stromal tumors

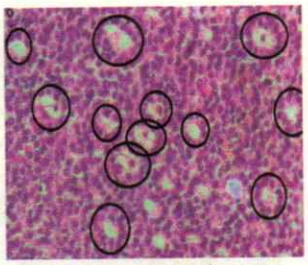
00:30:43

Granulosa cell tumor :



- Young > Elderly.
- Usually produce estrogen.
- Can be associated with endometrial hyperplasia/ endometrial carcinoma & precoccious puberty.
- Genetics : FOX L2 gene mutation.
- Gross : Yellow coloured (lipids).

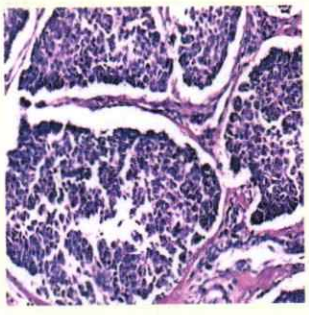
HPE :



Call exner bodies

- Nests of cells.
- Call exner bodies (pseudorosettes flower with highly acidophilic material).
- Coffee bean nuclei : Nuclear grooves (longitudinal).

Coffee bean nuclei :



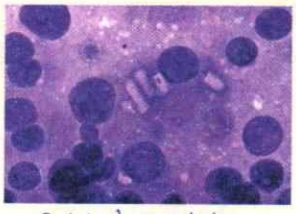
- Papillary carcinoma of thyroid.
- LCH.
- Brenner's tumor.
- Chondroblastoma.
- Granulosa cell tumor.

Active space

Leydig cell tumor :

Reinke's crystals :

Yellow rod shaped crystals.



Reinke's crystals

Fibroma	Thecoma	Fibrothecoma
Solid and unilateral	Solid and unilateral	Solid and unilateral
HPE : Dense fibrous tissue, spindle cells. Fibroma + Ascites + Hydrothorax : meig's syndrome.	Fibroblasts with lipid droplets.	Mixture of both

Metastasis

00:38:40

Krukenberg's tumor :

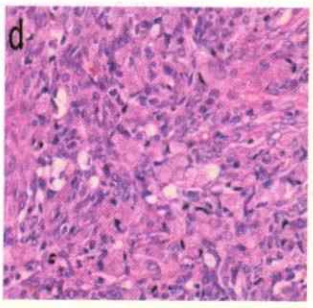
Diffuse gastric CA metastazing to ovary (mc).

There can be other metastasize also.

Gross :

- Bilateral.
- Symmetric enlargement.
- Intact capsule.

HPE : Presence of signet ring cells.



Signet ring cells

Gestational trophoblastic disease

00:41:37

Hydatiform mole :

Grape like vesicles.

Can mimic pregnancy.

Grape like vesicles

Active space

Partial mole	Complete mole
Genetics : Single egg fertilized by more than one sperm. Triploid (69 chromosome).	One empty egg fertilized by one sperm. Diploid (46 chromosome)
Fetal parts +	Fetal parts absent
Mucosal edema ++	Mucosal edema +
Patchy trophoblastic proliferation	Diffuse trophoblastic proliferation
Some villi are normal	All the villi are edematous
Minimal risk of choriocarcinoma	2–3% risk of choriocarcinoma

Disease	Histopathology	Marker
Serous epithelial tumor	Cells with cilia, Psammoma bodies.	CA 125
Yolk sac tumor	Schiller duval bodies	AFP, Alpha 1 antritrypsin
Teratoma	Skin, bone, cartilage, teeth and hair	
Choriocarcinoma	Cytotrophoblast, Syncytiotrophoblast, no villi	hCG
Embryonal carcinoma	Primitive cells No villi	CD 30+, CK +
Granulosa cell tumor	Call exner bodies Coffee bean nuclei	
Sertoli cell tumor		Inhibin
Leydig cell tumor	Reinke's crystal	
Dysgerminoma	Cells in nodules with fibrous septa containing lymphocytes	PLAP, LDH, hCG
Brenner's tumor	Transitional epithelium	
Krukenberg's tumor	Signet ring cell	

MCQs :

Q. A 32-year-old female presents with the recent onset of oligomenorrhea followed by amenorrhea, and then the loss of female secondary characteristics. She has also developed acne, deepening of her voice, and temporal balding. Which one of the following ovarian tumors would most likely produce these symptoms?

A. Epithelial tumor.

B. Stromal tumor.

Active space

C. Germ cell tumor.

D. Surface tumor.

Q. A 30 year old woman in her 14th week of pregnancy presents with uterine bleeding and passage of small watery fluid and tissue. She is found to have a uterus that is larger than her estimated gestational age. The uterus is filled with cystic, grape like structures that do not penetrate the uterine wall. No fetal parts are found. The most likely abnormality is :

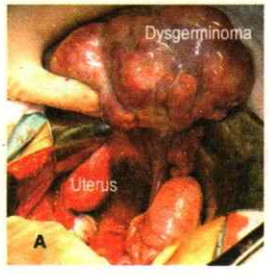
A. Partial H. mole.

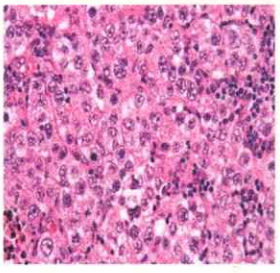
B. Complete H. mole.

C. Invasive mole.

D. Stromal tumor.

Q. A 28 year old female came with abdominal pain and adnexal mass. Her Ca125 and LDH was marginally elevated and CA 19.9 was not elevated. She was operated and specimen sent for histopathology. Below is the image of the gross and microscopic picture. Your diagnosis is :





A. Dysgerminoma.

B. Teratoma.

C. Papillary serous cystadenocarcinoma.

D. Choriocarcinoma.

Q. A 28 year old female presents with complaints of mass per abdomen. On examination, a mass was found on left adnexa with multiple solid, cystic areas. The patient was operated and the mass was removed as shown. What is true regarding the mass?

A. Specimen shows multiple solid cystic areas suggestive of dermoid cyst.

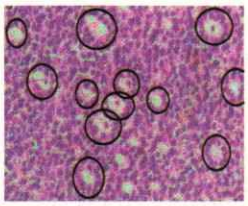
B. Specimen shows cystic areas suggestive of serous cystadenoma.

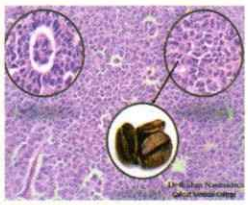
Active space

C. Shows dysgerminoma.

D. Shows carcinosarcoma.

Q. A 35 year old nulliparous female who desires future fertility presents with right side adnexal mass. At exploratory laparotomy a mass is seen in Rt ovary, the histopathology shows following image. What is the most likely diagnosis ?





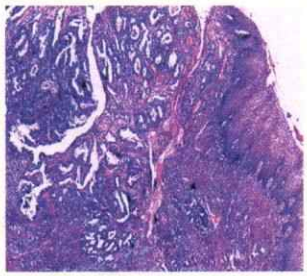
A. Yolk sac tumor.

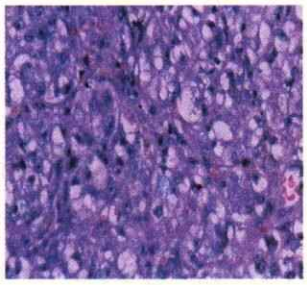
B. Brenner tumor.

C. Granulosa cell tumor.

D. Serous cystadenoma.

Q. A 25 year old sexually active female presented with dyspareunia followed by vaginal bleeding and shows red, friable mass on anterior wall of vagina. Histopath is shown below. Which of the following is likely associated with patients condition?





A. Adrenal hyperplasia.

B. Gardenella vaginalis.

C. HPV infection.

D. DES exposure.

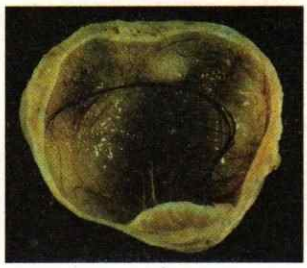
Q. A 47-year-old woman has noted a pressure sensation, but no pain, in her pelvic region for the past 5 months. On physical examination there is a right adnexal mass. An ultrasound scan shows a 10 cm fluid-filled cystic mass in the right ovary, along with ascitic fluid. A fine needle aspirate of the mass is performed and cytologic examination of clear fluid aspirated from the mass reveals clusters of malignant epithelial cells surrounding psammoma bodies. Which of the following neoplasms is she most likely to have?

Active space

A. Endometrioid carcinoma.
B. Serous cystadenocarcinoma.
C. Malignant mesothelioma.
D. Mature cystic teratoma.
E. Squamous cell carcinoma.

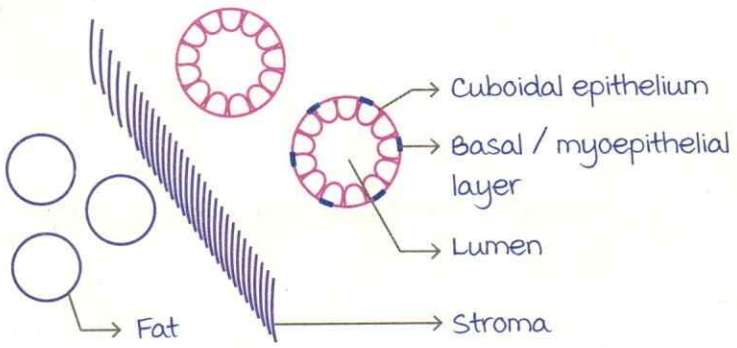
Q. A 22-year-old woman passes grape-like masses of tissue per vagina in the 16th week of her first pregnancy. She had not felt any fetal movement at any time. On physical examination she measures 18 weeks in size. A D&C is performed, yielding 1000 cc of 0.5 to 1.5 cm fluid-filled vesicles. Microscopic examination of this tissue shows large avascular villi along with trophoblastic proliferation. Which of the following is the best method to employ for her follow-up care?
A. Chest radiograph.
B. Serum beta-HCG.
C. Endometrial biopsy.
D. Pelvic ultrasound.
E. Pap smear.

Q. Abnormal bleeding per vagina for the past 5 months prompts a 62-year-old woman to see her physician. She has never been pregnant and went through menopause 10 years previously. On physical examination her BMI is 33. There are no abnormal findings on physical examination. An endometrial biopsy is performed and on microscopic examination shows a well-differentiated endometrial adenocarcinoma. Which of the following ovarian neoplasms is she most likely to have?
A. Papillary serous cystadenocarcinoma.
B. Krukenberg tumor.
C. Mucinous cystadenoma.
D. Granulosa cell tumor.
E. Immature teratoma.



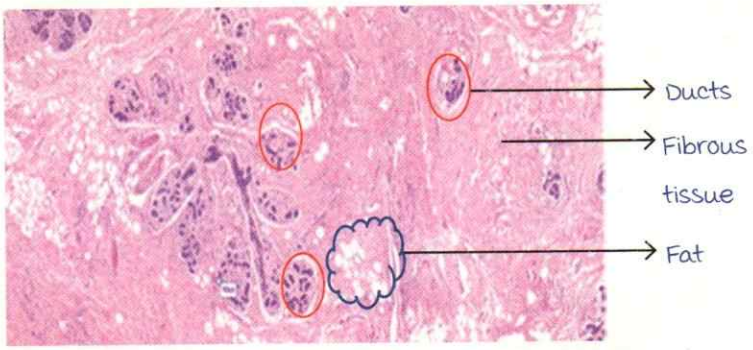
Active space

BREAST PATHOLOGY



Normal histology of breast :
Breast is mainly composed of fat.
It has stroma, composed of fibrous tissue.
It also has several ducts and lobules.
The ducts are lined by double layered epithelium.
In the bottom of these ducts there are flattened cells forming the basal layer/ myoepithelial layer.
The ducts are lined by simple cuboidal epithelium.

Similar histology seen in : Endometrium and prostate gland.



Inflammatory lesions of the breast 00:03:22

Acute mastitis :
Occurs usually in the first month of lactation.
Causative factor is Staph. aureus.

Signs of inflammation are present.

Active space

Breast will be :

- Oedematous and red.
- Tender.
- Warm to touch.

Periductal mastitis :

Also known as squamous metaplasia of lactiferous duct.
Also known as Zuska's disease.
The normal ductal epithelium changes to squamous epithelium.
The squamous cells secrete a lot of keratin, leading to keratin plugging of these ducts, causing abscess and fistula formation.

Risk factors:

1. Smoking
2. Vit A deficiency.

Biopsy is not done, as it is a painful condition.

Case : A 35 year old student who is smoking comes with a breast abscess. On biopsy squamous changes are noted. What is the diagnosis?
Answer: Zuska's disease.

Fat necrosis of the breast :

Case : A 40 year old who was driving a car met with an accident and had a steering wheel injury. The breast after the injury has become severely swollen and painful. What is the pathological change seen in the breast.
Answer: Fat necrosis.

It is a clinical (history of trauma) and radiological diagnosis.
Presents as a painful erythematous sub-areolar mass.

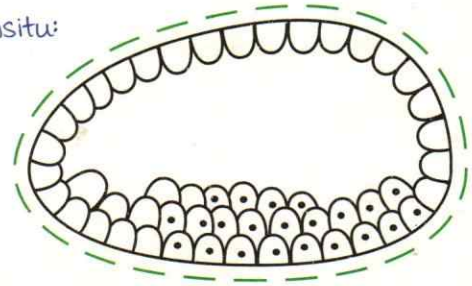
Active space

Epithelial lesions of the breast

00:09:49

Pathological Lesions	Relative risk (Absolute lifetime risk)
Non-proliferative breast changes: Mild hyperplasia, duct ectasia, cysts, apocrine metaplasia, adenosis, fibroadenoma without complex features.	1.0 (3%)
Proliferative disease without atypia: Moderate or florid hyperplasia, sclerosing adenosis, complex sclerosing lesion, fibroadenoma with complex features.	1.5–2 (5%–7%)
Proliferative disease with atypia: Atypical ductal hyperplasia, atypical lobular hyperplasia.	4–5 (13%–17%)
Carcinoma insitu. Lobular carcinoma insitu, ductal carcinoma in situ	8–10 (25%–30%)

Carcinoma insitu:



Atypical cells limited by basement membrane

Atypical cells limited by the basement membrane i.e., the basement membrane is intact.

It can be further classified into :

1. Ductal carcinoma insitu.
2. Lobular carcinoma insitu.

Ductal carcinoma insitu:

Active space

This is divided into 2 types:

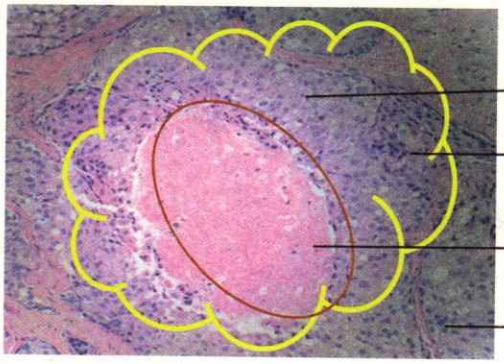
1. Comedo DCIS.

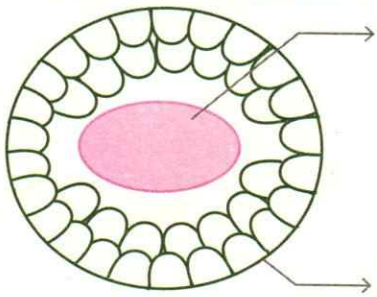
Poor prognosis.

Central area of necrosis.

Atypical epithelial cells seen around it.

Basement membrane and myoepithelial cell layer are intact.





2. Non-Comedo DCIS.

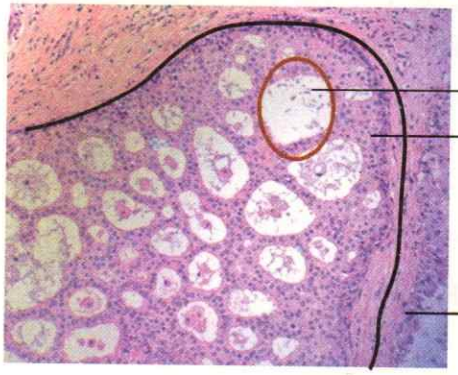
Clinically, produces calcification. Can be seen on mammography.

Types :

- Cribriform DCIS.

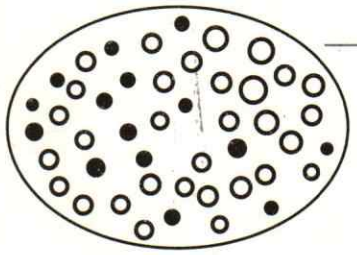
  Cookie cutter spaces.

  Sieve like pattern.



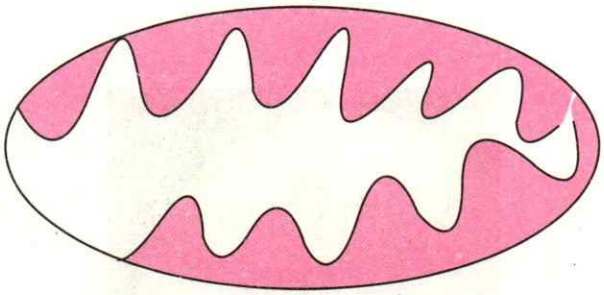
Active space

- Solid DCIS.
  If the entire duct is completely filled with cells it is called a solid DCIS.



- Papillary DCIS.
  When the duct is filled with finger like projections called papillae.

Papillary DCIS



- micropapillary DCIS.
  If the length of the papillae is smaller.

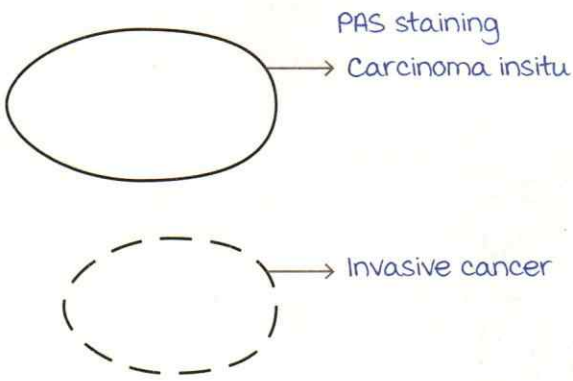
All DCIS causes calcification and can be visualised in mammography.

Lobular carcinoma /LCIS. 00:20:05

Does not produce calcification.
Cannot be picked up on mammography.

PAS stain (stain for basement membrane) can be done to differentiate between carcinoma insitu and invasive cancer.
In carcinoma insitu, basement membrane is intact.
Whereas in cases of invasive cancer, breaks can be seen in the basement membrane.

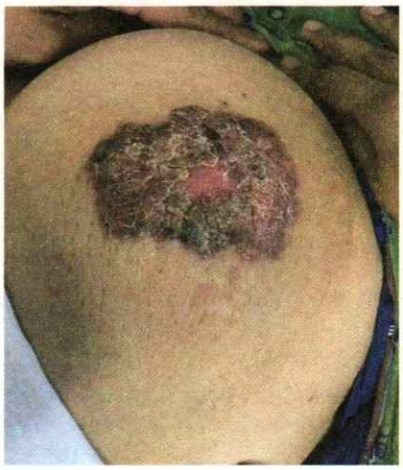
Active space



P63 is an important marker for the myoepithelial layer and the basal layer.
If its absent it indicates invasive cancer.

Paget's disease of nipple :

Paget's Disease

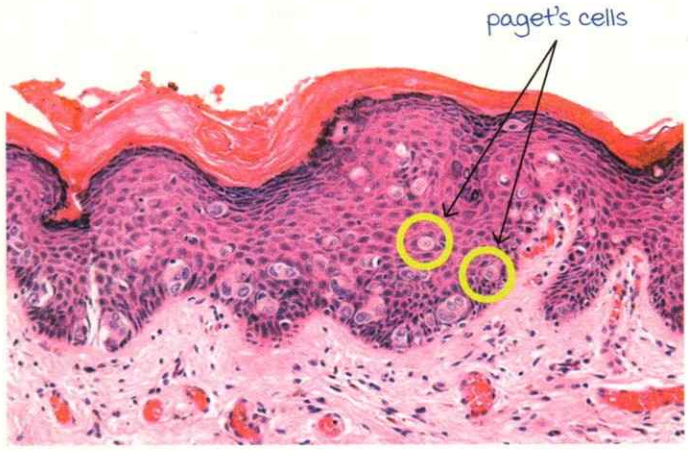


Also seen in the vulva.
Unilateral scaly erythematous eruption of nipple.
Symptoms : Pruritis.
Differential diagnosis : Eczema of breast.
Eczema is usually bilaterally.
Clinical significance : Usually indicates the presence of an underlying malignancy.
Malignant / atypical cells move out from the duct and invade the nipple- areola complex.
Biopsy :
Large pale vacuolated cytoplasm, with perinuclear clearing.
ER, PR negative.

Active space

Overexpression of HER -2 neu.

PAS positive and diastase resistant.



Breast carcinoma

00:27:20

High incidence.

Risk factors

1. Sporadic
   - Age.
   - Early menarche
   - Late menopause.
   - Nulliparity.
   - Obesity/ sedentary lifestyle/ high fat diet.
   - Smoking.
   - No breast feeding.
   - Family history.
   - Prolonged estrogen exposure.

2. Familial / genetic.
   - BRCA1.
   - BRCA2.
   - P53.
   - CHEK2.

Active space

Gene (syndrome)	% of single gene cancers.	Risk of breast cancer to age 70.	Other cancers
High penetrance germline mutations (>4 fold increased risk, 3-7% of breast cancer)			
• BRCA1 (familial breast and ovarian cancer).	~ 55%	~40-90% females, 1% males.	Ovarian (~20- 40%) fallopian tube, pancreas, prostate & others
• BRCA2 (familial breast and ovarian cancer).	~35%	~30-60% females, 6% males.	Ovarian (~10- 20%), pancreas, prostate, others
• TP53 (Li-Fraumeni)	~1%	~ 50-60% females, <1% males.	Sarcoma, leukemia, brain tumors, others
• PTEN (Cowden)	~1%	~20-80% females, <1% males.	thyroid, endometrium, others.
• STK-1 (peutz-Jeghers)	~1%	~40-60% females.	Ovarian, colon, pancreas,others
• CDH1 (hereditary diffuse gastric cancer)	<1%	~50% female	Gastric signet ring cell gastrinoma, colon.
• PAPLPB2 (hereditary breast cancer)	~1%	~30- 60% females, <1% males	Pancreas, prostate
moderate penetrance germline mutations (2-4 fold increased risk; 5-10% of breast cancer)			
• ATM (ataxia-telangiectasia)	~5%	~15-30%	
• CHEK2 (hereditary breast cancer)	~5%	~10-30% females	Prostate, thyroid, colon, kidney

Active space

BRCA1 :

Chromosome 17 (p53, NF-1 also located on chromosome 17)

Tumour suppression gene.

Increased risk of breast cancer, ovarian cancer.

BRCA1 positive tumours are triple negative (ER, PR, HER-2).

Medullary like features are seen.

BRCA2:

Chromosome 13.

Tumour suppression gene.

Increased risk of breast cancer, ovarian cancer, male breast cancer and prostrate cancer.

P53:

Chromosome 17.

Can lead to Li-Fraumeni syndrome where the patient can develop breast cancer.

Tumour suppression gene.

Most common gene mutated in sporadic breast cancer.

CHECK2:

Chromosome 22.

Increased risk of breast cancer and thyroid cancer.

Classification of breast cancer 00:36:38

1. Molecular.
2. Morphological.

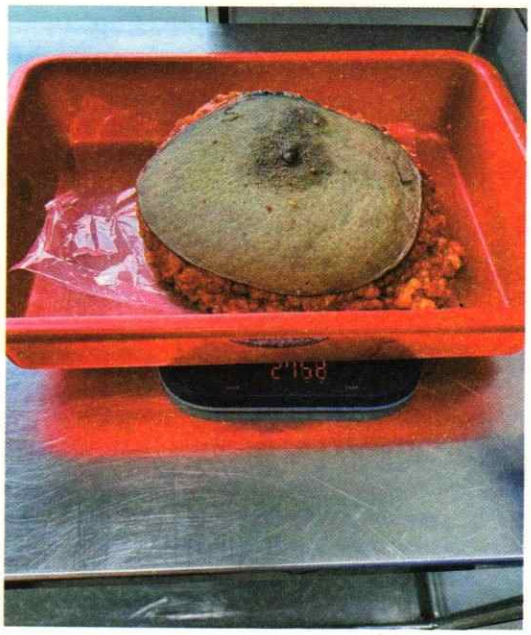
   Infiltrative/ Invasive ductal cancer (IDC) No special type (NOS,NST) : most common type.

   Special type :

   - Lobular cancer.
   - Medullary cancer.
   - Mucinous cancer.
   - Papillary cancer.
   - Tubular cancer.

The specimen is kept in 10% neutral buffered formalin.

Active space



The gross specimen is sent to the pathology lab where the following steps are done :
The length, breadth and width of the lesion and nipple-areola complex are measured.
Serial cuts are made in the specimen.
Localisation of the lesion is done.
Usually in the cases of infiltrating ductal carcinoma, the lesion appears greyish white.
In case of a mucinous lesion, a lot of mucin or jelly like & whitish areas can be appreciated.
Whereas, a medullary cancer will grossly show fleshy mass.
A ductal breast cancer is whitish, irregular and gritty.
In lobular cancer small multiple foci can be appreciated in single or both breasts.

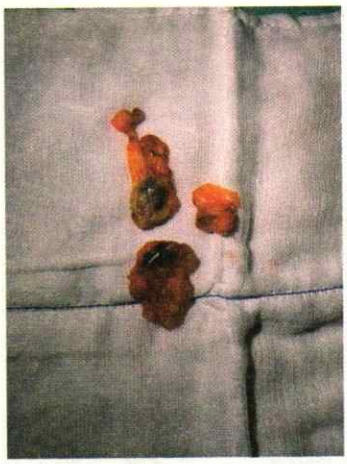
Sentinel lymph node biopsy :

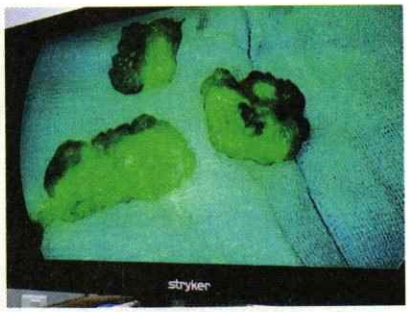
It is the first lymph node in the lymphatic basin to which the primary tumour spreads.
Identified by a dye testing. The dye is _____
It is done in:

- Breast cancer.
- Vulval carcinoma.

Active space

- Malignant melanoma.





Frozen section :

Made by cryostat.

No fixative for a sample for frozen section.

Stain : Oil red O stain.

Advantages :

- To see the margins.
- Sentinel lymph node invasion.
- Spread of the tumour.

Infiltrating ductal cancer NST 00:47:50

Most common type.

Most common site is the upper outer quadrant.

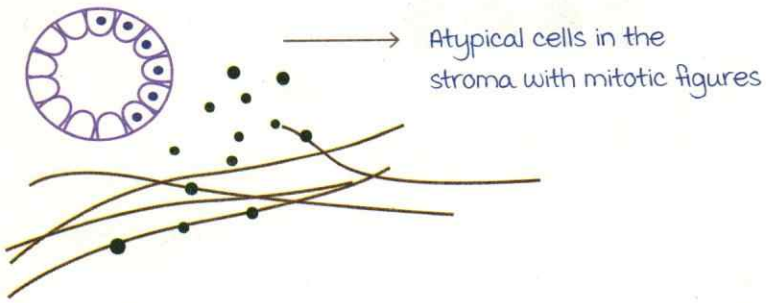
Grossly : Irregular whitish appearance with gritty feel.

H&E :

Ducts are lined by pleomorphic cells.

No basal layer or myoepithelial layer in the ducts.

Mitosis.



Active space

Atypical cells are also seen in the stroma along with some mitotic figures.

Ductal cancer can be further divided into :

- Well differentiated
- Moderately differentiated
- Poorly differentiated.

This is dependent on the Bloom Richardson score (BR score).

1. Percentage of tubules.
2. Degree of pleomorphism.
3. Number of mitosis.

Invasive lobular carcinoma of the breast :

Usually bilateral and multicentric (multiple foci in the same breast).

Excellent prognosis.

Characteristic pattern of spread of lobular carcinoma to the meninges and peritoneum called carcinomatosis meningitis.

Pathogenesis :

Mutation of CDHI gene leads to the loss of E-Cadherin (adhesion molecules).

Mutation of CDHI gene leads to the loss of E-Cadherin is also seen in diffuse type of gastric adenocarcinoma.

Microscopically:

1. Dyscohesive cells .
2. Small and monomorphic cells.
3. Cells are lined one after the other. This is called as single file pattern or Indian file pattern.

 Single file pattern

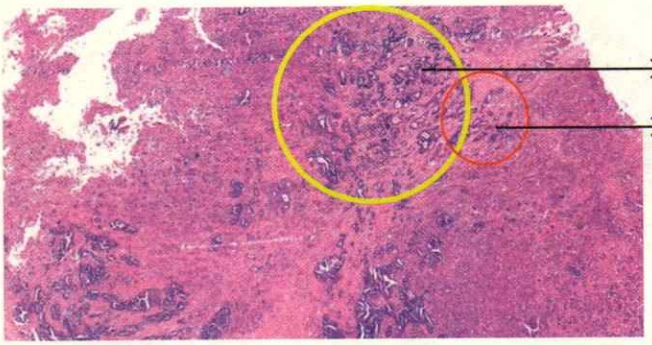
4. Signet ring cells can be present.
5. Desmoplasia is minimal.

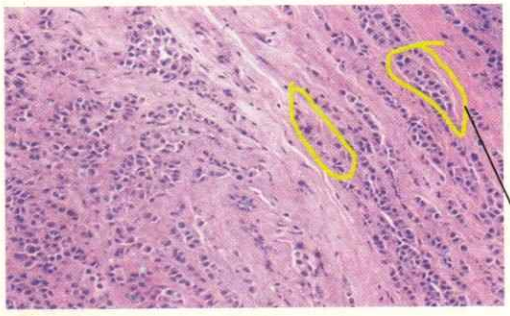
Excellent prognosis.

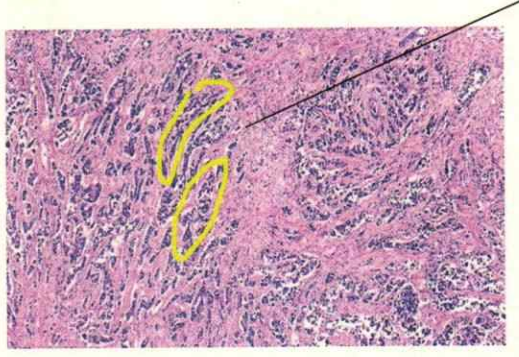
Pattern of spread of Lobular carcinoma to meninges/ peritoneum : Carcinomatosis meningitis.

Active space

Ductal Cancer







Medullary carcinoma of breast

00:59:41

BRCA 1 positive.

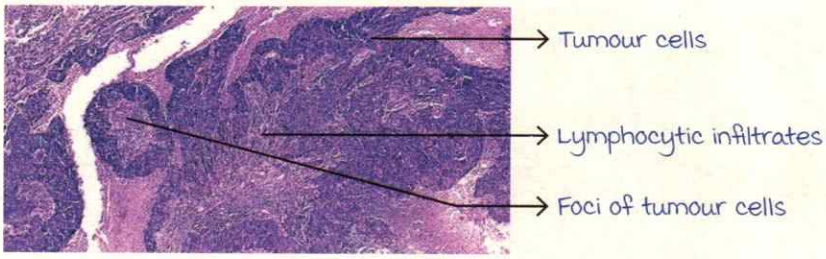
Triple negative.

Grossly : Fleshy.

Microscopically,

1. Sheets/ Syncytium of highly pleomorphic cells.
2. Mitosis.
3. Pushing borders.
4. Lymphoplasmacytic infiltrate.

Active space



Mucinous cancer :

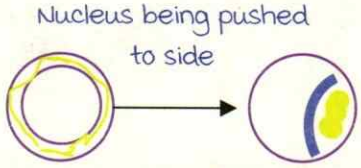
Excellent prognosis.

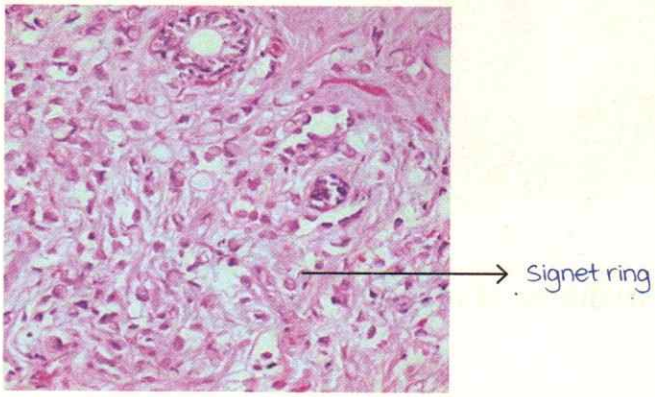
Also known as the colloid cancer of the breast.

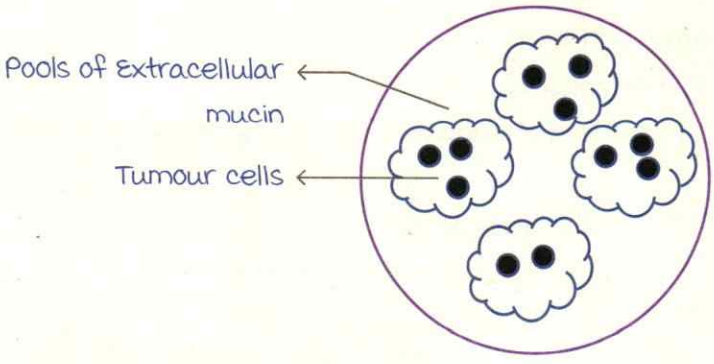
Mucin/jelly like appearance.

Mucin can be secreted :

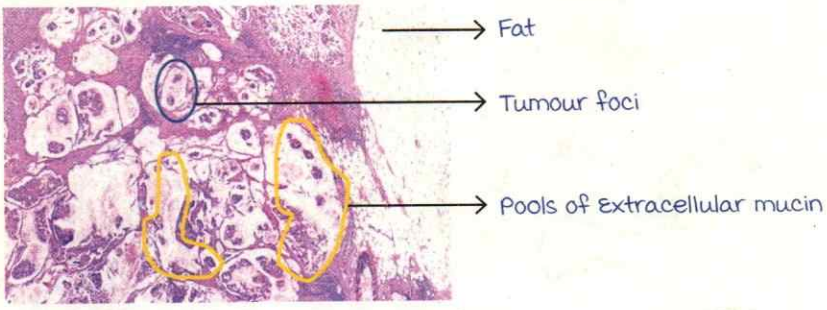
- Extracellular mucin : Pools of mucin with tumor cells.
- Intracellular mucin : Nucleus will be pushed to the periphery by the mucin, creating a signet ring cell appearance.
  Also seen in mucinous carcinoma of colon.







Active space



Tubular carcinoma of breast :
Small monomorphic cells forming angulated tubules.
Excellent prognosis.

IHC Markers

01:07:33

markers :

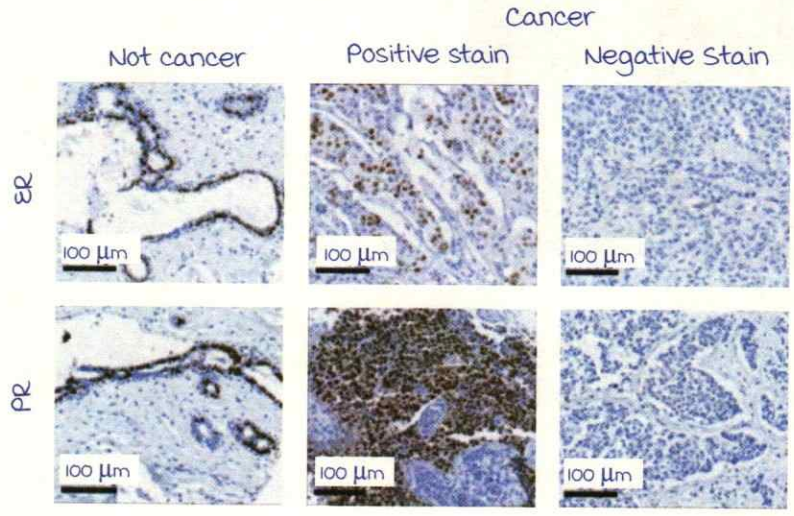
- ER : Oestrogen receptor.
- PR : Progesterone receptor.
- HER2 neu.

ER, PR are nuclear receptors therefore the nucleus get stained.
Whereas HER2 neu is a membranous receptor, when stained membrane is positive.

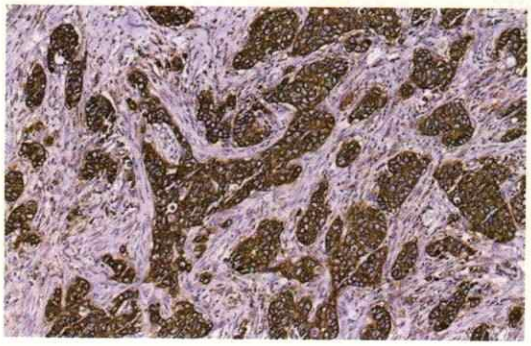
Significance :
If the tumour is ER, PR positive :
The tumour is responsive to hormonal treatment with tamoxifen.
Side effect : Endometrial hyperplasia.
Repeated endometrial biopsies done as a follow up to assess the presence of endometrial hyperplasia as it can progress to endometrial cancer.
Good prognosis.

If the tumour is HER2 neu positive :
Responds to treatment with Herceptin / Traztuzumab.
Bad prognosis.

Active space



HER2 neu positive : Staining the membranes



Allred scoring system for ER and PR :

- Proportion of cells which are positive.
  - 0: No cells (+).
  - 1: <1 % cells (+).
  - 2: 1-10% cells (+).
  - 3: 11-33% cells (+).
  - 4: 34-66% cells (+).
  - 5: 67-100% cells (+).
- Intensity.
  - 0: Negative.
  - 1: Mild positivity.
  - 2: Moderate positivity.
  - 3: Strong positivity.

HER2 neu scoring system.

0 & 1 : Negative.

Active space

2 : is called equivocal.

In this the patient is sent for FISH (fluorescent in situ hybridisation) analysis after which HER2neu/CEP 17 ratio scoring is done.

If score >2.2 Then positive.

3: Positive.

MARKERS(CLONES)	RESULTS		INTERPRETATION	IMAGE
ER (EP-1)	% of cells with nuclear staining in the invasive component of the tumor	90%	Positive	
	Intensity of staining	Strong		
	Allred score	8		
PgR (EP-2)	% of cells with nuclear staining in the invasive component of the tumor	90%	Positive	
	Intensity of staining	Strong		
	Allred score	8		
Her-2/neu (EP-3)	No staining observed	Score 0	Negative	

Prognostic factors :

Most important prognostic factor for breast cancer, in the absence of metastasis, is axillary lymph node status.

The most important prognostic factor for breast cancer if the patient has metastasis : ER, PR, HER2 neu status.

Other factors include :

- Stage of tumour.
- Type of tumour.
- Size of tumour.
- Lymphovascular invasion.

Molecular classification of breast cancer 01:19:58

It is based on Gene expression profiling.

Expression of ER, PR and HER 2neu are assessed.

There are 5 categories :

Luminal A :

- ER (+), PR(+), HER2 neu (–).
- most common molecular type.

Active space

- Well differentiated tumours with good prognosis.
- Best prognosis among all the types.
- Seen in elderly patients.
- Low Ki67 index.

Luminal B.

- ER (+), PR(+), HER2 neu (+).
- Triple positive breast cancer.
- Well differentiated tumours with good prognosis.
- Low/ high Ki67 index.

Basal like :

- ER (–), PR(–), HER2 neu (–).
- Triple negative breast cancer (TNBC).
- Poorly differentiated tumours with poor prognosis.
- Worst prognosis among all the types.
- High Ki67 index.
- Seen in peri menopausal women.
- Medullary like features.
- BRCA I positive.

HER2 neu positive tumours.

ER (–), PR(–), HER2 neu (+).

Poorly differentiated tumours with poor prognosis.

High Ki67 index.

Claudin type :

Triple negative cancer.

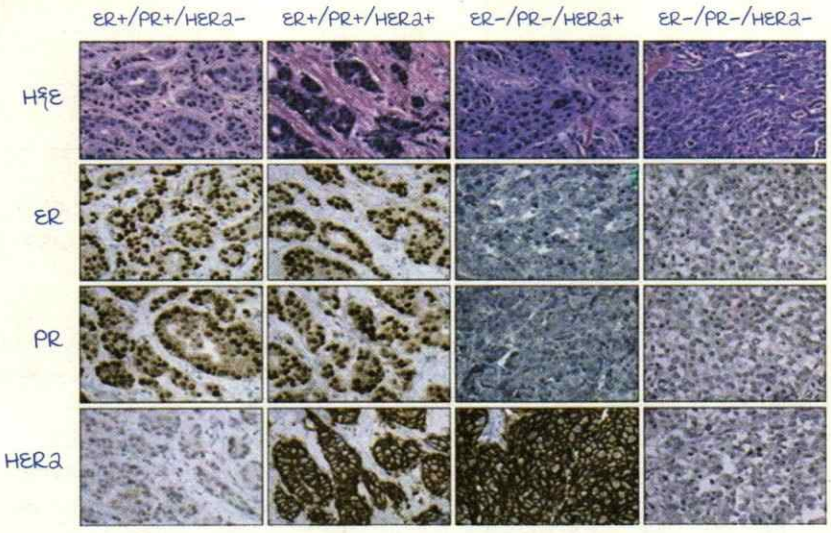
Reduced expression of claudin type genes.

Usually are cytokeratin negative (CK).

Best prognosis among them : Luminal A type.

Worst prognosis among them : Basal like TNBC.

Active space



Defining features	Luminal (ER-positive/ HER2 negative)		HER2 posisitve	TNBC (ER-Negative)
Percent of breast cancer.	~40%–55% (low to moderate proliferation)	~10% (high proliferation)	~20%.	15%
most similar group defined by mRNA profiling.	Luminal A	Luminal B	HER2-enriched (ER-negative), Luminal B (ER-positive)	Basal like
most common gene mutation	PIK3CA (45%), TP53 (12%)	PIK3CA (29%), TP53 (29%)	PIK3CA (39%), TP53 (70–80%)	PIK3CA (9%), TP53 (70–80%)
Typical special histologic types.	Tubular grade 1 or 2 lobular, mucinous, papillary.	Grade 3 Lobular	Some apocrine, some micropapillary.	medullary features, metaplastic.
Typical patient groups.	Older women, men, cancers detected by mammographic screening.	BRCA2 mutation carriers.	Young women, TP53 mutation carriers (ER positive).	Young women, women of African heritage, BRCA mutation carriers.

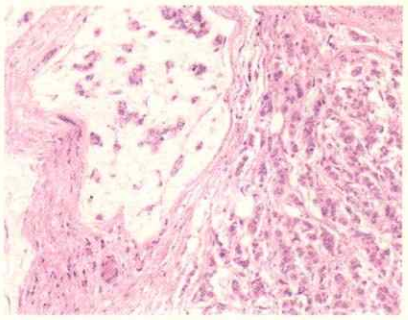
Active space

Complete response to chemotherapy	< 10%.	– 10%	ER positive –15%; ER negative –30%–60%.	30%
metastatic pattern	Bone (70%), more common than viscera (25%), or brain.	Bone (80%) more common than viscera (30%) or brain (10%)	Bone (70%), Viscera (45%), and brain (30%) all are common.	Bone (40%), Viscera (35%), and brain (25%) common.
Relapse pattern	Low rate over many years, long survival possible with bone metastasis.	Early peak at < 10 years, late recurrence possible.	Bimodal with early and late (10years) peaks.	Early peak at years < 8 years, and late recurrence rare with metastasis rare.

Questions :

Q : A 35 year old women presents with a lump in the upper outer quadrant of her breast. Histopathology side is shown below. What is the most likely diagnosis?

A. Papillary carcinoma
B. Lobular carcinoma
C. Colloid carcinoma
D. Medullary carcinoma



Q : A 47 year old women undergoes routine mammographic screening and there are multiple small areas of increased density, though a single distinctive mass lesion is not detectable either by palpation or by mammography. A fine needle aspiration biopsy of an abnormal density reveals cells suspicious for a malignancy. An excisional breast biopsy yields a diagnosis of lobular carcinoma in situ of the breast. Which of the following is the most likely finding associated with this women's carcinoma?

A. No residual carcinoma.
B. Opposite breast involvement.
C. Absent family history of breast cancer.
D. Concomitant Paget's disease of the nipple.

Active space

E. Negative oestrogen receptor assay.

Q : A 49 year old women notes increasing size of her right breast over the past. This breast is not painful, but the heaviness cause some discomfort. On physical examination the overlying skin and nipple appear normal. There is no nipple discharge. There is no axillary lymphadenopathy. Mammography reveals a solid 12cm circumscribed mass. The mass is biopsied, and on microscopic examination shows a cellular stromal component along with an epithelial component. Which of the following is the most likely diagnosis?

A. Fibroadenoma.

B. Phyllodes tumor.

C. Sclerosing adenosis.

D. Hamartoma.

Phyllodes tumor has both epithelial and stromal component, and is a large solid mass.

Also called cystosarcoma phyllodes, which has a leaf like pattern.

High stromal cellularity and mitotic figures.

Phyllodes tumor and fibroadenoma are stromal tumors.

Q : A 49 year old women goes to her physician for a routine health maintenance examination. A screening mammogram is performed and shows a 3cm irregular density in her left breast that has microcalcifications. A needle biopsy of this area shows ducts containing solid sheets of malignant cells, with central necrosis and calcification. There is no invasion. A lumpectomy with wide excision to clear margins is performed along with axillary lymph node sampling that shows no metastases. Malignant cells are positive for HER2 but negative for estrogen receptor. Which of the following is the most likely outcome for this women?

A. Recurrence in the opposite breast.

B. Cure with no further therapy.

C. Response to therapy with tamoxifen.

D. Developement of inflammatory carcinoma.

E. Her children will inherit BRCA1 mutation.

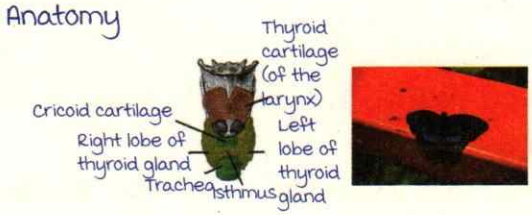
Active space

NON NEOPLASTIC LESIONS : THYROID

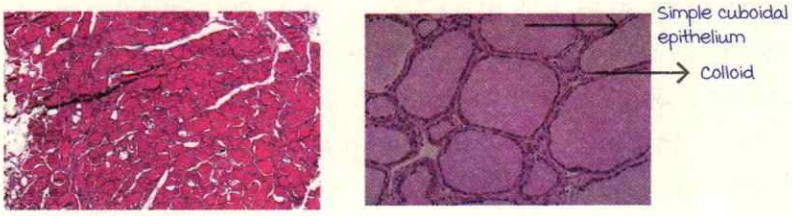
Anatomy of thyroid

00:00:58

Thyroid disorders are more common in females.
It is a butterfly shaped organ.
Has right and left lobe which are joined together with the isthmus.
It is located anterior to the trachea.
The parathyroid gland lies posteriorly.



Histology :
Consist of thyroid follicles which are lined by cuboidal epithelium.
The follicles are filled with colloid which is a pink colour material.
Colloid contains thyroglobulin and is PAS positive.



Histology

When the cuboidal epithelium gets activated it gets converted to columnar epithelium.

For example, a patient develops Graves' disease / hyperthyroidism the cells get activated to produce more colloid by conversion of the cuboidal epithelium to columnar epithelium.

Active space

Thyroid also consist of para follicular cells (C cells of thyroid).
These cells secrete calcitonin.
Associated Disorder : medullary carcinoma of thyroid.

Thyroid disorders 00:06:16

Broadly of two types :
Hyperthyroidism :

Causes : Primary : Graves' disease, toxic multinodular goitre, toxic adenoma iatrogenic

Secondary : TSH secreting pituitary tumour.

Clinical features :

- Tremors.
- Tachycardia.
- Warm moist skin.
- Weight loss.
- Agitation.
- Sweating.
- Heat intolerance.
- Goitre.
- Hunger and thirst.
- Atrial fibrillation.
- Anorexia.
- Diarrhoea.

Grave's disease 00:08:56

It is the most common cause of endogenous hyperthyroidism.
Pathogenesis :
Type II hypersensitivity reaction (anti body mediated).
Antibody present in Graves is called Anti-TSI (thyroid stimulating immunoglobin) or anti-LATS (long acting thyroid stimulator).
These antibodies are responsible for the condition.
This can be associates with CTLA4, PTPN22, HLAB8.
more common in females.
Average age : 20 to 40yrs.

Active space

Triad :

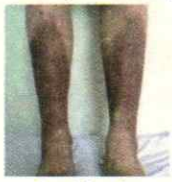
Infiltrative dermopathy skin lesions (skin is shiny) also called as pretibial myxoedema.

Infiltrative ophthalmopathy manifests as proptosis.

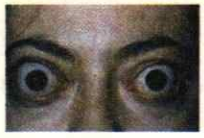
Hyperthyroidism.

Infiltration occurs because of the deposition of mucopolysaccharides like hyaluronic acid.

Clinical presentation



Pretibial myxoedema



Proptosis

Gross appearance

00:14:22

There is diffuse symmetric enlargement of thyroid "Beefy red gland".

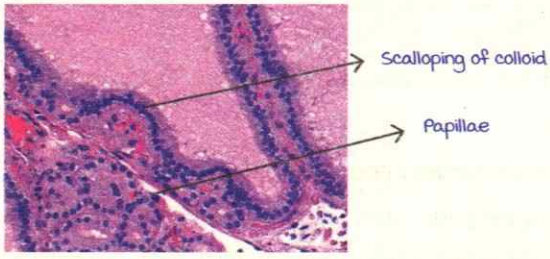
Gross

Microscopically :

Hyperplastic follicles.

Papillae : Follicles take the shape of a papilla (not true because they don't have a fibrovascular core).

Scalloping of the colloid; colloid gets scooped out from the epithelium.



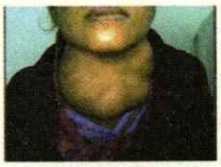
Toxic multinodular goitre :

Microscopic features : Colloid filled follicles of variable sized with degenerative changes like calcification or haemosiderin laden macrophages.

Active space

Diffuse Goitre

Multinodular Goitre

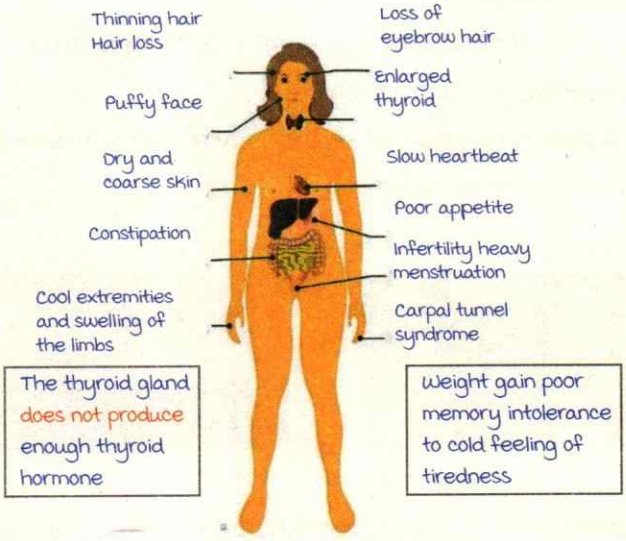


Hypothyroidism 00:19:07

most common cause is iodine deficiency.

most common cause of hypothyroidism in iodine sufficient areas is !_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Hypothyroidism



Thyroiditis :

It is the inflammation of the thyroid gland.

1. Hashimoto's thyroiditis :

   Females > males.

   most common cause in iodine sufficient areas of world.

   Autoimmune destruction if the thyroid gland.

Anti-bodies responsible :

- Anti - TSH receptor antibody.
- Anti - thyroglobulin antibody.
- Anti - microsomal antibody.

Active space

Associated genes :

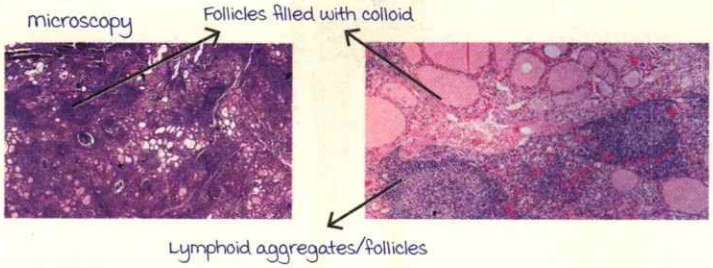
- CTLA4
- PTPN22
- HLAB8

Initially patient presents with Hashitoxicosis, followed by hyperthyroidism.

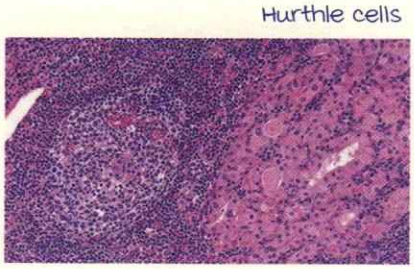
Grossly :
Diffuse homogenous enlargement of the thyroid gland.

Microscopy in Hashimoto's 00:23:34

1. Lymphoid follicles /aggregates also called as struma lymphomatosum.
   Lead sto increase to increase risk of NHL (marginal zone lymphoma /maltoma).
   Lymphoid aggregates/follicles are not supposed to be seen in normal cases.



2. Hurthle cell change/oncocytic change/oxyphil cells/ Ashkenazy cells :
   Characteristic feature of Hashimoto's.
   Abundant eosinophilic (due to excess mitochondria).
   Granular cytoplasm.
   Abundant eosinophilic cytoplasm is seen because of excess mitochondria.



Active space

Complications :

- Papillary cancer of thyroid.
- NHL marginal zone lymphoma.
- Increased risk of other autoimmune disorder (SLE, Sjogrens).

Sub-acute lymphocytic thyroiditis 00:30:15

Painless enlargement of thyroid gland.
Seen postpartum.
Self-limiting.
Biopsy shows :
Lymphocytic aggregates
(can be differentiated from Hashimoto's thyroiditis is the absence of Hurthle cells)

1. De Quervain's thyroiditis :
    - Sub-acute granulomatous thyroiditis.
    - Risk factor : Secondary to infections (mumps, measles, coxsackie).
    - Self-limiting.
    - Painful thyroid gland enlargement.
    - Biopsy shows giant cells and granulomas.
2. Riedel's thyroiditis :
    - Dense fibrosing thyroiditis.
    - Fixed swelling.
    - Gland becomes stony hard (D/D : cancer), because of extreme fibrosis.

MCQs :

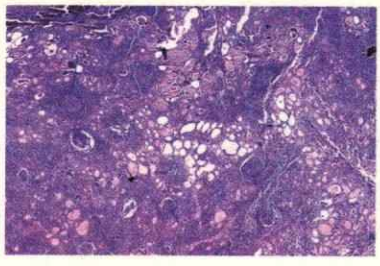
1. A 30 year old woman from Barcelona has noted enlargement of her neck over the past 4 months. On physical examination, she has a diffusely enlarged thyroid that is not painful on palpation. Her TSH level is 2.0mU/L. A subtotal thyroidectomy is performed and histologically the tissue shows follicles with papillary infoldings lined by tall columnar cells. Which of the following is the most likely diagnosis?
    A. Subacute granulomatous thyroiditis.
    B. Papillary carcinoma.
    C. Multinodular goitre.
    D. Hashimoto's thyroiditis.
    E. Graves' disease.

Active space

2. A few days following viral fever, a 50 year old female presented with pain in neck, fever, malaise and firm enlargement of both the lobes of thyroid. On investigation thyroid antibodies were normal and serum T4 was high normal probable diagnosis is :
   A. Autoimmune thyroiditis.
   B. Lymphoma of thyroid.
   C. Granulomatous thyroiditis.
   D. Riedel's thyroiditis.

3. A 28 year old woman has difficulty concentrating at work for the past month. She is constantly getting up and walking around visiting co - workers. She complains that the work area is too hot. She seems nervous and often spills her coffee. She has been eating more but has lost 5kg in the past 2 months. On physical examination her temperature is 37.5 degrees Celsius, pulse 101b/m, respiratory rate 22/min and blood pressure 145/85mmHg. Which of the following laboratory finding is most likely to be present in this woman?
   A. Decreased catecholamines.
   B. Decreased iodine uptake.
   C. Decreased TSH.
   D. Decreased plasma insulin.

4. A 32 year old female presented with weight gain, loss of appetite and easy fatigability.

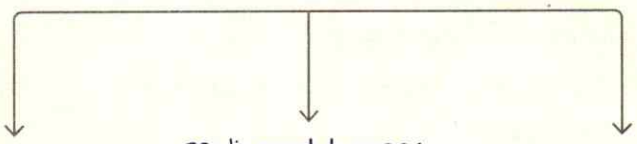


On examination, a swelling was noted in the anterior aspect of neck which moves with deglutination. Biopsy from the neck revealed the following. What is your diagnosis?
   A. Follicular CA thyroid.
   B. Hashimoto's thyroiditis.
   C. Graves' disease.
   D. Riedel's thyroiditis.

Active space

THYROID TUMORS

Thyroid tumors can be divided in to three categories :



Benign : Follicular adenoma.

Malignant tumor :
4 types of malignancies;
- Papillary carcinoma.
- Follicular carcinoma.
- Medullary carcinoma.
- Anaplastic carcinoma.

Lymphoma : Occurs rarely.

When to suspect malignancy ?
- Single.
- Solitary nodule.
- Cold nodule on scan.
- In a young male with a previous history of radiation exposure.

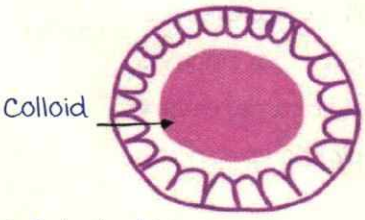
Criteria for adequacy of FNAC of thyroid.
A specimen should display at least 6 groups of follicular cells, with each group composed of at least 10 cells preferably on a single slide.
There are 3 expectations :
- A diagnosis of Thyroiditis may be made if abundant inflammatory cells are present.
- A benign colloid nodule may be diagnosed if abundant thick colloid is present as the presence of abundant colloid reliably identifies most benign processes.
- A diagnosis of atypia or malignancy if atypical or malignant cells are identified.

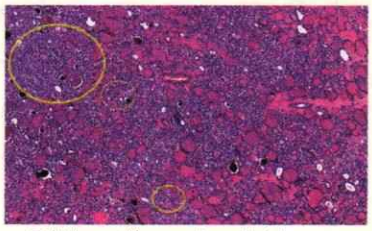
Active space

Follicular adenoma :

00:04:42

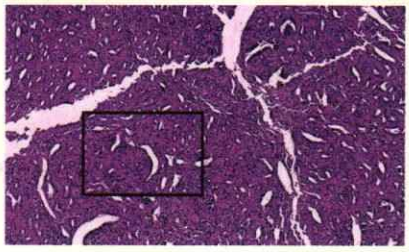
- Benign tumor.
- Females > males.
- Younger age group.
- Well circumscribes lesion.
- On microscopy : Proliferation of small follicles with scanty colloid.
- No capsular or vascular invasion.




Follicles with scanty colloid

It has 2 variants :

- Hurthle cells adenoma (>50% cells : Hurthle cells) : Has abundant eosinophilic granular cytoplasm.
- Hyalinizing trabecular adenoma.


Hurthle cells

Malignancies of thyroid.

Feature	Papillary	Follicular	medullary	Anaplastic
Incidence	most common			Least common
Risk factor	Radiation Thyroglossal cyst Hashimoto's thyroiditis	Iodine deficiency MNG		
Origin	Follicular cells	Follicular cells	Parafollicular cells	Follicular cells
metastasis	Lymphatic	Hematogenous	Both	Both
Genetics	BRAF(m.c), RET-PTC	K-RAS(m.c) PI3K	RET(on chromosome 10), MEN II	P53
Prognosis	Best			Worst
H&E	Orphan Annie	Follicles	Amyloid	

Active space

BRAF mutation is also seen in :

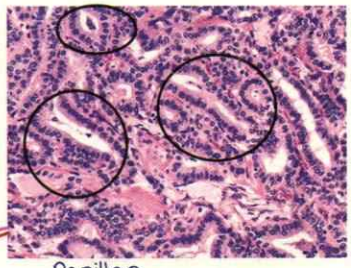
- Pilocytic astrocytoma.
- Papillary cancer of thyroid.
- Malignant melanoma.
- Hairy cell leukaemia.
- Langerhans cells histiocytosis.

Microscopy

00:14:48

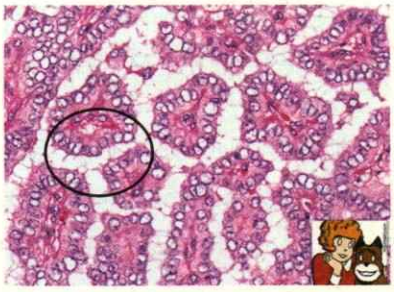
Papillary carcinoma of thyroid :

1. Papillae : Finger like projection with a fibrovascular core (RBCs or blood vessels).



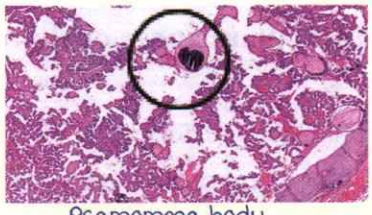
Papillae

2. Orphan Annie eye nuclei : The papillae are lines by cells with optically clear nuclei (high power, cells appear empty).



Orphan annie nuclei

3. Presence of Psamomma bodies : Foci of dystrophic calcium calcification.
Calcium appears densely basophilic.
The stain for calcium is Von Kossa and Alizarin red S.
Also seen in :
Papillary RCC.
Meningioma.
Serous cyst adenocarcinoma of ovary.
Mesothelioma.
Prolactinoma.

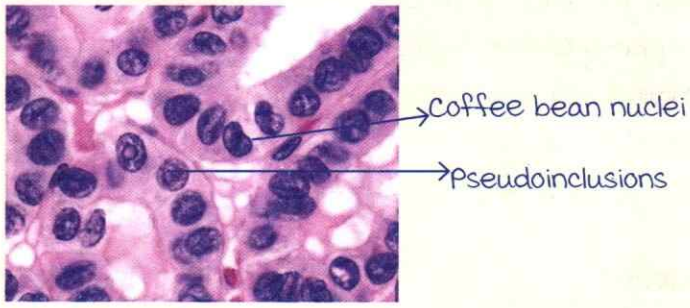


Psamomma body

4. Coffee bean nuclei : Grooves are seen in the nuclei.
It is also seen in :
    - Brenner tumor.
    - Granulosa cell tumor of ovary.
    - Langerhans cells of histoplasmosis.

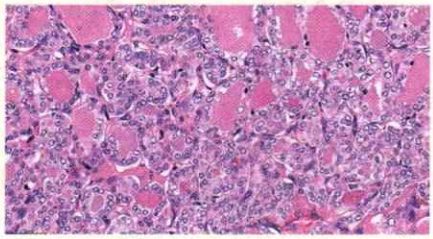
Active space

5. Nuclear pseudo inclusions :



Variants of papillary carcinoma :

1. Encapsulated variant.
2. Follicular variant of papillary cancer : The cells are arranged in the follicles.
   The nucleus appears empty (pseudoinclusions, Orphan Annie, coffee bean).


Follicular variant papillary cancer

3. Tall cell variant : Poor prognosis.
4. Diffuse sclerosing variants : Poor prognosis.
5. Papillary microcarcinoma : When the size of the tumor is <1 cm, it is called Papillary microcarcinoma.

Follicular cancer of thyroid

00:24:44

Follicular carcinoma of thyroid :

- Second most common.
- Metastasis : By hematogenous route.
- Risk factor : Long standing goitre and iodine deficiency.
- K-RAS is the most common mutation seen.

Microscopy :

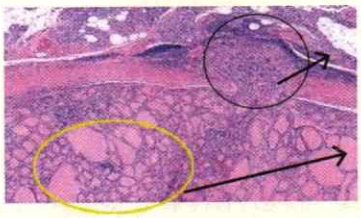
Follicular adenoma and carcinoma : The cells are arranged in follicles.

The differentiating feature that is :

Follicular adenoma : Capsular or vascular invasions are absent.

Active space

Follicular carcinoma : Capsular (mushroom) or vascular invasions are present.
(Hepatic adenoma and carcinoma can also be differentiated like this).



Follicular carcinoma

Thyroid follicles filled with colloid :

- Capsular invasion.
- Cells are moving out of the capsule like a mushroom and invading the capsule.

FNAC is not useful in the diagnosis of follicular carcinoma as it cannot distinguish between the adenoma and carcinoma.

Medullary cancer of thyroid

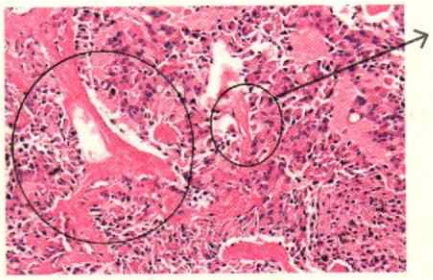
00:28:28

Sporadic
(more common 80%)

- Adults
- Unilateral

Familial

- Bilateral
- multicentric
- RET chromosome 10
- Von Hippel Lindau syndrome
- MEN 2 syndrome
- Neurofibromatosis

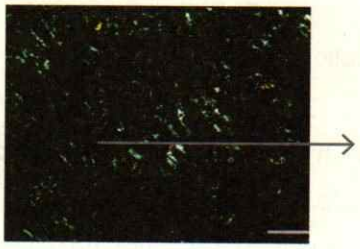


- Arises from parafollicular cells of thyroid which secretes calcium.
- The tumor marker is calcitonin.
- The tumor marker for calcitonin negative cancer is CEA.

Active space

Microscopy :

- Spindle shaped cells.
- A-cal amyloid is produced.
- Best stain for amyloid is Congo red stain : It gives a apple green birefringence (due to cross beta pleated sheet structure) under polarising light.



Amyloid under polarising light.

Anaplastic carcinoma

00:31:31

Least common.

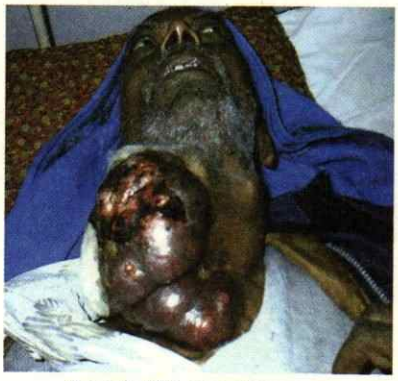
Worst prognosis.

Rapidly enlarging mass in an elderly person.

Microscopic,

- Spindle shaped cells.
- Sarcomatoid cells.
- Giant cells.

All of the cells show pleomorphism.



Anaplastic carcinoma.

Lymphoma :

Seen in elderly.

Risk factor : Hashimoto thyroiditis.

Type : Maltoma.

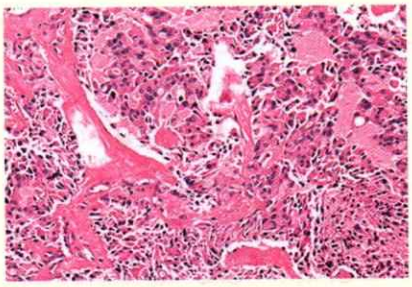
Revision Questions :

Q. A 40 year old woman has noted enlargement of her anterior neck region over the past 8 months. On physical examination her vital signs include T: 36.8 degrees C,

P: 64/min, RR: 16/min, BP: 155/105. There is diffuse, symmetrical thyroid enlargement without tenderness.

Active space

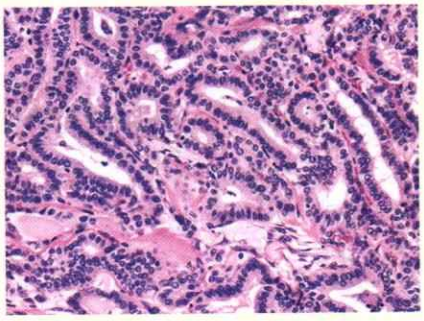
Chest radiograph is normal. Fine needle aspiration of the thyroid yields cells consistent with a neoplasm. Laboratory studies show that she is euthyroid, but her serum ionized calcium level is elevated. She is taken to surgery and frozen sections of several thyroid masses show a malignant neoplasm composed of polygonal cells in nests. A thyroidectomy is performed. Which of the following neoplasms is she mostly likely to have ?



A. Anaplastic carcinoma.
B. Medullary carcinoma.
C. Papillary carcinoma.
D. Metastatic renal cell carcinoma.

Hint : Amyloid can be seen in the image.

Q. A 37 year old male presented with enlarged, non-tender nodule in thyroid gland. There were no thyroid antibodies detected in his serum. T3, T4 and TSH are normal. The histopathology of thyroid after thyroidectomy is shown below. most likely cause of the nodule is :



A. Viral infection.
B. Dietary iodine deficiency.
C. P53 gene mutation.
D. Tyrosine Kinase receptor gene mutation.

Hint : The image is suggestive of clearing of nuclei & papillae can be seen.

Active space

ADRENAL MEDULLA

Phaeochromocytoma

00:01:04

Tumor of adrenal medulla.

Produces catecholamines.

Rule of 10's :

- 0% are bilateral.
- 10% are extra-adrenal (Paraganglioglioma).
- 10% occur in children.
- 10% is malignant :
  Only criteria for malignancy in pheochromocytoma is metastasis .
- 10% Do not present with hypertension :
  90% Patient of pheochromocytoma usually present with episodic paroxysmal hypertension.

In young adult with episodic paroxysmal hypertension

↓

Rule out pheochromocytoma.

↓

Assess urinary catecholamines and V-mandelic acid.

25% of pheochromocytoma are familial (previously 10% are familial) .

Familial pheochromocytoma (fap) :

Bilateral.

Occurs in younger age group .

Genes in FAP :

2 types :

- Genes that increase the growth factor receptor signalling:
  RET, Neurofibromatosis type 1.
- Genes that increase activity of HIF 1 alpha & HIF 2 alpha :
  Von Hippel-Lindau (VHL).
  SDH, B, C & D (Succinyl dehydrogenase).

Active space

SDH is also implicated in gastrointestinal stromal tumor (GIST).

Familial syndromes associated with pheochromocytomas			
Syndrome	Gene	Associated lesion	Other features
Multiple endocrine neoplasia type 2A (MEN-2A)	RET chr. 10	Pheochromocytoma	1. Medullary thyroid carcinoma. 2. Parathyroid hyperplasia
Multiple endocrine neoplasia, type 2B (MEN-2B)	RET Chr. 10	Pheochromocytoma	1. Medullary thyroid carcinoma. 2. Marfanoid habitus. 3. Mucocutaneous ganglioneuroma
Neuro fibromatosis, type 1 (NF1)	NF 1 (Gene 17)	Pheochromocytoma	1. Neurofibromatosis 2. Café-au-lait spots 3. Optic nerve glioma.
Von Hippel-Lindau (VHL)	VHL (Chr. 3)	Pheochromocytoma, paraganglioma (uncommon)	1. Renal cell carcinoma 2. Hemangioblastoma 3. Pancreatic endocrine neoplasm
Familial paraganglioma 1	SDHD	Pheochromocytoma, paraganglioma	
Familial paraganglioma3	SDHC	Paraganglioma	
Familial paraganglioma 4	SDHB	Pheochromocytoma, paraganglioma	

NF1 – Neurofibromin
SDHB – Succinate Dehydrogenase Complex, subunit B
SDHC – Succinate Dehydrogenase Complex, subunit C
SDHD – Succinate Dehydrogenase Complex, subunit D
Chr. – Chromosome

Active space

Polycythemia paraganglioma syndrome 00:01:04

EPAS 1 gene mutation.

↓

increased HIF-2 alpha activity.

Phaeochromocytoma:

Grossly : Brown in colour

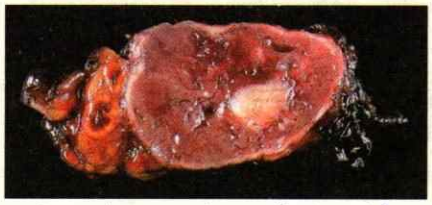
Haemorrhagic areas.

Chromaffin reaction :

Fresh tissue incubated in potassium dichromate solution .

↓

Turns yellowish/
yellow-brown.
Due to catecholamines



phaeochromocytoma (yellowish)

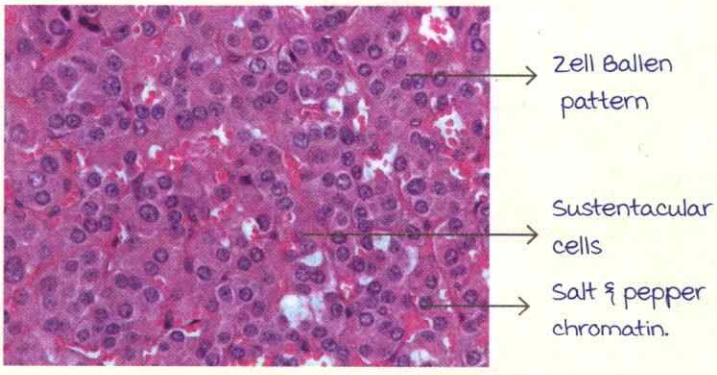
microscopy :

Polygonal to spindle shaped cells arranged in small nests.

Zell ballen pattern.

salt and pepper chromatin (the chromatin pattern).

Due to finely stippled chromatin (like salt and pepper have been mixed)



Also seen in neuroendocrine tumor like :

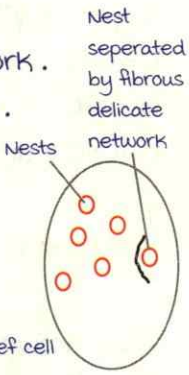
1. Pheochromocytoma.
2. Carotid body tumor.
3. Medullary carcinoma thyroid. (might also).
4. Small cell carcinoma of lung.

Active space

Chief cells.

The nest is separated by delicate fibrous network.

In the fibrous network sustentacular cells seen.



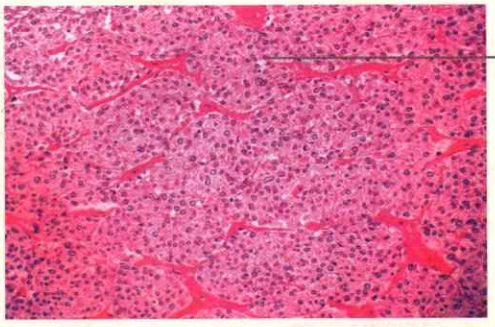
Immunohistochemical markers (IHC) :

also for any neuroendocrine tumor & pheochromocytoma :

- Neuron specific enolase (NSE).
- Chromogranin.
- Synaptophysin.

Sustentacular cells are S-100 positive.

Electron microscopy : dense core neurosecretory granules.



Tumor markers :

Urinary catecholamines

Excretion of vanillyl mandelic acid and homovanillyl acid.

Neuroblastoma

00:17:44

One of the most common extracranial solid tumours of childhood.

Blastemal tumors are more common in children.

The average age is usually < 4 years.

Most common site of a neuroblastoma is_____

Most common presentation is usually abdominal distension.

In child with abdominal distension + tumor rule out neuroblastoma.

Pathogenesis :

1. N-MYC amplification.

Active space

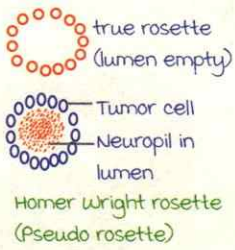
3 types of MYC oncogene :
C-MYC (Burkitts lymphoma)
N-MYC (Neuroblastoma).
L-MYC (Lung carcinoma).

2. ALK gene mutation (in 2%).

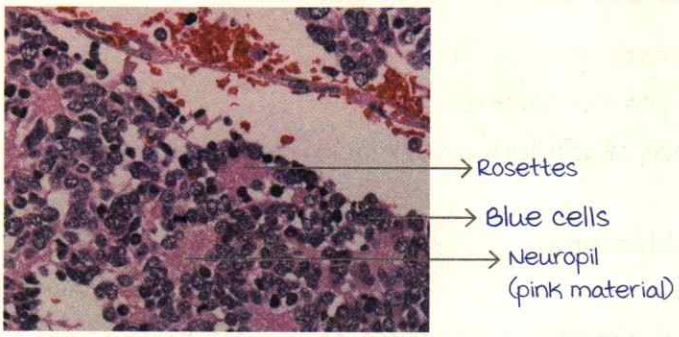
Grossly :
Small circumscribed to large size
Hemorrhage and necrosis +

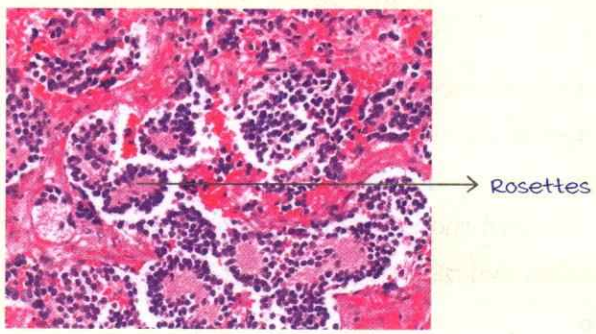
Microscopy :
Small round blue cell (most blastemal tumor of childhood).
Scanty cytoplasm.

Homer Wright rosette (Pseudorosette).
Homer Wright rosette also seen in :
Medulloblastoma
Ewing's sarcoma.



Rosette
Flower Like.
True Rosette : Lumen : Empty.
Pseudorosette : Lumen contains blood vessel/ fibril .





Flexner winterstiener rosette (true rosette) : seen in retinoblastoma.

Active space

Small round blue cell tumors of childhood with scanty cytoplasm are seen in :

1. Retinoblastoma.
2. Neuroblastoma.
3. Hepatoblastoma.
4. Nephroblastoma/ Wilm's tumor.
5. medulloblastoma.
6. Ewing's sarcoma :
   - Xray shows onion skin appearance.
   - Translocation : T 11 : 22.
7. PNET
8. Lymphoma.
9. Rhabdomyosarcoma.

Other findings in microscopy of neuroblastoma :

Intratumoral calcification (calcium is basophilic).

Ganglionic differentiation.

Schwannian stroma (resembles schwann cells).

Variable	Favourable	Unfavourable
Stage	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age	<18 months	>18 months
Histology		
Evidence of schwannian stroma and gangliocytic differentiation.	Present	Absent
Mitosis-karyorrhexis index	<200/5000 cells	>200/5000 cells
DNA ploidy	Hyper diploid or near- triploid	Near-diploid
N-MYC	Not amplified	Amplified
Chromosome 17q gain	Absent	Present
Chromosome 1p loss	Absent	Present
Chromosome 11q loss	Absent	Present
TRKA expression	Present	Absent
TRKB expression	Absent	Present
Telomerase expression	Low or absent	Highly expressed

Most common site of metastasis : Lymph node > bone.

Undergoes spontaneous regression.

Active space

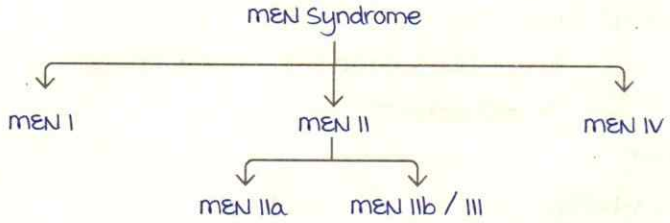
Multiple endocrine neoplasm (MEN) 00:30:39

Characterstics :

Bilateral.

Aggresssive.

In younger age group.



MEN I :

Also known as wermer syndrome.

Mutation in MEN I gene on chromosome 11.

Clinically :

Lesions in : 3Ps

Pituitary :

Prolactinoma (most common).

30-40% cases.

Parathyroid :

~90 cases.

Adenoma.

Hyperplasia.

Pancreatic :

30-70%.

Insulinoma / Gastrinoma.

Gastrinoma most common in duodenum.

Werner syndrome :
Premature aging
Defect in DNA helicase.

MEN IIa syndrome :

also known as Sipple syndrome.

Gain of function mutation on RET on chromosome 10.

Clinically : 2Ps 1m

Phaeochromocytoma
40-50% cases.
Bilateral.
Extraadrenal.

Parathyroid
10-20%
cases

medullary carcinoma thyroid
100% cases.
Bilateral
Calcitonin marker.
(from parafollicular system)

Active space

MEN IIb syndrome :

Also known as MEN III syndrome.

Mutation of RET on chromosome 10.

clinically :

Phaeochromcytoma + 5 M's :

- Marfanoid Body.
- Mucosal Ganglioneuromas.
- Medullary Cornel nerve Fibres.
- Megacolon (Ulcerative colitis).
- Medullary carcinoma of thyroid.

MEN IV syndrome :

Mutation on CDKN1B gene which reduces p27.

Also called as MEN X syndrome.

Clincally : features of MEN IIb syndrome + genitourinary tumors.

MCQs :

Q. Zell ballen pattern is seen in :

A. Lymphoepithelial cyst.

B. Cholesteatoma.

C. Carotid body tumor.

D. Thyroglossal cyst.

Q. Which of the following is a favourable factor in neuroblastoma :

A. Age<18 months.

B. Amplification of N-MYC.

C. Increase in telomerase.

D. Absence of schwannonian stroma.

Q. Rosettes are seen in all except:

A. Neuroblastoma.

B. Retinoblastoma.

C. Medulloblastoma.

D. Neurocysticercosis.

Active space

Q. A 56 year old woman has had diffuse, dull, constant abdominal pain for the past 2 months. On physical examination no abnormal findings are noted. An abdominal CT scan shows a 3 cm right adrenal mass. The right adrenal is excised and on microscopic examination the mass is composed of cells resembling adrenal cortex. Which of the following features is the most reliable indicator that this mass is malignant?

A. Cellular atypia.
B. Presence of mitoses.
C. Invasion.
D. Size of the mass.
E. Cellular necrosis.

Q. The mother of an 11 month old infant had noted enlargement of the baby's abdomen within the past month. This is confirmed by the osteopathic physician, who notes that the baby is otherwise normally developed. An abdominal CT scan reveals a 6 cm mass, with some scattered calcifications, above the right kidney. Laboratory studies show a greatly elevated urinary vanillylmandelic acid (VMA), while the urinary homovanillic acid (HVA) is only slightly increased. The mass is removed and microscopically is composed of sheets of small blue cells. What is the most likely diagnosis?

A. Congenital adrenal hyperplasia.
B. Adrenal cortical carcinoma.
C. Neuroblastoma.
D. Non- Hodgkin lymphoma.
E. Pheochromocytoma.
F. Aldosteronoma.

Active space

PITUITARY & PARATHYROID GLAND

Pituitary gland 00:00:25

Lesions :

- Adenoma
- Carcinoma
- Craniopharyngioma.

Anatomy : 2 Lobes.

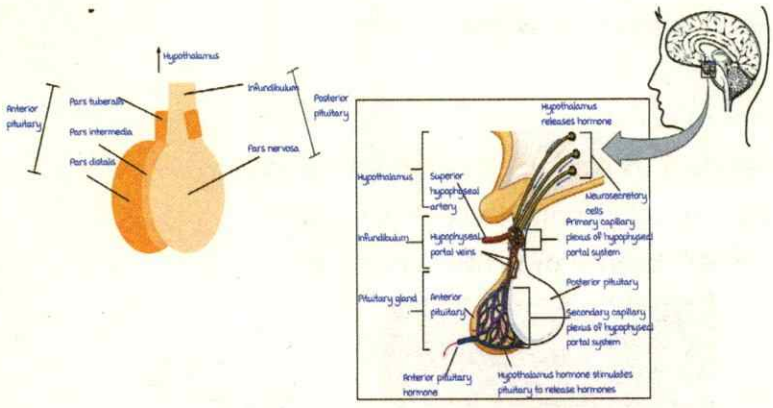
Anterior (80%) :

Produces : GH, ACTH, TSH, MSH, LH, FSH & Prolactin.

Posterior (20%) :

Produces ADH (vasopressin) & Oxytocin

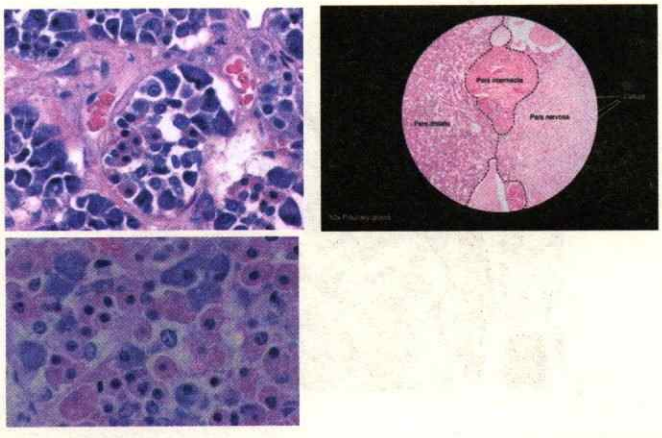
Stored in Herring Bodies.



Histology : Normal pituitary gland consists of -

Acidophils (eosinphilic/pink coloured cells)

Basophils (basophilic/ blue coloured cells).



Active space

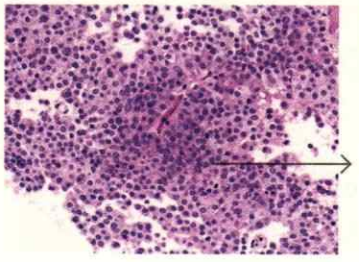
Acidophils (mnemonic : SAL).
Somatotrophs(GH)
Acidohpils
Lactotrophs (Prolactin).
Corticotrophs , Thyrotrophs, Gonadotrophs : Basophils

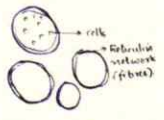
Pituitary adenoma

00:04:29

Most common pituitary tumor.
Most common type of pituitary adenoma : _____
2 types :
< 1 cm : Microadenoma.
Functional tumor : Produce hormones .
> 1 cm : Macroadenoma.
Non functional tumor : Produce pressure symptoms.
Gross :
Well circumscribed & encapsulated.

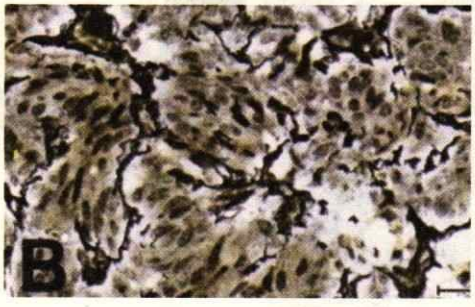
In microscopy :
Sheets of monomorphic cells (similar looking).
Round to polygonal with central nuclei.
Sparse/absence of reticulin network .





monomorphic cells

Reticulin : Black colour on silver stain.
Sparse reticulin network is a characteristic feature.



Active space

Pituitary carcinoma 00:08:48

An adenoma is non-metastatic.
Only indicator of a carcinoma is metastasis or invasion.
similarly seen in parathyroid & other endocroine tumors.

Genetic alterations in pituitary tumor

Gene	Protein function	Oncogenic mutations	m/c associated pituitary tumor
GNAS	α subunit of stimulatory G-protein, Gsα	Somatic activating mutation	Somatotroph adenoma
USP8	Deubiquitinase	Somatic activating mutation	Corticotroph adenoma
Protein Kinaes A, regulatory subunit 1a (PRKAR1A)	Negative regulator of protein kinase A (PKA) leading to increased cAMP production	Germline inactivating mutations (Carney complex)	Somatotroph or lactotroph adenoma
MEN 1	Transcription regulator	Germline inactivating mutations(multiple endocrine neoplasia, type 1)	Somatotroph, lactotroph or corticotroph adenoma
CDKN1B (p27/KIP)	Negative cell cycle regulator	Germline inactivating mutations (MEN-1-like syndrome)	Corticotroph adenoma
Aryl hydro carbonreceptor interacting protien (AIP)	Receptor for aryl hydrocarbons and a ligand-activated transcription factor	Germline inactivating mutations (familial isolated pituitary adenoma syndrome).	Somato troph or lactotroph adenoma (especially in patient younger than 35 years of age)
HRAS	mitogenic signaling, cell growth and survival	Somatic activating mutation	Pituitary carcinoma
DICER 1	microRNA processing	Germline inactivating mutation	Pituitary blastoma

Classification of pituitary adenomas

Active space

Adenoma Type	Hormone	Trans-cription Factor	Morphologic variant	Associated syndrome
Somatotroph adenoma	GH	PIT-1	Densely granulated adenoma.	Gigantism (children)
	GH	PIT-1	Sparsely granulated adenoma.	Acromegaly (adults)
	GH, PRL (in same cells)	PIT-1, ERα	Mammo-somatotroph adenoma.	
	GH, PRL (in different cells)	PIT-1, ERα	Mixed somatotroph-lactotroph adenoma	
Lactotroph adenoma	PRL	PIT-1	Sparsely granulated adenoma.	Galactorhea and amenorrhea (in females)
	PRL	PIT-1	Densely granulated adenoma.	
	PRL, GH (focal and variable)	PIT-1, ERα	Acidophilic stem cell adenoma	Sexual dysfunction, infertility
Thyrotroph adenoma	TSH	PIT-1	Thyrotroph adenoma	Hyperthyroidism
Corticotroph adenoma	ACTH	TPIT	Densely granulated adenoma.	Cushing syndrome.
	ACTH	TPIT	Sparsely granulated adenoma.	Nelson syndrome Mass effect
	ACTH	TPIT	Crooke cell adenoma (prominent intracytoplas-mic cytokeratin filaments)	(20% of corticotroph adenomas are hormonally silent)
Gonadoroph adenoma	FSH, LH	SF-1, GATA-2, ERa	Gonadotroph adenoma	Mass effect ± hypopit-uitary (most gonadotroph adenoma are hormonally silent)
Null cell adenoma	None	None	-	Mass effects
Pluri-hormonal adenoma	GH, PRL, TSH	PIT-1	-	-

Active space

Craniopharyngioma 00:15:06

Suprasellar tumor.

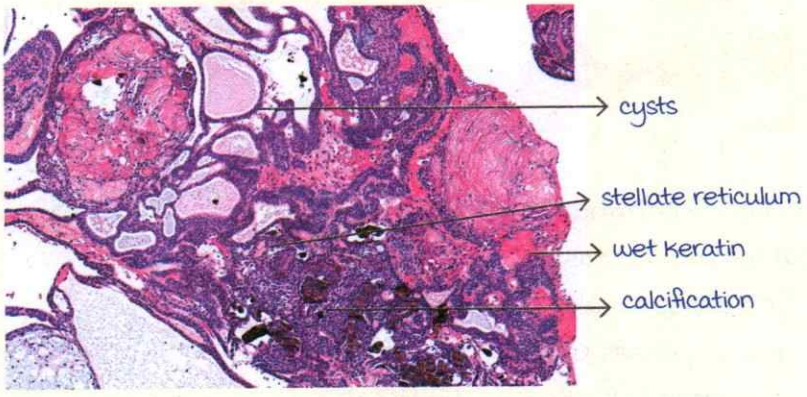
3-4 Tumor, circumscribed tumor

Pressure symptoms on optic chiasma ⟶ Bitemporal hemianopia

Gross examination :

Cysts : Filled with oil called machinery oil.

2 Types	Adamantinomatous	Papillary
Seen in	Children	Adult
microscopy	Stratified squamous epithelium	Stratified squamous epithelium
Wet Keratin	Present	Absent
Calcification	Present	Absent
Cysts	Present	Absent
Stellate reticulum	Present	Absent



Calcification :

stain for calcium : Alizarin red, Von Kossa.

Seen in :

- Craniopharyngioma.
- Oligodendroglioma.
- meningioma (dystrophic due to Psammoma bodies).

Parathyroid gland 00:20:26

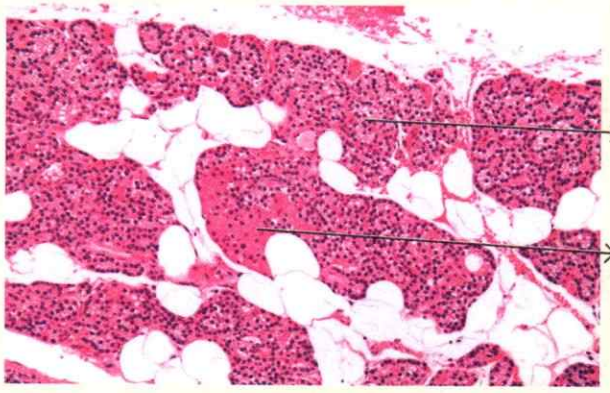
Four pea shaped glands.

Present on posterior surface of thyroid gland.

Active space

3 types of cells

- Chief cells :
  Most common type.
  Round-polygonal cells with central nuclei.
  Secrete PTH.
- Oxyphil cells :
  Abundant eosinophilic granular cytoplasm (due to excess mitochondria).
  Also seen in hurthle (hashimoto's thyroiditis), oxyphil, oncocytic cells.
- Water clear cells : Clear cells due to presence of glycogen.



Function of parathyroid :

Calcium homeostasis :

Increases renal tubular reabsorption.
Also increases GI absorption of calcium.
Conversion of vitamin D to its active form in Kidney.

3 types of hyperparathyroidism

Primary hyperparathyroidism :

3 main causes :

- Parathyroid adenoma (85–90%) – single gland enlargement
- Parathyroid hyperplasia (5–10%) – all 4 glands enlarged.
- Parathyroid carcinoma :
  <1% of cases.
  Metastasis (most important factor).

Active space

Parathyroid adenoma 00:28:06

Most common cause .

In 85 to 90% of cases

Single gland enlargement

Pathogenesis :

Increase in PTH

↓

Increase release of calcium from bones.

↓

Hypercalcemia.

Increased urinary excretion of calcium & phosphate.

Biochemical profile :

S. PTH increased .

S. Calcium increased.

S. Phosphate decreased

Gross : Single gland enlargement .

Solitary , well circumscribed.

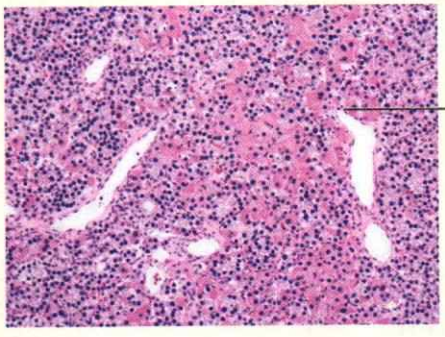
Cells most prominent in parathyroid are chief cells.

Sheets and cords of chief cells are seen.

If more number of oxyphil cells are present, tumor is called as Oxyphil cell adenoma or Hurthle cell adenoma .

These are cells with abundant eosinophilic granular cytoplasm .

Absence of the reticulin network.



Parathyroid hyperplasia 00:31:35

In 5-10% of cases .

All 4 glands are enlarged.

Active space

Histology is similar parathyroid adenoma : Sheets /cords of monomorphic cells .

Genetics of parathyroid adenoma :

2 genes are implicated.

MEN I & IIa : Can be associated with parathyroid lesions.

Cyclin D1 inversion .

Hyperparathyroidism patient due to adenoma/ hyperplasia clinically present with :

- Painful bones :

  Most common.

  Cortex of the bones affected.

  m/c affected bones : Phalanges, vertebrae, femur.

  Salt and pepper skull.

  Bony lesion can present in 3 forms :

  - Osteoporosis because calcium is moving out.
  - Brown's tumors :

    Increased vascularity in the bones .

    Haemorrhage

    ↓

    Accumulation of hemosiderin laden macrophages.

    ↓

    Imparting brown colour.

  - Osteitis fibrosa cystica :

    Due to :

    Increased osteoclastic activity + peritrabecular fibrosis

    ↓

    Lead to cystic lesions .

    Also called Von Recklinghausen Disease of bone.

    Neurofibromatosis type I is called Von Recklinghausen Disease .

- Abdominal groans : Colicky.
- Renal stones : Recurrent.
- Psychic moans : Neuropsychiatric manifestations.

Active space

Secondary hyperparathyroidism 00:37:15

Primary defect is in extraparathyroid site.

Causes :

- Chronic renal failure (most common cause).
- Lithium toxicity.
- Reduced calcium absorption.
- Malabsorption (any intestinal disorder).
- Vitamin D deficiency .

Pathogenesis in chronic renal failure :

Decreased conversion of Vitamin D to its active form.
↓
Leads to decreased Vitamin D.
↓
Calcium decreased
↓
Stimulus for PTH
↓
Increased PTH.

Biochemical profile :

- S. PTH increased .
- S. Calcium decreased.
- S. Phosphate increased (no urinary excretion).

Tertiary hyperparathyroidism 00:39:30

Irreversible.
Difficult to treat.
Occur in long standing chronic renal failure.
One of the gland turns adenomatous/produces PTH autonomously.

MCQs :

Q. A clinical study is performed of subjects from birth to age 80 years who were documented by laboratory testing to have hypocalcemia. Medical records of these subjects are analyzed and the disease conditions documented in these subjects recorded. A subset of these patients had hypocalcemia documented in infancy. Which of the following

Active space

conditions is most likely to have been present in this subset of patients?

A. Parathyroid carcinoma.
B. Vitamin D deficiency.
C. Chronic renal failure.
D. DiGeorge syndrome.
E. Parathyroid adenoma.

Answer : DiGeorge syndrome (Mnemonic : CATCH 22).

Cleft lip
Abnormal facies.
Thymic hypoplasia.
Cardiac abnormalities.
Hypocalcemia (3rd & 4th pharyngeal arches affected which is the origin of parathyroid & thymus).
Deletion of 22q 11.

Q. Diagnostic feature of a parathyroid carcinoma is :

A. Atypia
B. Mitosis
C. Metastasis
D. All of the above

Q. A 33-year-old previously healthy man has lateral visual field deficits, but his residual vision is 20/20. His facial features have changed over the past year. His shoe size has increased. A head CT scan reveals enlargement of the sella turcica. Which of the following hormones is most likely being secreted in excessive amounts in this man?

A. Antidiuretic hormone.
B. Prolactin.
C. ACTH.
D. Growth hormone.
E. Luteinizing hormone.

This is a case of acromegaly.

Q. GNAS mutation is associated with malignancy of which cells?

A. Lactotroph.
B. Thyrotroph.
C. Somatotroph.
D. None.

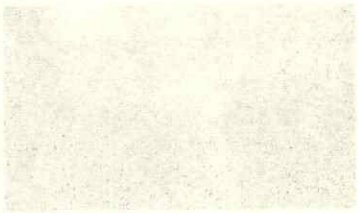
Active space

Q. A 15-year-old boy has had worsening headaches for 2 months. On examination he has diminished peripheral vision, but no loss of visual acuity. A head CT scan reveals a 4 cm mass expanding the sella turcica and eroding the sphenoid bone. The mass is cystic with scattered calcifications. Which of the following is the most likely diagnosis?

A. Prolactinoma
B. metastatic seminoma
C. Empty sella syndrome
D. Anaplastic astrocytoma
E. Craniopharyngioma
F. Osteosarcoma.

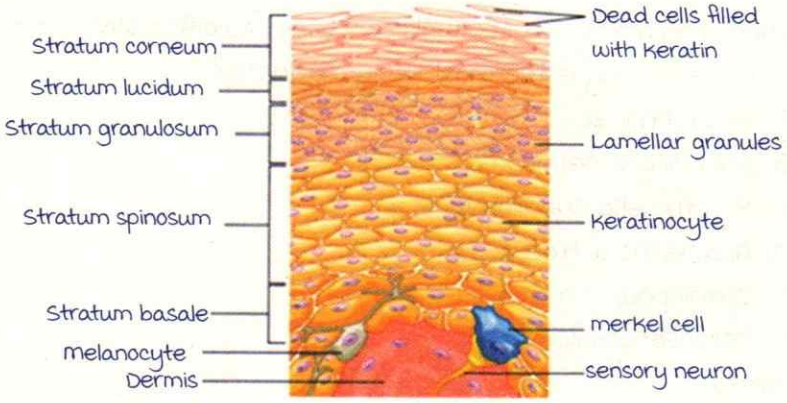
Hints :

mass expanding sella tursica, cystic lesion , sphenoid bone ersoion, scattered calcification suggests of craniopharyngioma.



Active space

DERMAPATHOLOGY



Presence of nuclei in Keratin is called parakeratosis and is an abnormality.

Skin have 3 parts :

Epidermis.

Dermis.

Hypodermis.

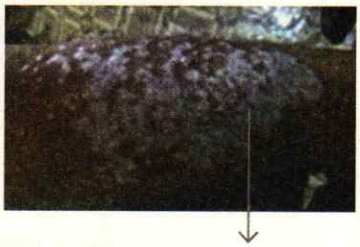
Layers of epidermis :

- Stratum (S) corneum.
  Above it pink eosinophilic Keratin without nucleus.
- S. lucidum.
- S. granulosum : Contains lamellar granules.
- S. spinosum.
- S. basale : Contains melanin (pigment of skin).

Psoriasis

00:03:42

Site : In elbow, knee, trunk.
Clinically pink plaque with silvery scales. On scraping off the silvery scales, pin point bleeding spots seen called as Auspitz sign.

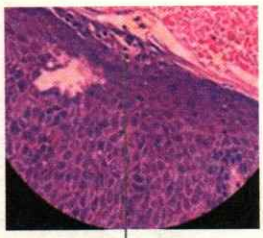


silvery scales

Active space

Microscopy :

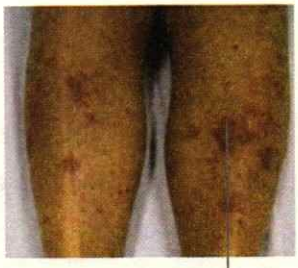
- Munro's microabcess :
  Neutrophilic infiltrate in S. corneum.
- Spongiform Pustules Of Kogot :
  Neutrophilic infiltrate in S. spinosum.



Munro's microabcess

Pautrier's microabcess seen in mycosis fungoides.
It is a cutaneous T cell lymphoma.

Q. 37 year old female presented with silvery scale. O/E Auspitz sign : Positive. Which histopathological feature seen ?
A : Munro's microabcess :
& Spongiform Pustules Of Kogot
Sometimes parakeratosis also seen.



Purplish plaque

Lichen planus

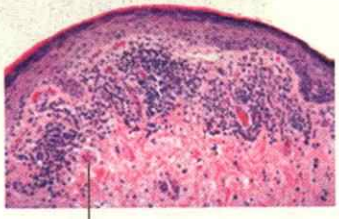
00:08:38

Purplish.
Papules.
Plaques.
Polygonal.
Planar.
Pleuritic

Mnemonics : 6P's

Microscopy :

- Band like lymphocytic infiltrate in upper dermis.



Band like lymphocytic infiltrate

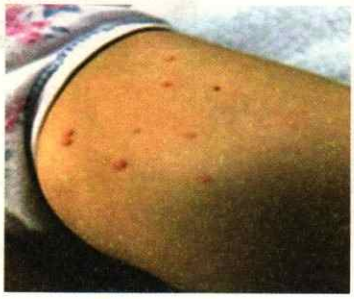
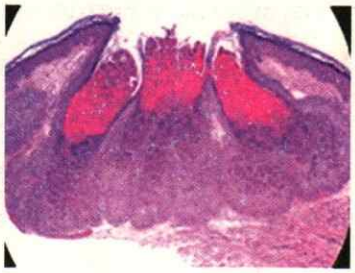
- Colloid bodies/Civatte bodies : Apoptoptic bodies seen in lower layer (S. basale).

Molluscum contagiosum :

Caused by Pox virus.

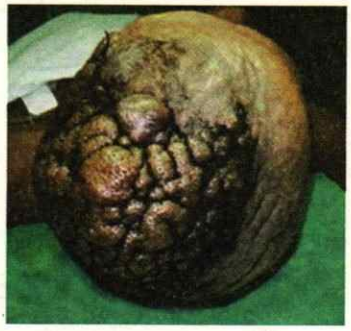
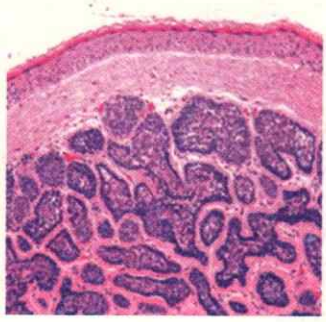
Active space

Clinically pearly dome shaped lesion.
Microscopy : Eosinophilic intracytoplasmic inclusions in S. corneum & S. granulosum called as molluscum bodies.

Cylindroma :

Also called as Turban tumor.
Occurs in scalp like turban.
Microscopy :
Zig saw arrangement of cell nest.
In between nest, there is pink basement membrane like material.

Seborrheic Keratosis :

Occur as paraneoplastic syndrome.
Acanthosis nigricans : Velvety thickening of axila, perineum etc.
Also as paraneoplastic syndrome called as sign of Leser-Trélat.
Seen in GI malignancy.

Active space

Malignancy of skin

- Basal cell carcinoma.
- Squamous cell carcinoma.
- Malignant melanoma.

Squamous cell carcinoma (SCC) 00:17:45

2nd most common skin malignancy.

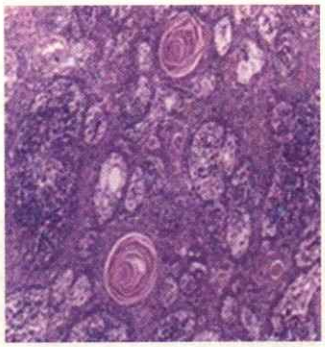
Risk factors : Radiation (ionizing).

UV rays.

Chronic ulcers.

Actinic keratosis.

Arsenic.



Microscopy :

Excess abnormal keratin synthesis seen as keratin pearls.

On high power desmosomes (bridges between squamous cells) can be visualized.

Border's classification :

Well differentiated : Well formed keratin pearls.

Moderately differentiated : Single cell keratinization.

Poorly differentiated :

No keratin, few squamous cell and pleomorphism.

Immunohistochemical markers :

Cytokeartin (CK), p63.

Basal cell carcinoma (BCC) :

Also called rodent ulcer as like rat will be nibbling but will not metastasize.

Glioma also will not metastasize.

Risk factors :

Genetic mutation in Sonic Hedgehog pathway.

Common in white people.

UV radiation.

Associated with Gorlin syndrome : Naevoid BCC with ovarian/

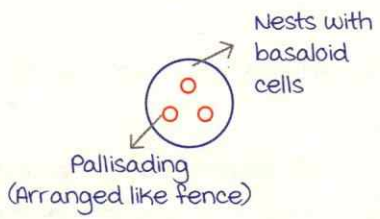
Active space

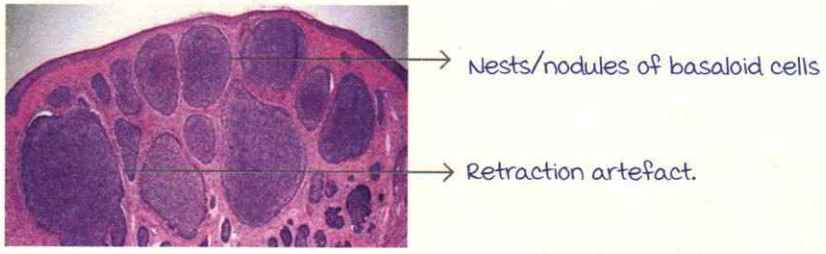
CNS tumors like medulloblastoma.

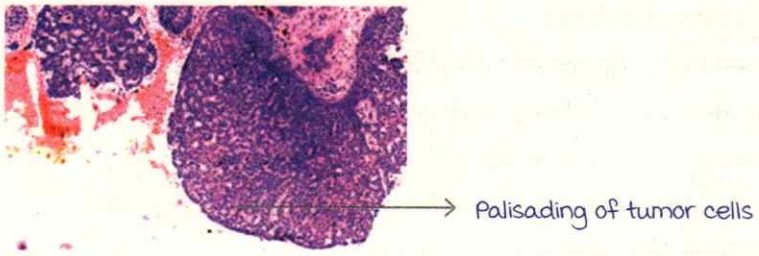
Clinically, as purplish nodule with telengiactasia.

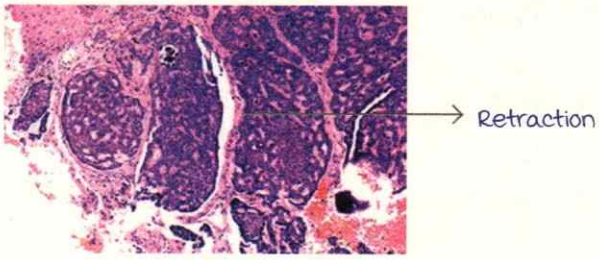
Microscopy:

- Nests/nodules of basaloid cells (resemble cells of S. basale).
  (Small cells, blue, hyperchromatic nuclei with scanty cytoplasm).
- Palisading of tumor cells in the outermost layer.
- Retraction/separation artifact:
  Nodules are separated in stroma by empty spaces.









Malignant melanoma (MM) 00:28:40

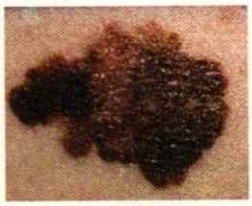
Highly aggressive tumor.

Risk factors:

P16 INK 4A (cell cycle regulator).

Active space

Kit & RAS abnormalities.
Problem in Telomerase.
BRAF mutations.



Changes in mole invoking suspicion of mm :

Asymmetry.
Border irregularity.
Color variability.
Diameter > 5mm.
Elevated.

Mnemonic : ABCDE

- Usually nucleoli is basophilic.
  Eosinophilic nucleoli (macronodular) is also seen in Hodgkin's lymphoma (Reed sternberg cells).
- Masson dichrome : Stain for collagen.

mm grows into 2 patterns :

- Radial :
  Superficial and horizontal growth in epidermis & upper dermis.
  No metastasizing.
- Vertical :t
  Deeper growth & in deeper tissue.
  Metastasize.

Microscopy :

- Pleomorphic cells with prominent nuclei & nucleoli.
- Eosinophilic nucleoli.
- Melanin pigment (black).
  Melanin derived from tyrosin.

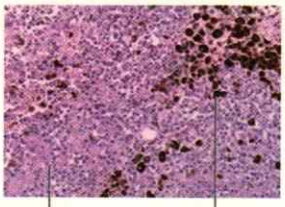
Stain used :
Masson Fontana (for collagen).
SCHMORL.
Dopa oxidase (best).

Active space

Immunohistochemistry marker :

HMB45, Melan A } Important.

S100 : Not very specific.



Pleomorphic cells Black pigments

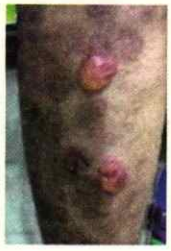
Bullous disorders of skin

00:36:09

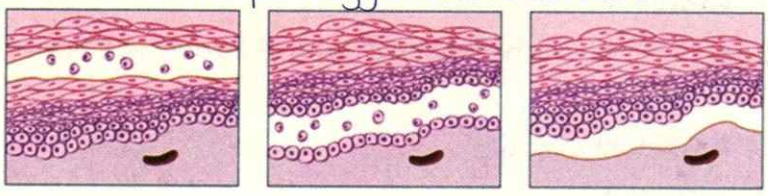
Blistering disorders.

Based on where bullae is :

- Subcorneal : Below S. corneum.
  Eg : Pemphigus foliaceous.
- Suprabasal : Above S. basal layer.
  Eg : Pemphigus Vulgaris.
- Subepidermal : Below epidermis.
  Eg : Bullous Pemphigoid.



Dermatopathology of bullous disorders



Subcorneal suprabasal Subepidermal

Pemphigus vulgaris

00:38:47

Autoimmune disorder.

Type 2 hypersensitivity reaction.

Antibodies against intercellular protein like Desmoglein 1 & 3.

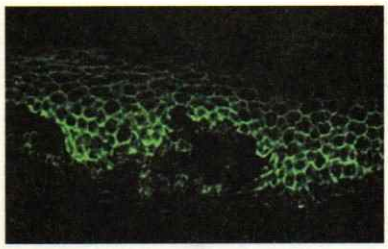
Presents with bullae on skin of face, scalp, trunk.

Microscopy : Suprabasal bulla.

Row of tomb appearance.

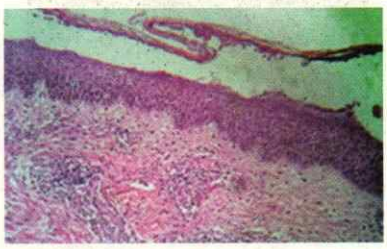
Immunofluroscence : Fish net / reticular pattern

Active space



Pemphigus foliaceous :

Subcorneal bulla.



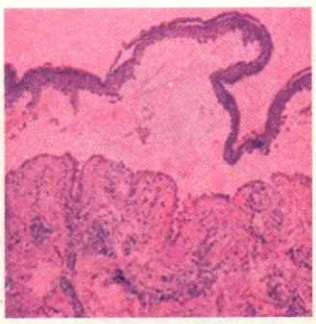
Bullous pemphigoid 00:42:54

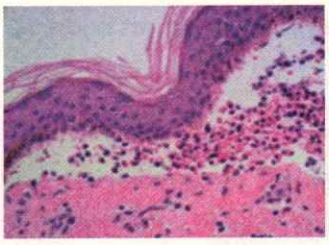
Type 2 hypersensitivity reactions.

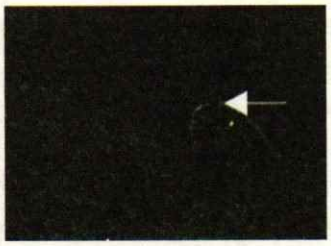
Antibodies against _____

Microscopy : Subepidermal bullae.

Eosinophills at dermoepidermal junction.







Active space

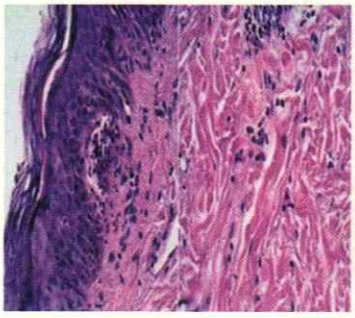
Dermatitis Herpetiformis(DH) 00:45:20

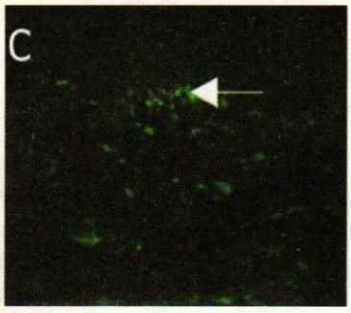
Associated with Coeliac disease .

Microscopy of DH :

Subepidermal bulla.

Neutrophilic abcesses (infiltrate) at the tips of the dermal papillae.

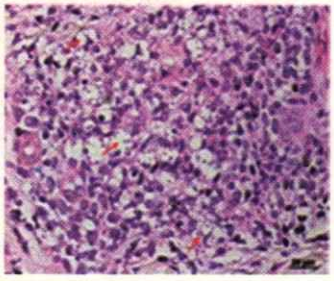




	Pemphigus Vulgaris	Bullous Pemphigoid	Dermatitis Herpetiformis
Antibody	IgG	IgG	IgG
Bulla	Suprabasal	subepidermal	subepidermal
IF	Fish net	Linear	Granular

A 26 year old man from eastern part of India presents with a shallow and slowly expanding ulcer with heaped up borders over the face. Biopsy reveals granulomas and the following findings. What is the most likely diagnosis?

A. Leishmaniasis.
B. Tuberculosis.
C. Lepromatous leprosy.
D. Primary syphilis.



Answer : Cutaneous leishmaniasis (leishmanian bodies : purplish, double dotted appearance).

A 28 year old man with gluten sensitivity presents with severely itchy papulovesicuar lesions on extremities knees, elbows and buttocks for one year. Direct IgA staining of the lesions showed IgA deposition as follows. What is the probable diagnosis?

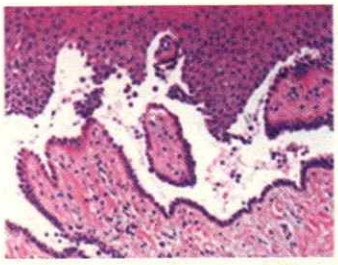
Active space

A. Bulluos pemphigoid.
B. Pemphigus vulgaris.
C. Dermatitis herpetiformis.
D. Epidrermolysis bullosa.

Answer : Dermatitis herpetiformis (granular pattern in IF).

A 45 year old woman presents with oral ulcers and bullae over the mucosa and skin on examination, the bullae are flaccid and filled with clear fluid. Histopathology of the lesion is show below. What is the most likely diagnosis?

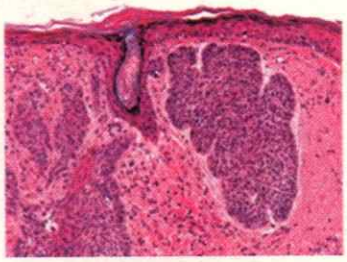
A. Pemphigus vulgaris.
B. Bulluous pemphigoid.
C. Dermatitis herpetiformis.
D. Pemphigus foliaceous.



Answer : Pemphigous vulgaris (supra basal bullae & row of tomb appearance).

A 52 year old man presents with pearly papule over the face containing prominent dilated subepidermal blood vessels and surface ulceration. A histological picture of the tumor is shown below. All are true about this tumor except :

A. Presence of multiple such tumors is seen in Gorlin syndrome.
B. It may be multifocal.
C. metastasis is common.
D. Incidence is increased in Xeroderma pigmentosa.



Answer : metastasis is common.
S/o basal cell carcinoma of skin : Pearly papule with telangiectasia, retraction, palisading seen.
Incidence is increased in Xeroderma pigmentosa.

Active space

BONE AND SOFT TISSUE LESIONS

Bone pathology

00:01:00

3 types of cells in bone :

Osteocytes : Maintain Ca^{2+} and PO_4^{3-} homeostasis.

Osteoblasts : New bone formation.

Osteoclasts : Mononuclear phagocytes of bones.

Marble bone disease :

Also known as Albers schonberg disease/Osteopetrosis.

Defect in _____

This leads to defect in osteoclastic activity.

Paget's Disease :

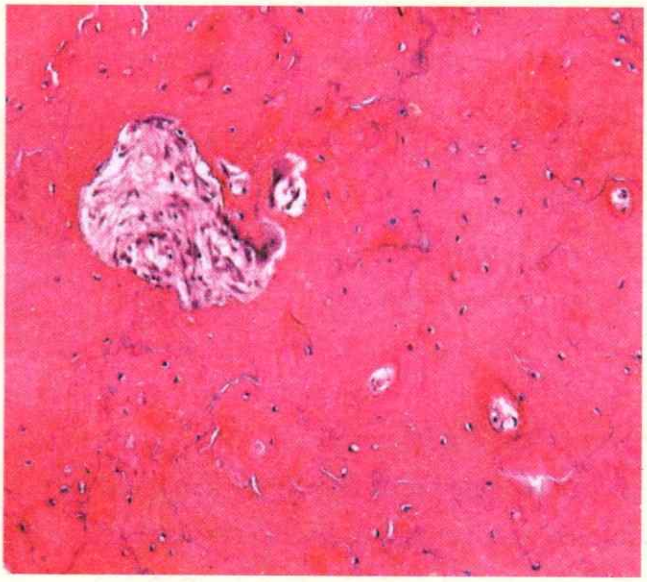
Defect :

Mutation of SQSTM 1 gene.

↑Bone mass ↑ALP / Alkaline phosphatase.

H & E :

Mosaic pattern / Jigsaw puzzle pattern.



Active space

Tumors	Age	Location	Genetics
Osteosarcoma	Bimodal age, 10 – 20 yrs	metaphysis of long bones, m.c site : Distal femur	Rb gene
Osteochondroma (exostosis)		metaphysis of long bones	EXT1, EXT2 gene defect
Giant cell tumor (osteoclastoma)	F>m. 20 to 50 yrs	Lower end of femur	
Chondrosarcoma	M>F, 40 years	Axial skeleton, pelvis, ribs, sternum	Ch 1p rearrangement
Ewings sarcoma	<20 yrs	Diaphysis of long bones	t (11 : 22)

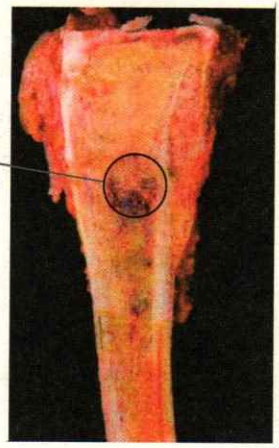
Chromosome 1p is also affected in oligodendroglioma.

Tumors	X-ray	microscopy	Gross
Osteosarcoma	Codman's triangle	New bone formation, lace like pattern	Large, tan white gritty masses
Osteochondroma (exostosis)			mushroom shaped protrusions
Giant cell tumor (osteoclastoma)		multinucleated osteoclast type giant cells	
Chondrosarcoma		malignant hyaline, myxoid cartilage, pleomorphic cells	
Ewings sarcoma	Onion skin appearance	Small, round, blue cells with rosettes	

Active space

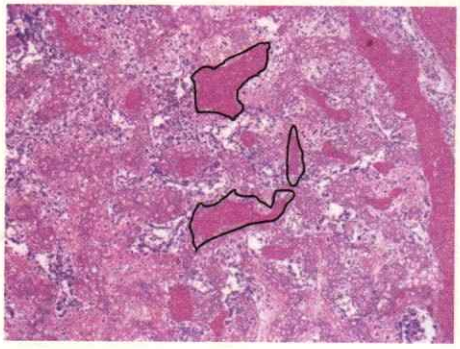
Osteosarcoma :

Large lesion in metaphysis with greyish white areas.



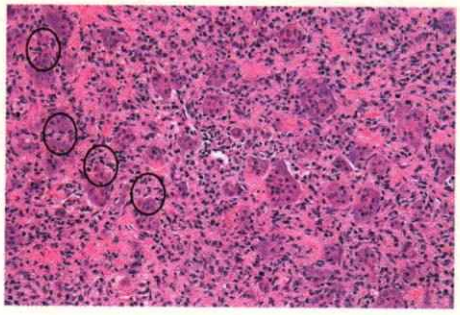
Microscopy :

Pink coloured lace like pattern of new bone formation.



Gaint cell tumor microscropy :

Multinucleated gaint cells : Gives high probablity of Gaint cell tumor. To be correlated with X ray, site of tumor and age of the patient.



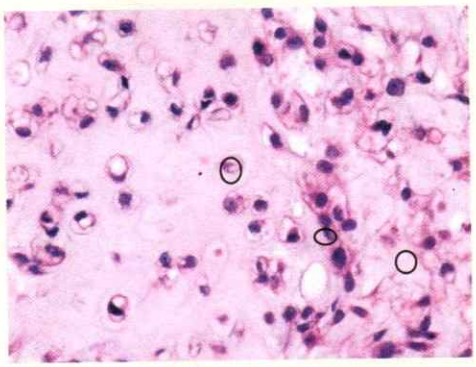
Chondosarcoma :

Shiny (due to cartilage).

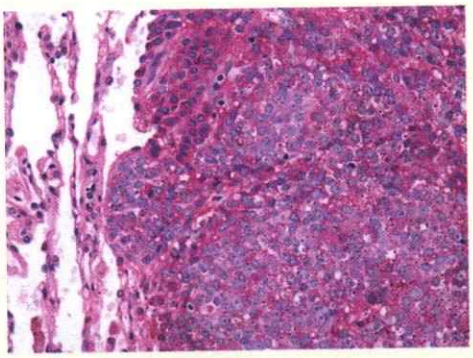
Active space

Chondrosarcoma :
Microscopy

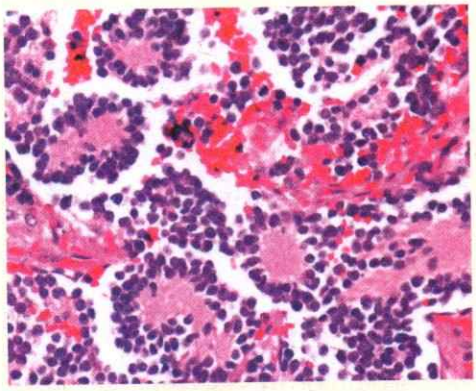
Pleomorphic cells in cartilage.



Ewing's sarcoma
Microscopy :
Small, round, blue cells with scanty cytoplasm and rosettes.
These cells are PAS + due to glycogen.
(magenta coloured in cells)



Rosettes :
Tumor cells are arranged around a central space which is not empty :
Pseudorosette known as Homer wright rosette.



Onion skins :

- Biopsy of malignant hypertension.
- Nerve biopsy of Chronic inflammatory demyelinating polyneuropathy.
- X-ray of Ewing's sarcoma.
- Electron microscopy of storage disorder.
- Electron microscopy of Tay sachs disease.
- Bile duct sclerosis of Primary sclerosing cholangitis (Onion skin fibrosis).
- Spleen in SLE (gross picture).

D/d of Small round blue cells tumors of childhood :

- Retinoblastoma
- Neuroblastoma.

Active space

- Nephroblastoma.
- Hepatoblastoma.
- Ewing's sarcoma/peripheral neuroectodermal tumor (PNET)
- Rhabdomyosarcoma.

True rosette. E.g : Flexner-Wintersteiner rosette seen in retinoblastoma)
Brain tumor with perivascular pseudorosettes : Ependymoma.

Soft tissues

00:14:33

Fat :

Lipoma : Benign tumor of fat.
Presents as round multiple nodules on skin which can increase in number.
Recurrence is seen even after removal in most cases.
Microscopy : Round empty vacuoles in cells.
Stain : Positive on Oil red O and Sudan black.

Liposarcoma :
Malignancy of fat tissue.
m/C sarcoma of adults.
Site : Proximal extremities and retroperitoneum.

Skeletal muscle :

Rhabdomyoma :
Benign tumor of skeletal muscle.
Site : head and neck, heart.

Cardiac rhabdomyoma :
Most common cardiac tumor in children.
Syndrome associated : Tuberous sclerosis.
Shows spider cells.

Rhabdomyosarcoma :
Malignancy of skeletal muscle.
m/C soft tissue sarcoma of childhood and adolescence.
Site : head and neck
Characteristic cells : Tadpole /strap cells.

Active space

Immunohistochemistry/IHC marker of any tumor of skeletal muscle origin (Rhabdomyoma/Rhabdomyosarcoma) :

- Desmin
- myogenin.
- myo D 1.

Embryonal rhabdomyosarcoma :

Common in children.

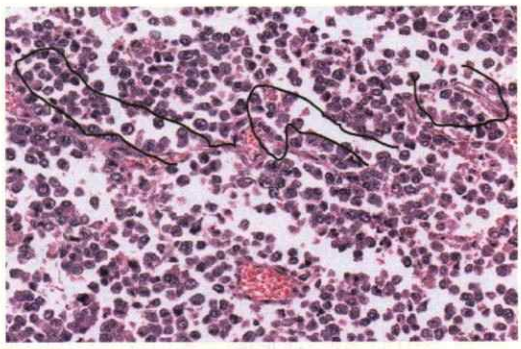
Defect : Chromosome 11 p.

Sarcoma botryoides :

Age < 5 years.

Gross feature : Grape like clusters.

H & E : Tennis racket cells.



Cells have alveolar arrangement.

marker for tumors arising from smooth muscles (Leiomyoma /Leiomyosarcoma) : Smooth muscle actin (SMA).

Tennis racket shaped organelles seen in elecron microscopy of Langerhan's cell histiocytosis.

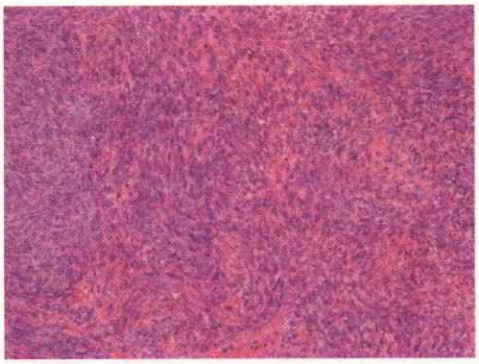
Synovial sarcoma :

m/c site : Around knee.

Biphasic : Epithelial + mesenchymal cells

Associated with : t (x : 18) translocation.

Stains : Keratin, Vimentin, S-100, epithelial membrane antigen /EMA.



Cells arranged in interlacing fascicles / epithelial arrangement : Spindle shaped cells.

Active space

CNS - NON NEOPLASTIC LESIONS

Normal cells of the CNS

00:01:06

Two types of cells :

- Neurons : Permanent cells so do not divide. Functional unit of the CNS.
- Glial cells : Three types :
    - Astrocytes : Formation of blood brain barrier, wound healing.
    - microglia : macrophages of the CNS.
    - Oligodendrocytes : Production of myelin sheath.

  Stain for myelin → Luxol fast blue.

  IHC marker for glial cells → GFAP (Glial Fibrillary Acidic Protein).

Injury in CNS

00:04:43

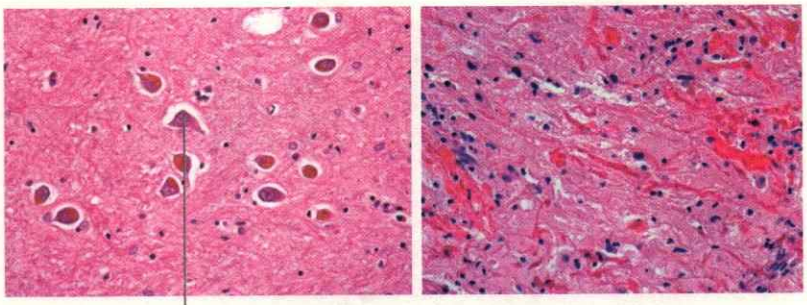
Neurons : Lose their nuclei and become densely eosinophilic → Red neurons.

Glial cells : Gliosis.

Astrocytes :

- Gemistocytic astrocytes : Densely eosinophilic/glassy cytoplasm.
- Corpora amylacea :
    - Pink colored pigment.
    - Heat shock proteins.
- Rosenthal fibres :
    - Thick, elongated, pink fibres.
    - Composed of heat shock proteins and ubiquitin.

Active space

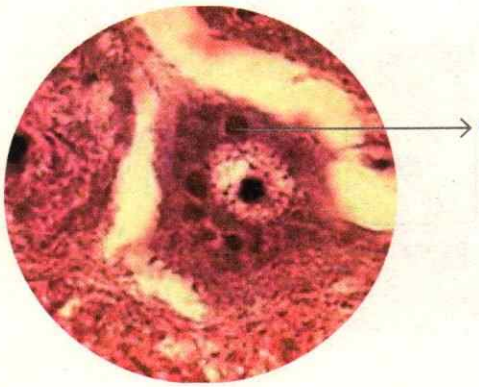


Gemistocytic astrocytes

Infections

00:08:56

1. Rabies :



Negri bodies

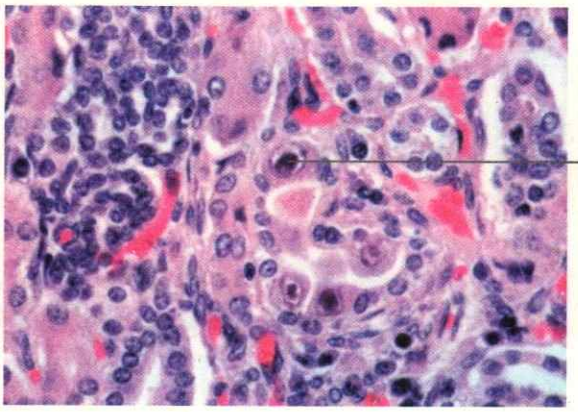
Negri bodies :

- Intracytoplasmic eosinophilic bodies.
- Composed of ribonucleoprotein.
- Seen in purkinje cells of cerebellum and pyramidal neurons of hippocampus.

2. CMV :

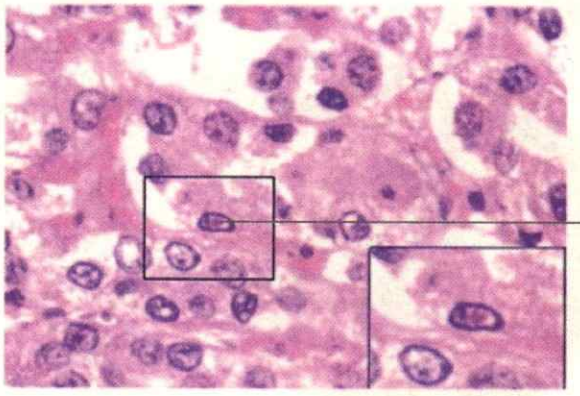
- Intranuclear basophilic inclusions owl's eye appearance.
- Seen in HIV patients.

Active space



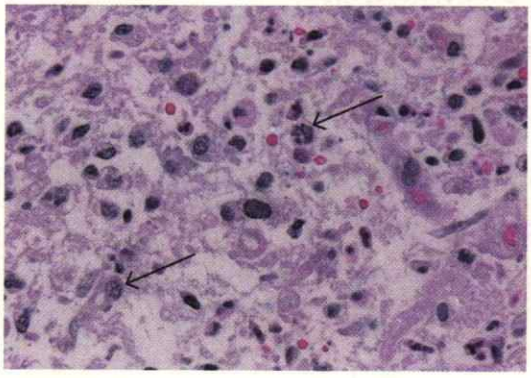
3. HSV I :

- Intranuclear eosinophilic inclusion → Cowdry type A inclusions.



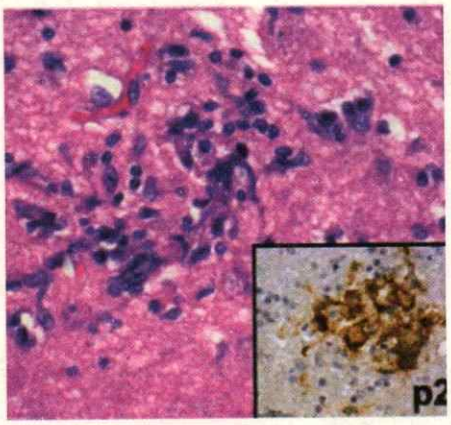
4. Toxoplasmosis :

- Purplish dots inside cells
- Seen in HIV patients.



Active space

5. Microglia nodule in HIV : Comprised of :
    - Lymphocytes/mononuclear cells.
    - Microglia.
    - Multi nucleated giant cells.

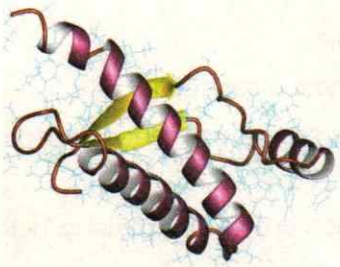


6. Cerebral malaria : Durk's granuloma.
7. Progressive multifocal leukoencephalopathy :
    - Usually caused by JC polyoma virus.
    - Affects the oligodendrocytes.
    - Demyelination of neurons.
    - Seen in immunosuppressed patients.
    - H & E : Eosinophilic inclusions (ground glass inclusions).

Prions

00:17:34

- Proteinaceous infectious particle.
- No DNA/RNA.
- Transmissible spongiform encephalopathies.
- Spongiform change seen in all prion diseases except FFI (Fetal Familial Insomnia).



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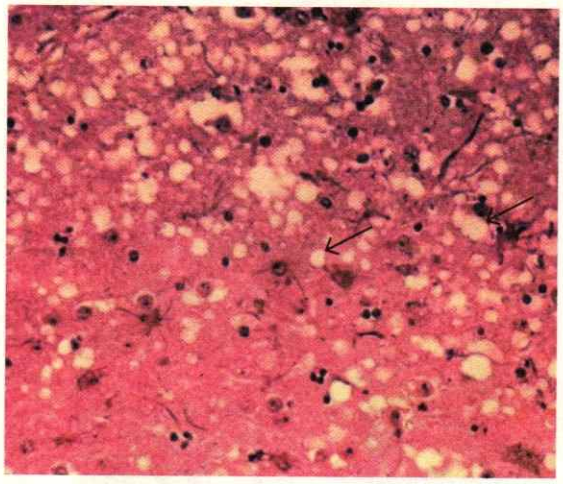
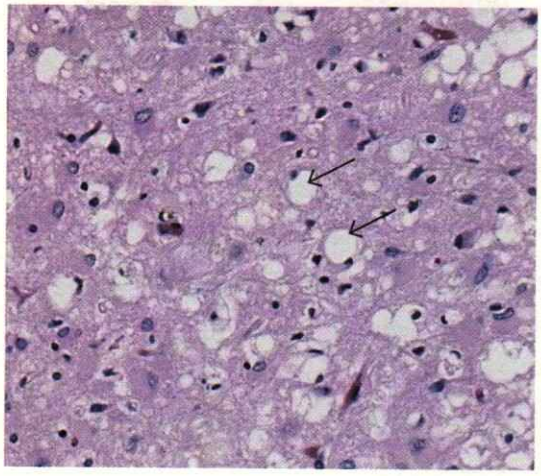




Prion spongiform changes

Diseases caused by prions :

- Humans :
  - CJD. (most common)
  - FFI.
  - KURU : Brain biopsy shows KURU plaque → PAS positive/congo red positive.
- Animals :
  - Scrapie.
  - mad cow disease.
  - Bovine spongiform encephalopathy.

Pathogenesis :

PrPc is a cellular prion protein with alpha helix structure.

PrPc mutation → PrPsc (scrapie) → beta pleated sheet structure → formation of APr (amyloid).

Active space

Neurodegenerative diseases of the CNS 00:24:06

Alzheimer's disease :

One of the most common causes of dementia in elderly.

Age of presentation > 50 years.

Affects parietal, temporal, and frontal lobe.

Pathogenesis :

- Aβ amyloid deposition.
- Due to mutation of APP gene (Amyloid Precursor Protein on ch. 21).
- It is a transmembrane protein degraded by 3 enzymes :
    - α secretase
    - β secretase
    - γ secretase.

If APP processed by α and γ secretase pathway → products very soluble → do not deposit in the brain → no disease → Non amyloidogenic pathway.

If APP processed by β secretase pathway → produces amyloid products → Aβamyloid (pathogenic). It keeps depositing in the nucleus basalis of meynert → dementia.

Genetic causes of alzheimer's disease :

Early alzheimer's disease :

APP gene on ch. 21.

PS1 gene on ch. 14

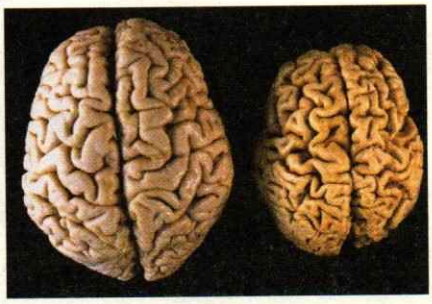
PS2 gene on ch. 1.

Late Alzheimer's disease : APOE gene on ch. 19.

Morphology of brain :

Grossly :

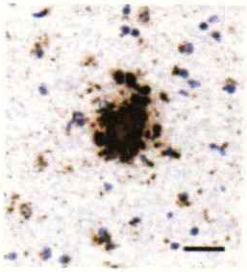
- Atrophy.
- Widening of sulci.



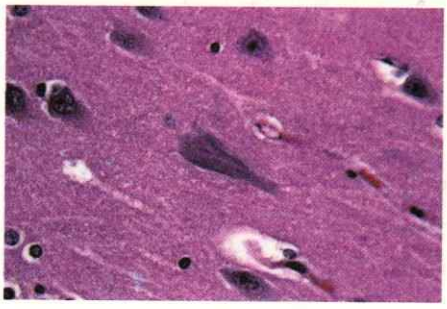
Active space

Microscopy :

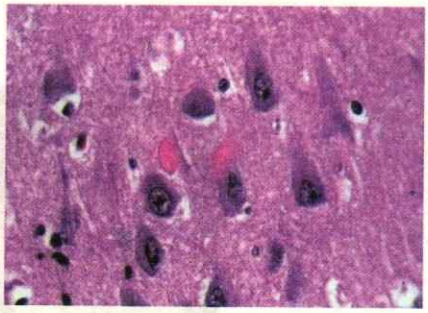
- Neuritic plaques : Aβ core two types : Aβ40 and Aβ42.
- Best seen on silver stain (Bielschowsky silver stain).
- Neurofibrillary tangles/flame cells : Thick elongated fibres. Composed of hyperphosphorylated tau protein. More the number, more is the dementia.
- Hirano bodies : Eosinophilic, thick, elongated bodies composed of actin.
- Cerebral amyloid angiopathy : Deposition of amyloid in blood vessels of the brain.
- Granulo vacouler degeneration.



Neuritic plaque



Neurofibrillary tangles



Hirano bodies

Active space

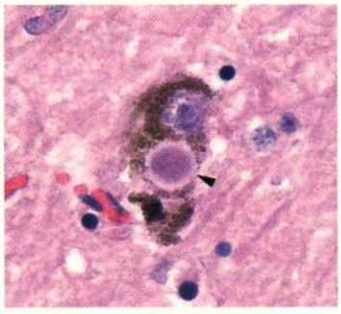
Parkinson's disease 00:38:12

Pathogenesis :

- Gain of function mutation in LRRK2 gene.
- Mutation involving the over expression of α-synuclein.

Gross appearance : Pale substantia nigra.

On Microscopy : Lewy bodies seen, Composed of α-synuclein.



Lewy body

Amyotrophic lateral sclerosis :

Pathogenesis : Mutation in SOD1 (CuZn SOD).

Microscopy :_____

Huntington's disease :

Pathogenesis :

Trinucleotide repeat mutation defect → CAG repeats (occurs in the coding region) → affects caudate nucleus → chorea.

MCQs :

Q. A 30-year-old G2 P1 woman delivers a stillborn male infant at 28 weeks gestation. Her previous pregnancy resulted in a normal term birth. At autopsy, the cerebrum of the fetus demonstrates extensive diffuse periventricular areas of necrosis with dystrophic calcifications. Infection in utero with which of the following organisms is most likely to have caused these findings ?

A. Taenia solium.

Active space

B. Toxoplasma gondii.

C. Poliovirus.

D. Candida albicans.

E. Treponema pallidum.

F. Group B Streptococcus.

Answer : B

Q. A 45-year-old male, known diabetic and hypertensive suffers a stroke. During this episode, which of the following cells are least susceptible to injury considering stroke was transient ?

A. Pyramidal cells of hippocampus.

B. Purkinje cells of cerebellum.

C. Astrocytes of cerebral cortex.

D. Watershed zones of cerebral cortex.

Answer : C.

Q. A 75-year-old man who had progressive memory loss for 3 years, died and autopsy was performed. The microscopic image is shown below. What is the most likely mechanism responsible for this condition ?

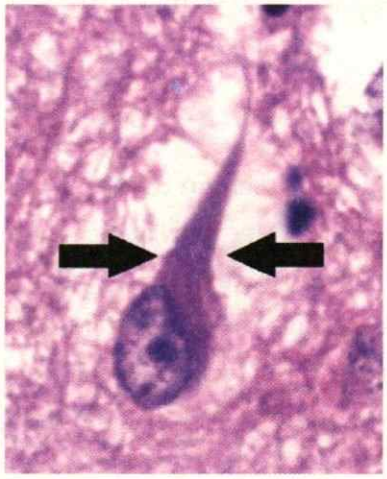
A. Change in prion protein.

B. Mutation in Tau protein aggregation of abeta peptide.

C. Deposition of lewy body.

D. Demyelination of neurons.

Answer : B.



Active space

CNS TUMOURS

CNS tumors :

m/c CNS tumor : Secondaries or metastasis.

m/c primary brain tumor : Glioma> Meningioma.

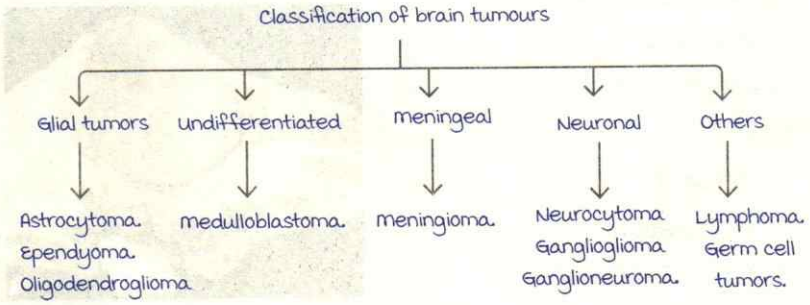
m/c brain tumor in children : Pilocytic astrocytoma.

m/c malignancy of CNS in children : _____

m/c tumor metastazing to the brain : Small cell lung carcinoma.

Classification of brain tumors

00:04:23



St. Anne mayo grading system :

Mnemonic : AMEN.

A : Atypia.

M : Mitosis.

E : Endothelial proliferation.

N : Necrosis.

Grade I : No AMEN.

Grade II : Only Atypia is present.

Grade III : Atypia and Mitosis.

Grade IV : 3 present out of AMEN.

As tumor progresses from Grade I to Grade IV it becomes poorly differentiated and the prognosis is poor.

Active space

For diagnosis :

- Age of the patient.
- Location of the tumor.
- Symptoms of the patient.

Astrocytoma

00:09:07

Divided into 4 grades.

I : Pilocytic astrocytoma : No AMEN.

II : Diffuse fibrillary astrocytoma : Atypia present.

III : Anaplastic astrocytoma : Atypia and mitosis present.

IV : Glioblastoma : AMEN present.

Poor prognosis as grades progresses.

Pilocytic astrocytoma :

Benign in nature.

WHO grade I tumor.

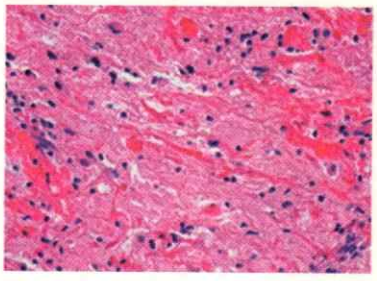
Three C's :

- Children.
- Cerebellum.
- Cystic nodules.

Gross : Cystic (mural nodules).

2 differential diagnosis of mural nodules :

Pilocytic astrocytoma and pleomorphic xanthoastrocytoma (PXA).



HPE : Biphasic pattern

1. Cystic structures.
2. Rosenthal fibres.
3. Eosinophilic granular bodies.

Excellent prognosis.

Glioblastoma

00:15:22

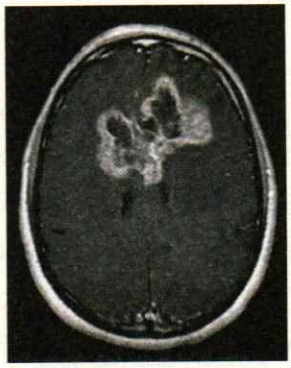
WHO grade IV astrocytoma.

Poor prognosis.

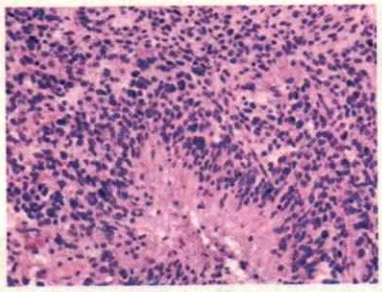
Usually affects cerebral hemisphere.

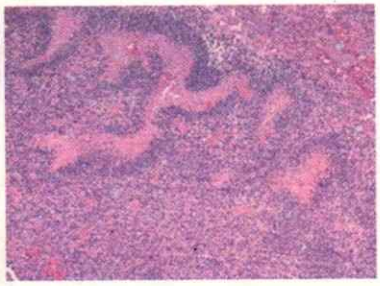
Cerebral cortex (frontal lobe).

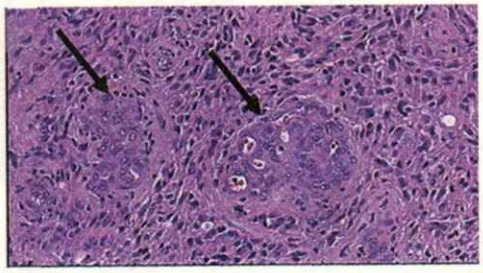
Active space



Crosses midline and hence called as butterfly tumor.
Usually seen in elderly people.
HPE : Atypia, mitosis, endothelial proliferation and necrosis present.
High cellularity and high pleomorphism.
Large number of mitosis.
Necrosis : Geographical or serpentine necrosis (pseudopallisading of tumor cells around necrotic area).
Glomeruloid bodies (endothelial proliferation).







WHO 2016 classification of glioblastoma :

IDH wild type	IDH mutant type
Aka primary glioblastoma.	Aka secondary glioblastoma.
Age : 55 years (elderly).	Age : 45 years.
90% cases.	10% cases.
Genetics : TERT, EGFR.	p53.
Extensive necrosis.	Less necrosis.
Supra tentorial.	Infra tentorial.

Wild type has a poorer prognosis.

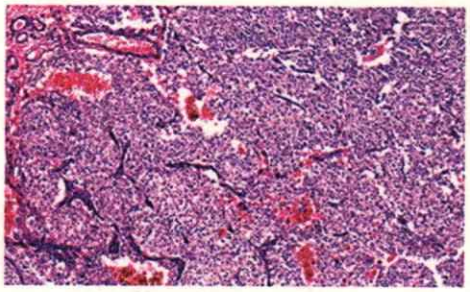
Active space

Oligodendroglioma

00:24:15

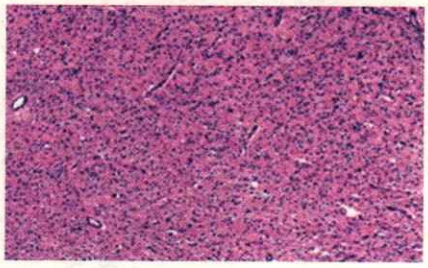
Age of presentation : 30-40 years (elderly).
Cerebral cortex (frontal lobe).
Genetics : 90% cases are due to IDH 1 and IDH 2 gene mutation and in some cases Co-deletion of 1p and 19q.

If co-deletion is present, tumor is chemo sensitive.



Gross examination : Calcifications.
D/D for calcifications in CNS tumors :
Craniopharyngioma.
Oligodendroglioma.
Meningioma.
HPE :

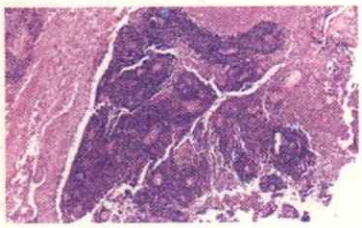
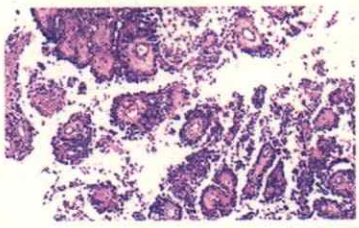
- Cells in sheets : fried egg appearance (central nuclei with perinuclear clearing).
- Anastomosing vascular channels : Chicken wire blood vessels.
- Calcifications.
- Perineuronal satellitosis.



(Fried egg appearance also seen in bone marrow biopsy of hairy cell leukemia).
Grade II tumor : Intermediate prognosis.

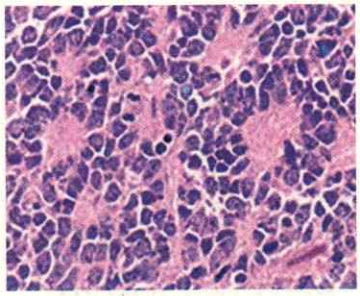
Ependymoma :
Middle age to elderly.
Usually found in spinal cord/ependymal lining of 4th ventricle.
Can be associated with NF-1 gene mutation.
Can spread by CSF.
HPE : Perivascular pseudo rosettes (tumor cells surrounding around blood vessels).

Active space

markers of glial tumors : Glial Fibrillary Acidic Protein (GFAP).

Medulloblastoma 00:34:21



Usually seen in children.
m/c malignancy in children.
Site : Cerebellum.
Syndromes associated :

- Li Fraumeni syndrome.
- Turcot syndrome.
- Gorlin syndrome.

Drop metastasis : Tumor cells falls from cerebellum like a drop from CSF and metastasize.
HPE : Small round blue cells with scanty cytoplasm (Homer wright rosettes).
Grade IV and poor prognosis.

Primary CNS lymphoma :

- Seen in HIV positive patients.
- DLBCL.
- HPE : Angiocentric growth and hooping pattern on the reticulin stain.

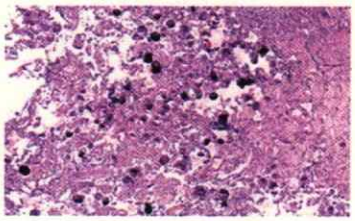
Meningioma 00:40:56

m/c CNS tumors in adults.
F >> M.
Responsive to progesterone.
Radiation exposure is a risk factors.
Can be associated with NF-1 and NF-2.
HPE : Psammoma bodies.
Meningioma exists in 6 different patterns :

1. Fibroblastic.

Active space

2. Meningothelial
3. Syncytial.
4. Transitional.
5. Secretory.
6. Psammomatous.



Psammoma bodies

2 types of meningioma :

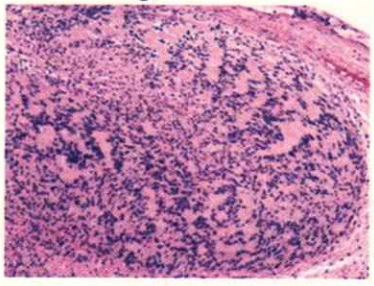
Atypical meningioma	Anaplastic meningioma
>4 mitosis/HPF + any 3 out of 5 : • High cellularity. • High NC ratio. • Prominent nucleoli. • Pattern less growth. • Presence of necrosis.	>20 mitosis /HPF.

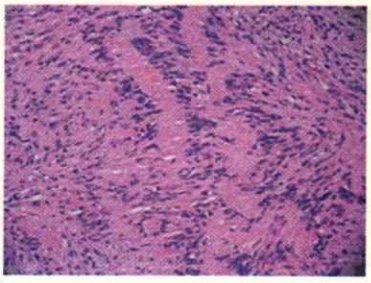
Schwannoma

00:45:54

Arises from Schwann cells. Aka bilateral acoustic neuroma.
Associated with NF-2 gene mutation on Chromosome 22.
Arises from inferior vestibulocochlear nerve.
Well circumscribed and well encapsulated tumor.
HPE :

- Hypercellular area : Antoni A pattern.
- Hypocellular area : Antoni B pattern.
- Verocay bodies.





GFAP positive CNS tumors :

- Astrocytoma.
- Oligodendroglioma.
- Ependymoma.

Active space

- Choroid plexus tumor.
- Glioblastoma.
- Medulloblastoma.

Tumor	Histological feature
Pilocytic astrocytoma	Rosenthal fibres microcysts
GBM	Serpentine necrosis Glomeruloid bodies
Oligodendroglioma	Fried egg Chicken wire blood vessels Calcification
Ependymoma	Perivascular pseudo rosettes
Medulloblastoma	Small round blue cells Homer wright rosettes
Meningioma	Psammoma bodies
Schwannoma	Antoni A Antoni B Verocay bodies

Tuberous sclerosis

00:52:33

2 gene mutations : TSC 1 and TSC 2.

TSC 1 : Hamartin.

TSC 2 : Tuberin.

Triad : Seizures, mental retardation and angiofibroma.

Autosomal dominant disorder.

- In brain :
  a. Increased risk of sub ependymal giant cell astrocytoma.
  b. Cortical tubers.
  c. Sub ependymal nodules.
- Skin : Ash leaf macules and Shagreen's patch.
- Lungs : Lymphangioleiomyomatosis.
- Kidney : Renal angiomyolipoma.
- Heart : Increased risk of Rhabdomyoma.

Active space

Von Hippel Lindau syndrome :

VHL gene mutation on chromosome 3.

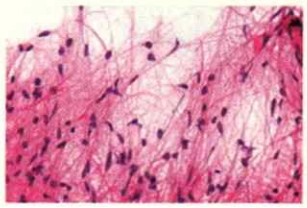
Autosomal dominant disorder.

Increased risk of :

- Clear cell renal cell carcinoma.
- Pheochromocytoma.
- Cerebellar hemangioblastomas.
- Pancreatic and epidermal cysts.

Turcot syndrome : Increases risk of brain tumors like medulloblastoma + FAP.

Q. A 4 year old child is brought with complaints of gait disturbances. On neurologic examination, nystagmus and hypotonia are noted. Contrast enhancing MRI of the brain shows enhancing nodule within the wall of a cystic mass. The mass is resected and histology shows this image. Which of the following statements is incorrect regarding this tumor ?



A. It is GFAP positive.

B. It is usually a slow growing tumor.

C. BRAF mutation is seen in this tumor.

D. It belongs to WHO grade II tumor.

Q. A 52 year old man has had headaches and difficulty concentrating for the past 2 months. He then begins to exhibit odd behaviour, including shooting his rifle in his back yard, which the neighbours find disconcerting. He then suffers a grand mal seizure, and is admitted to the hospital. MR imaging of the brain reveals a large mass with extensive necrosis in the left cerebral hemisphere extending across corpus callosum into the right hemisphere. Which of the following neoplasms is he most likely to have?

A. Meningioma.

B. Glioblastoma.

Active space

C. Medulloblastoma.

D. Metastatic adenocarcinoma.

E. Pilocytic astrocytoma.

Q. A 36 year old woman has noted increasing numbers of disfiguring nodular masses involving the skin of her trunk and extremities. She has experienced frequent headaches over the past month. On physical examination these 0.5 to 2 cm subcutaneous masses are firm and non-tender. MR imaging of the brain shows an ill-defined 4 cm mass of the right parietal lobe. An abdominal CT scan shows a 3 cm mass involving the left adrenal gland. Laboratory studies show increased urinary free catecholamines. No other family members are affected by these problems. A mutation involving which of the following genes is most likely to be present in this woman?

A. APC.

B. CFTR.

C. K-RAS.

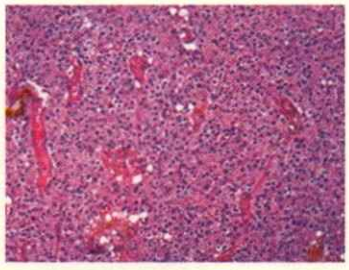
D. NF-1.

E. N-MYC.

F. TP53.

G. RB.

Q. A 45 year old male patient presents to the OPD with recurrent seizures, headache, and projectile vomiting. MRI brain reveals heterogenous tumor with calcification in frontal lobe. The histology of the tumor is given below. Which of the following is the most common genetic alteration in this tumor?



A. Deletion of chromosome 1p and 19q.

B. Loss of 9p.

C. Mutation in CDKN2A.

D. Mutation of isocitrate dehydrogenase genes.

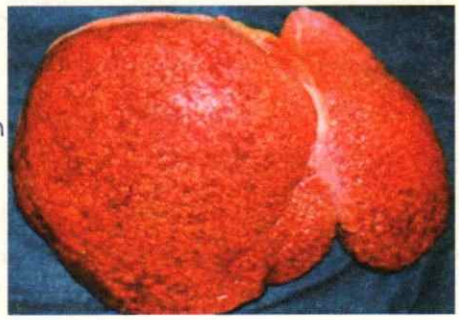
Active space

SYSTEMIC PATHOLOGY IMAGES : PART 1

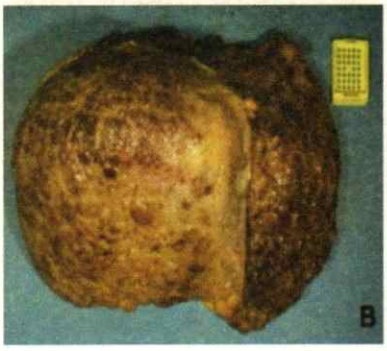
Liver

00:00:22

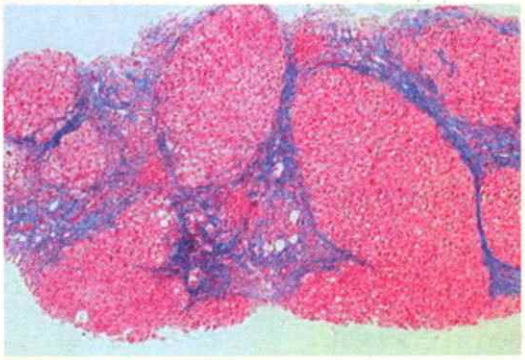
Gross sepcimen of micro nodular liver cirrhosis, showing small nodules which are less than 3 mm.



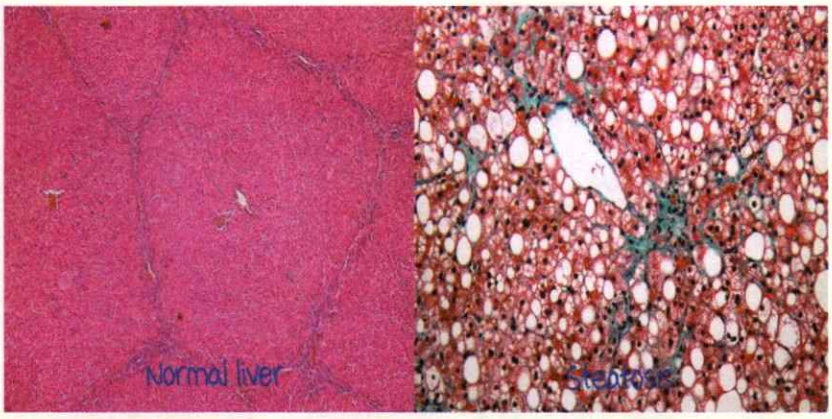
Macronodular cirhhosis : Nodules are more than 3 mm.



Cirrhosis is development of parenchymatous nodules which are separated by fibrous septa.
Masson trichome stain : Collagen fibres.

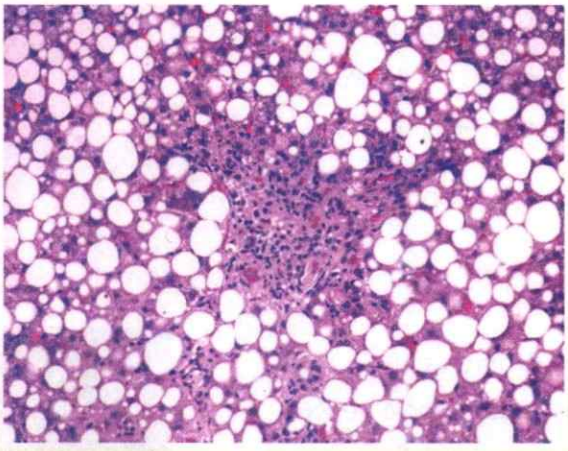


Active space

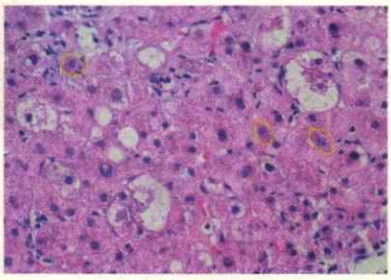


Steatosis is the fatty change in the liver.
It can be micro or macro vesicular.
It is stained by oil red O or sundan black B.

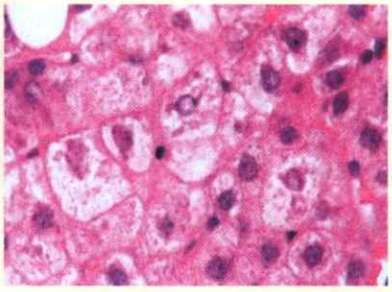
Macrovesicular steatosis



Alcoholic liver disease : mallory hyaline body. Composed of intermediate filaments like CK8 & 18.

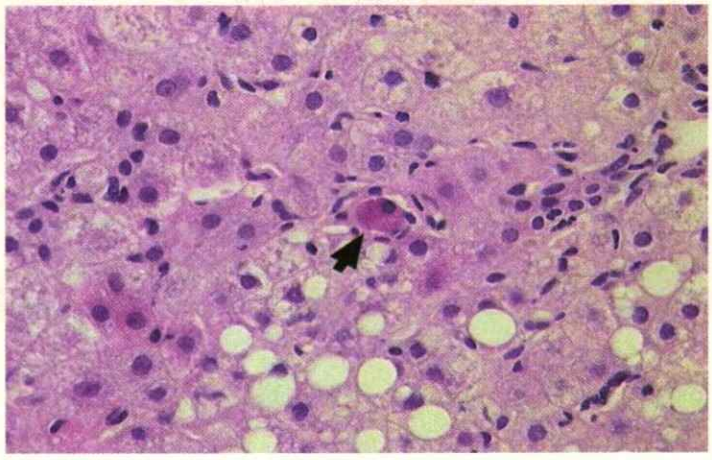


Ballooning degeneartion of hepatocytes : Acute hep B infection.

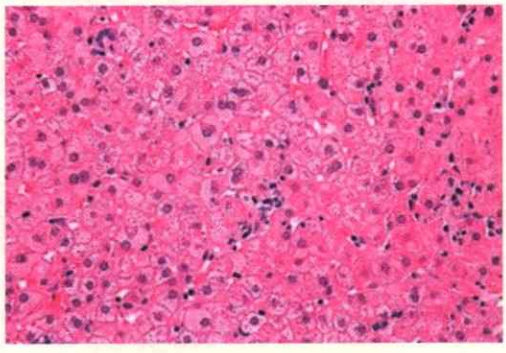


Active space

Councilman body : Apoptotic body (eosinophilic).
Seen in hepatitis B infection.

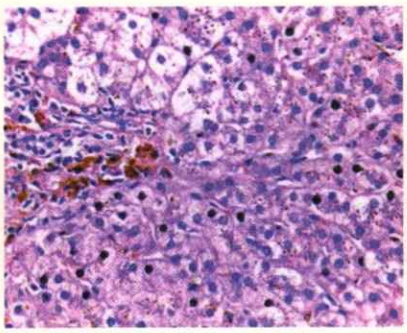


Ground glass hepatocytes :
Chronic hep B virus.
Due to HbsAg.



Nutmeg liver :
Due to chronic venous congestion of liver.

Hemochromatosis :
Both dilated >>>> restricted CM can occur.
Brown pigments :
Due to hemosiderin or lipofuschin (ageing patients) deposition.
Blackish pigmentation is due to

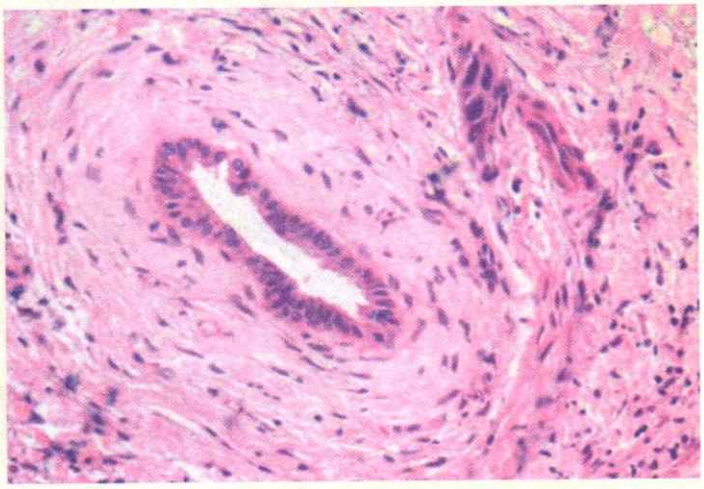


Active space

melanin (derived from tyrosine).

Primary sclerosing cholangitis :

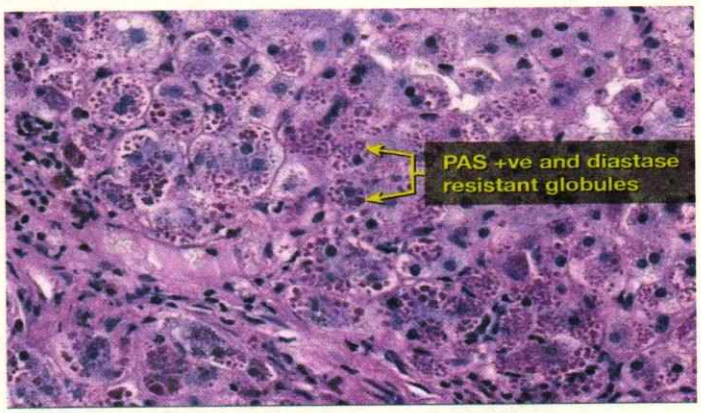
Onion skin fibrosis around the bile duct.



Alpha 1 antirypsin deficiency : Liver biposy.

In lungs : Panacinar emphysema.

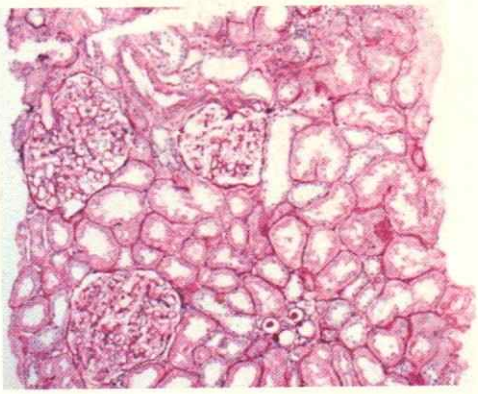
In liver : Cirrhosis.



Kidney

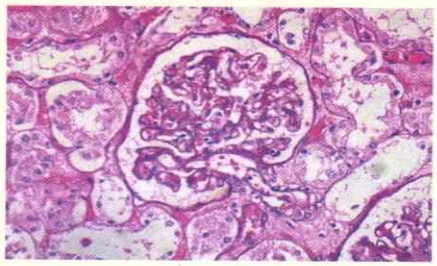
00:12:02

Normal kidney biospy :
3 glomeruli along
with tubules are seen.

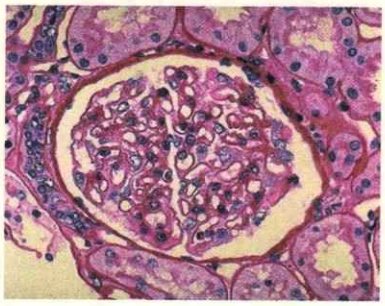


Active space

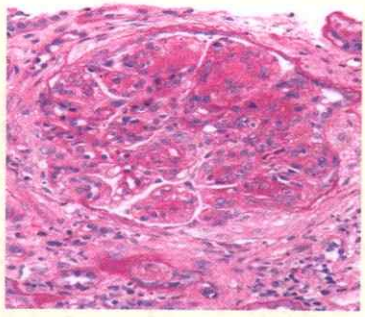
PAS stain of normal kidney : Showing mesangial cells in the glomeruli.



Normal glomerular biospsy : PAS stain. 1-2 cells in the mesangium.

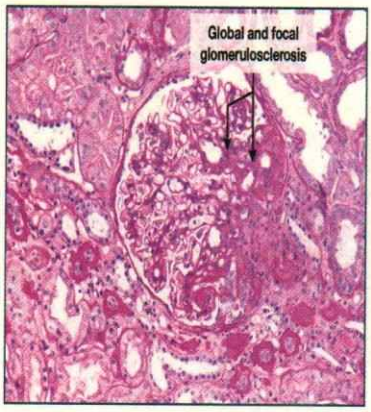


Hypercellular glomeruli with olbliterated capillary lumen. Pinkish deposition. For diagnosis : EM is required.

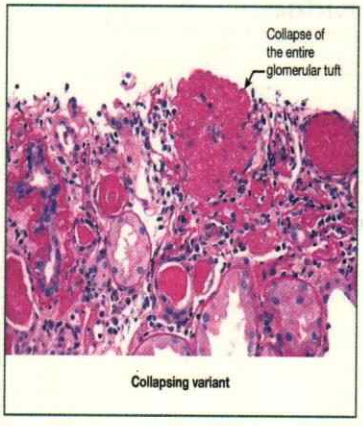


FSGS : Segmental pinkish deposition (sclerosis). Focal : < 50% of the glomeruli are affected.

Focal segmental glomerulosclerosis - Light microscopy



Focal segmental glomerulosclerosis - Light microscopy



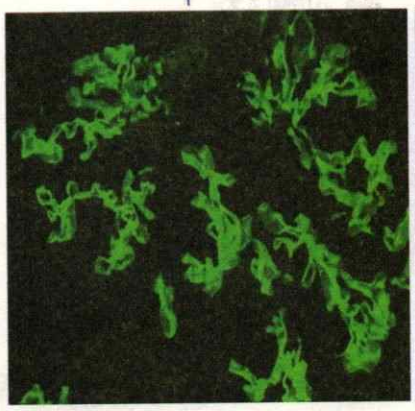
Active space

Immunofluroscence pattern :

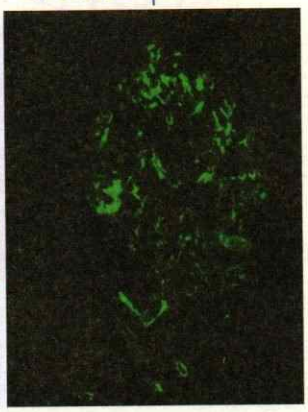
Linear : Anti GBM diseases like Good Pasteur's syndrome.

Granular : PSGN (lumpy-bumpy appearence).

Linear pattern



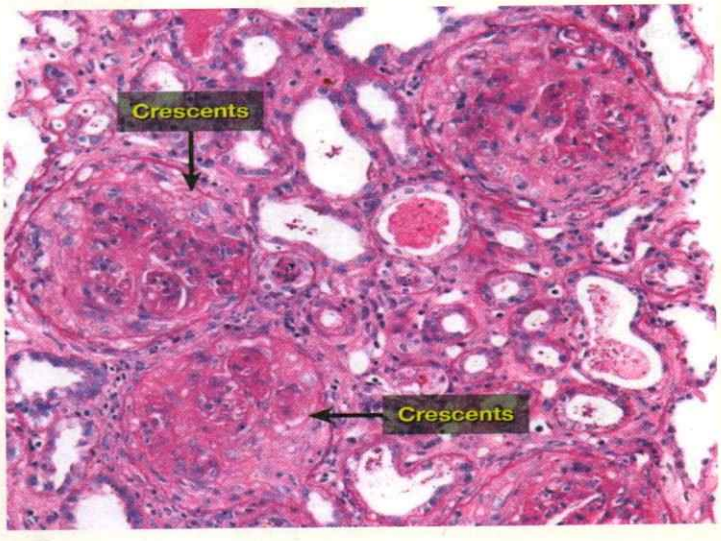
Granular pattern



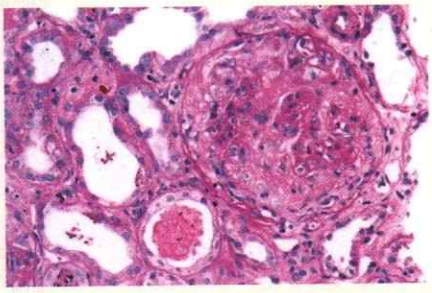
RPGN : Presence of crescents (half moon).

Crescents are formed by prolifertaion of parietal epithelial cells, fibrin and macrophages.

more the number poorer is the prognosis.

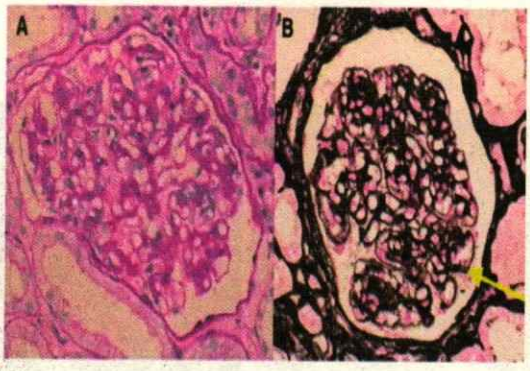


Crescents :

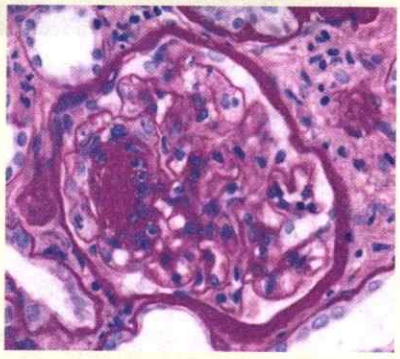


Active space

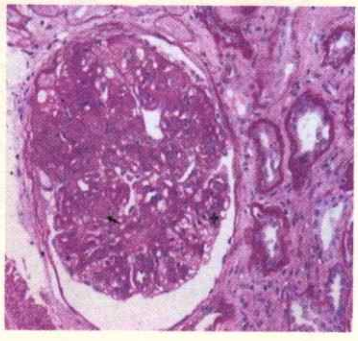
Silver stain : Duplicated GBM (tram track apperence).
Seen in MPGN.



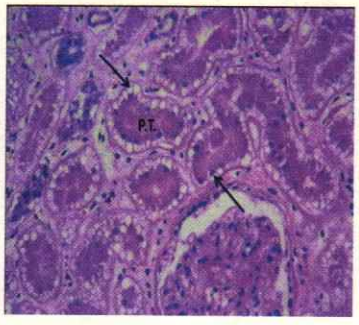
Kimmelsteil wilson lesion :
PAS positive nodular glomerulosclerosis.
M/specific finding of DN on histopathology.
Other common findings :
Diffuse glomerulosclerosis.
BM thickening.



Diffuse glomerulosclerosis



Armani Ebstein lesion :
PAS + glycogen vacuoles in the tubules.
Seen in severe DN.



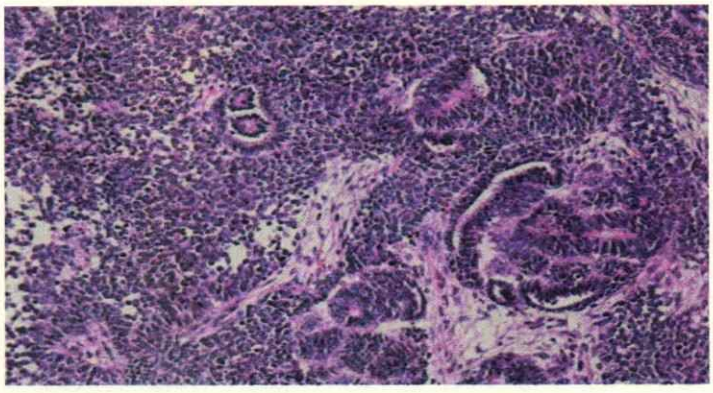
Active space

Wilms tumor/nephroblastoma :

One of the tumors of small, round blue cell tumors of childhood.

Triphasic tumor : 3 types of components :

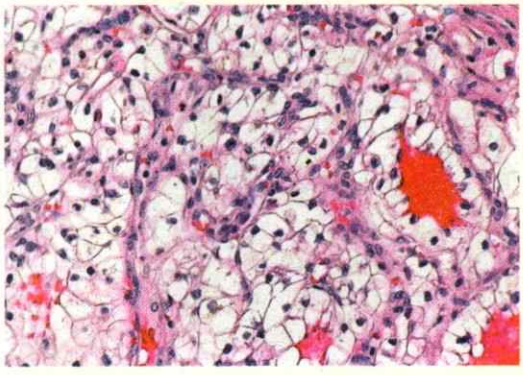
- Blastemal (primitive).
- Epithelial (gland formation).
- Mesenchymal (fibrous tissue).



Clear cell RCC :

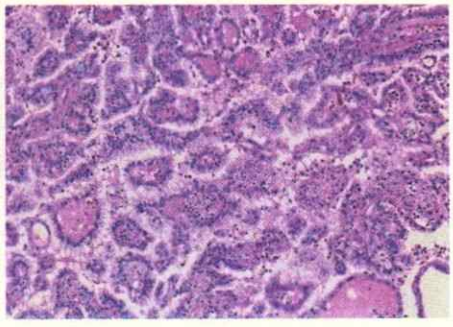
Due to glycogen (PAS +).

VHL gene mutation on chormosome 3.



Papillary RCC :

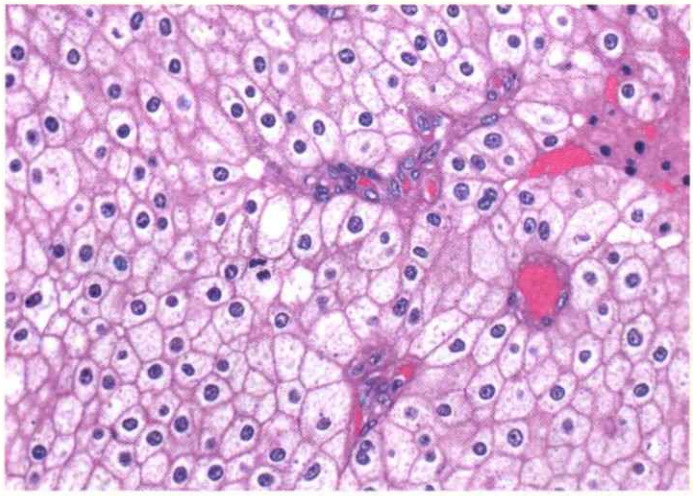
Papillae filled with foamy histiocytes.



Active space

Chromophobe RCC : Best prognosis.

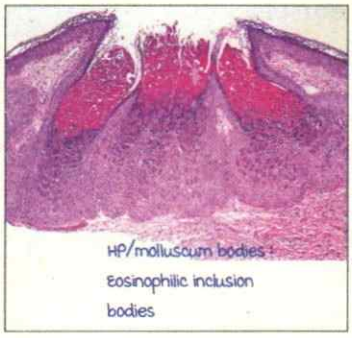
Plant like appearence (central nuclei with thick membrane).



Genital tract

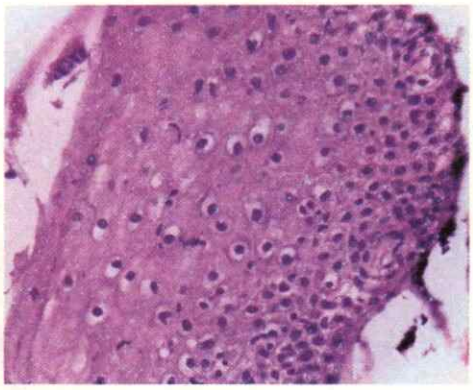
00:26:22

Molluscum contagiosum :



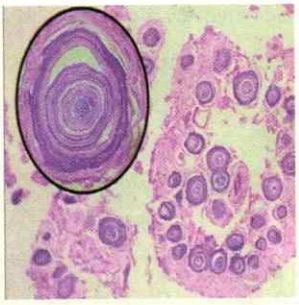
HPV genital warts :

Koilocytes :
Perinuclear halo.
Thick membrane.
Resin like nuclei.

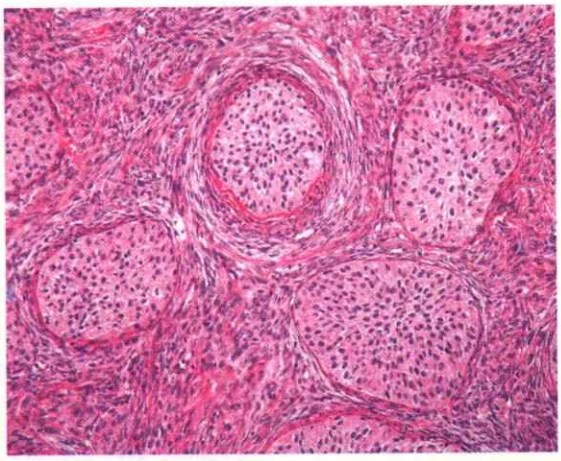


Active space

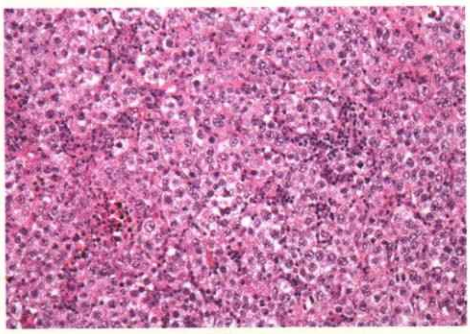
Papillary ovarian tumor :
Psamomma body (dystrophic calcification).
Serous cystadenocarcinoma.
DD for psamomma bodies :
meningioma.
Prolactinoma.
PCT.
Papillary RCC.



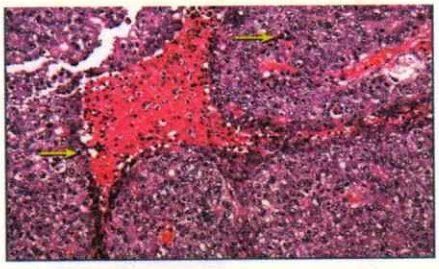
Brenners tumor :
Bladder like epithelium.



Seminoma/dysgerminoma :
AFP is negative.
PLAP +, HCG +.
Young male/female.
Nodules of cells separated by fibrous septa (infiltrated by lymphocytes).

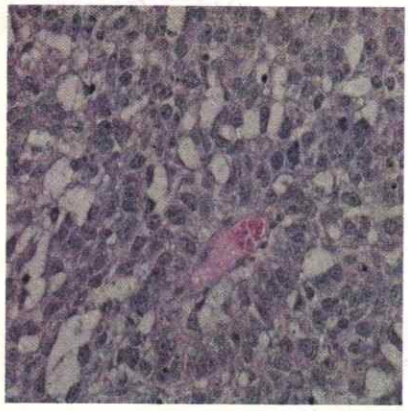


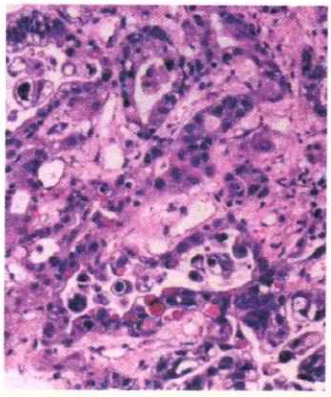
Embryonal carcinoma : Pleomoprhic cells with hemorrhage.



Active space

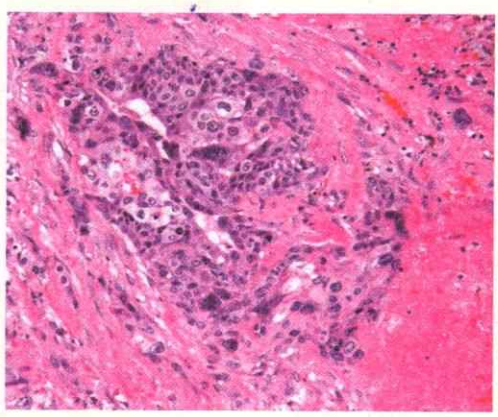
Schiller duval bodies/glomeruloid body :
Yolk sac tumor/endodermal sinus tumor.
AFP +.



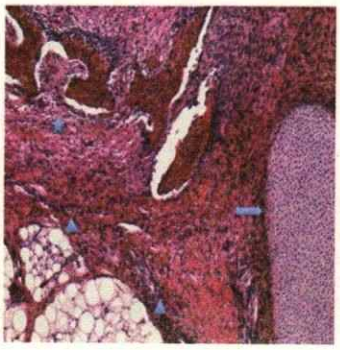


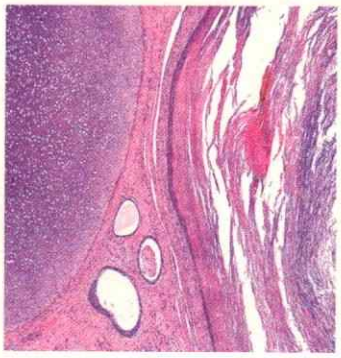
Another glomeruloid body is seen in GBM.

Choriocarcinoma :
Synctiotrophoblasts (multinuclear cells).
Cytotrophoblasts (mononuclear cells).
Presents with hemorrhagic necrotic mass.
Cannon ball metastasis in lungs.
HCG elevated.



Teratoma : m/s : Cartilage, Keratin, gland, fat etc.,
Gross : Bone, cartilage, hair, teeth seen.
Dermoid cyst : When it becomes cystic.





Active space

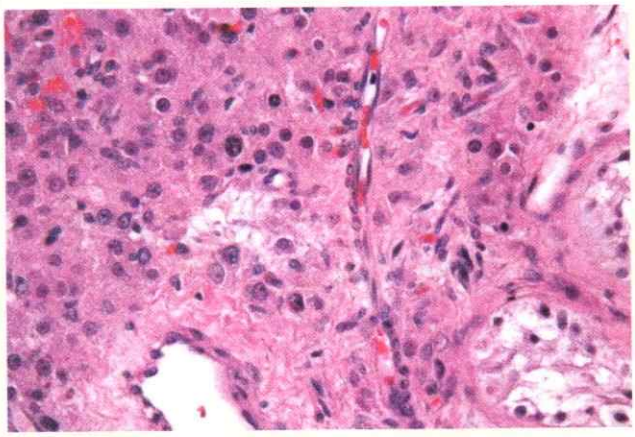
Mature teratoma : Benign.

Immature teratoma :

Showing neural/primitive/blastemal elements seen.

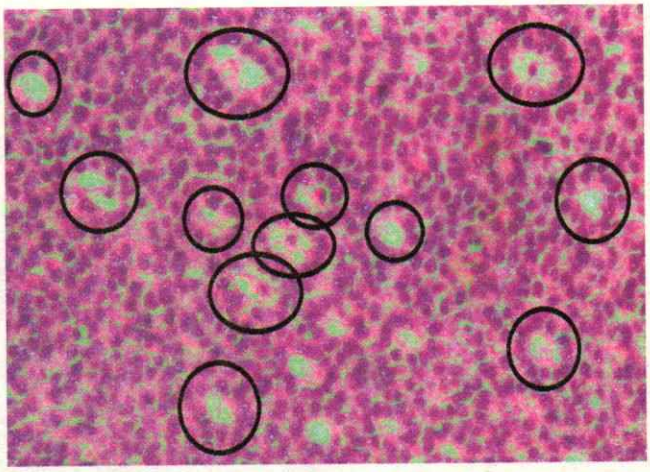
Malignant.

Leydig cell tumors : Rienke's crystals.



Granulosa cell tumor of ovary :

Call exner bodies.

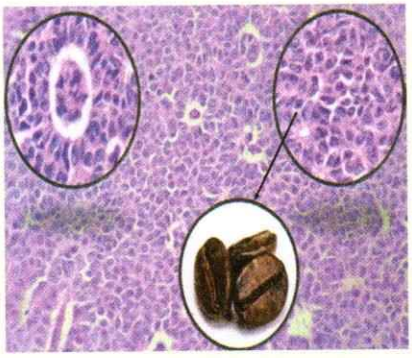


DD for coffee bean nuclei :

Brenners tumor.

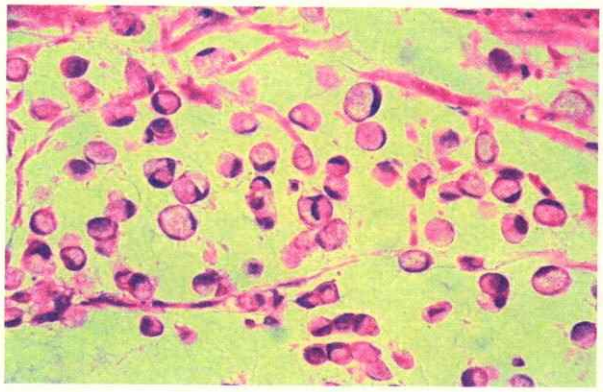
PCT.

Granulosa cell tumor of ovary.



Active space

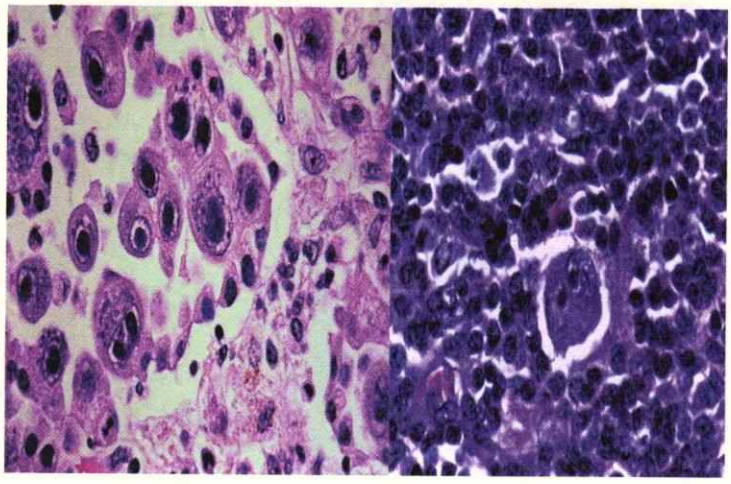
Krukenberg's tumor : From diffuse gastric cancer.
Presents as b/l ovarian mass.
Signet ring cells seen.



CNS

00:41:45

CMV infections : Owls eye inclusions.

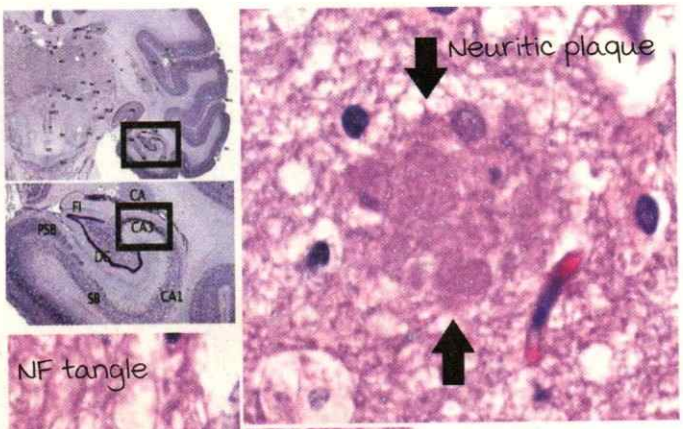


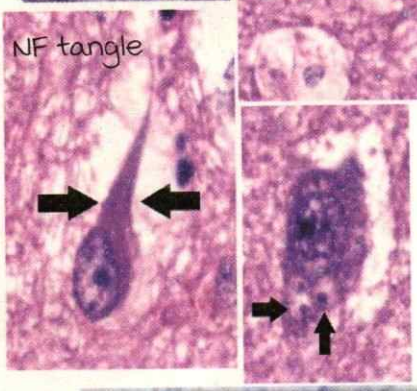
RS cell : Hodgkins lymphoma

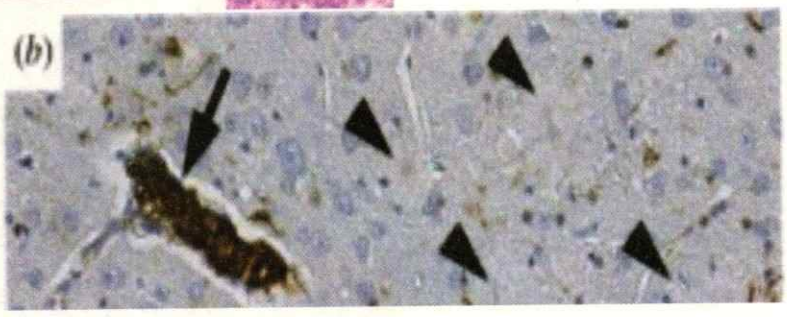
Active space

Alzheimiers disease :

Neuritic plaque & NF tangles : Seen with silver stain.

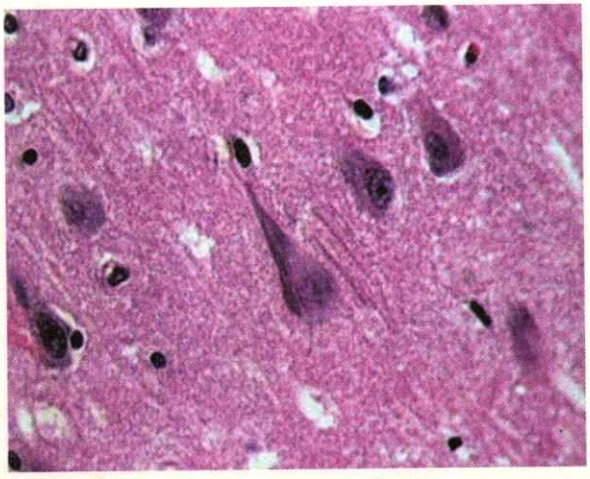






NF tangles :
There number indicates severity of the disease.

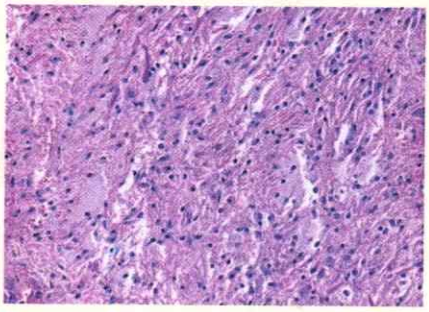
Abeta amyloid is deposited.



Active space

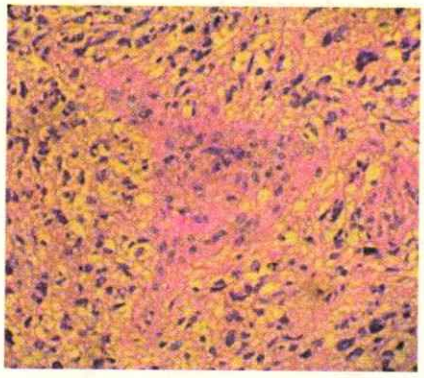
Pilocytic astrocytoma :

Pink fibrillary fibres (rosenthal).

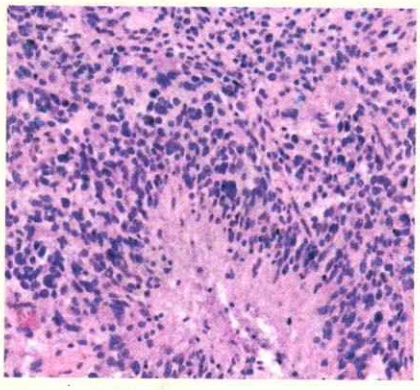


Glioblastoma multiforme (GBM) :

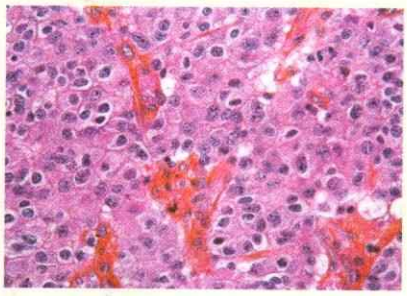
Glomeruloid body : Due to endothelial vascular proliferation.



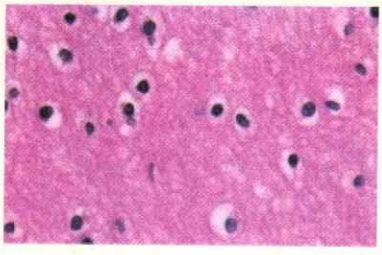
Serpentine/geographical necrosis.



Oligodendroglioma :
Chicken wire blood vessels (anastomosing vascular channels).
Calcification.



Fried egg appearence :
Seen in hairy cell leukemia & oligodendroglioma.

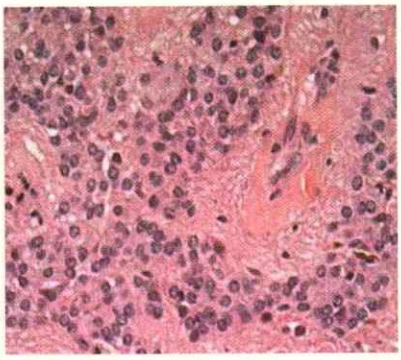


Active space

Ependymoma :

Involves ependymal linings.

Perivascular pseudo-rosettes.



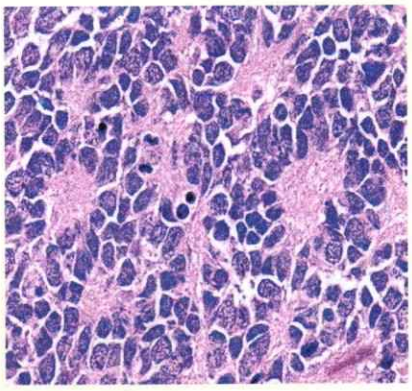
Medulloblastoma :

Small round blue cell tumor of childhood.

M/c malignancy of chidlren.

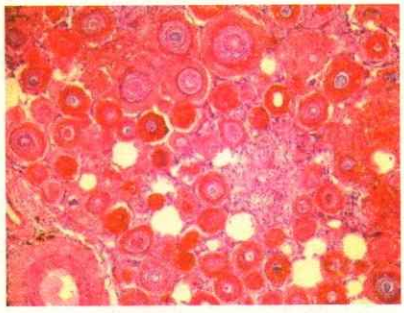
Poorly differentiated.

Sheets of small round blue cells arranged in the form of rosettes.



Meningioma :

Psamma bodies.



Schwannoma :

NF-2 gene mutation (chromosome 22).

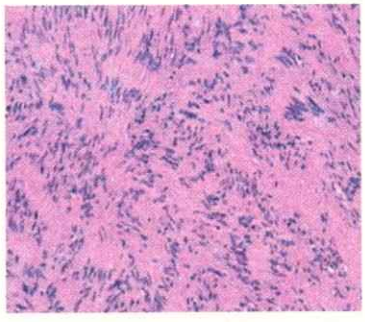
Tumor of 8th cranial nerve.

M/s :

Hypercellular area : Antony A pattern.

Hypocellular area : Antony B pattern.

Empyty spaces : Verrocay bodies.

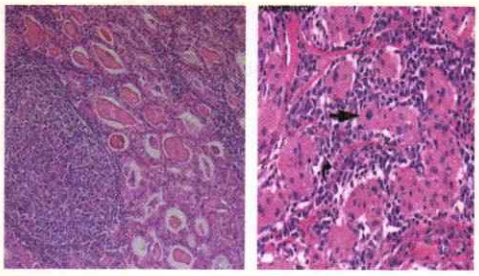


Active space

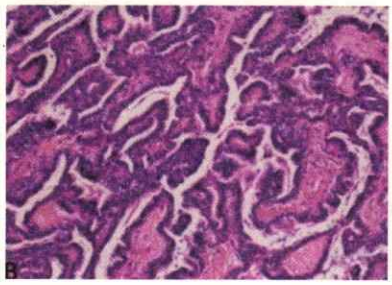
Thyroid gland

00:54:08

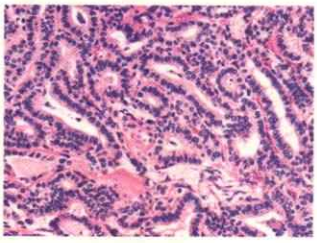
Hashimotos thyroiditis :
Lymphoid follicles.
Increased risk of PCT, lymphoma.
Hurthle cells (oncocytes) : Excess of mitochondria.



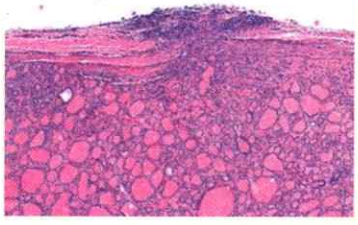
Papillary carcinoma of thyroid (PCT) :
Finger like projections with a fibrovascular core.
Nuclei : Eye of Orphan Annie (clear).



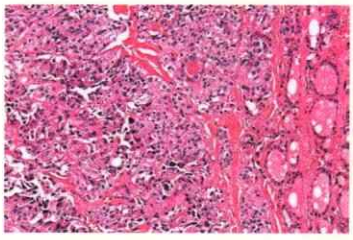
Nuclear pseudo inclusions.
Coffee bean nuclei.
Psamomma bodies.



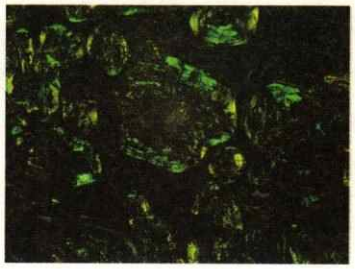
Follicular carcinoma of thyroid :
Capsular invasion by tumor cells.
FNAC cannot diagnose.



Medullary carcinoma of thyroid :
Pinkish amyloid material seen.
ACal amyloid.



Stain : Congo red under polarising lens shows apple green birefringence.



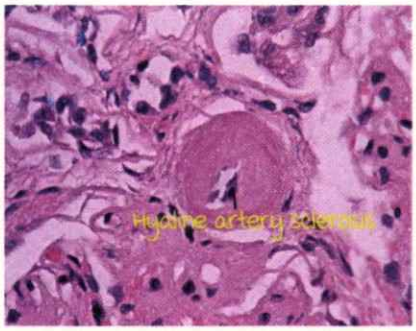
Active space

SYSTEMIC PATHOLOGY IMAGES : PART 2

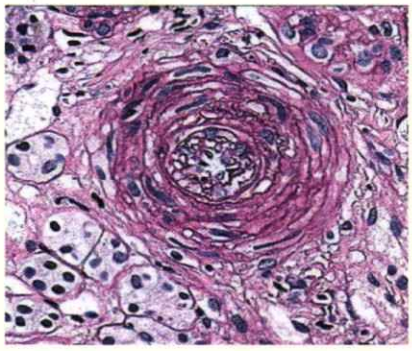
Blood vessels

00:01:06

Hyaline is the pink homogenous thickening of arterial wall obliterarting the lumen leading to luminal narrowing.
Can be seen in : Benign hypertension.



Multiple layers (concentric laminar thickening) appear as Onion skin apperance of arteriolar wall (Hyperplastic arteriosclerosis) seen in malignant hypertension.



Onion skin appearance

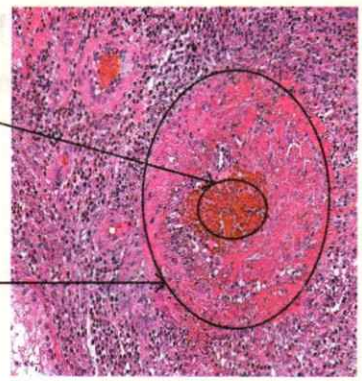
Case presentation :
40yr old male patient suddenly dies ; usually had a BP of 200/150 mmHg. Basal ganglia seems to be damaged & lots of hemorrhages seen. Patient dies of stroke.

Other onion skin appearance in pathology :

- Ewing sarcoma X-ray.
- Electron microscopy of Tay- sach's disease.
- Nerve biopsy of chronic inflammatory demyelinating polyneuropathy.
- Biopsy of primary sclerosing cholangitis.
- SLE spleen (grossly).

Active space

Fibrinoid necrosis is seen in Polyarteritis nodosa / PAN.

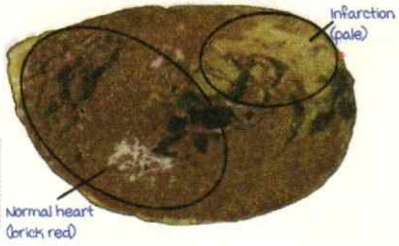


Heart

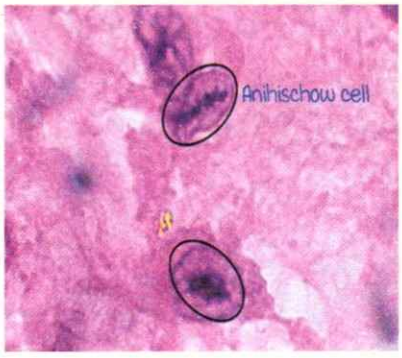
00:06:18

Stain for myocardial infarction : Triphenyl tetrazolium chloride.

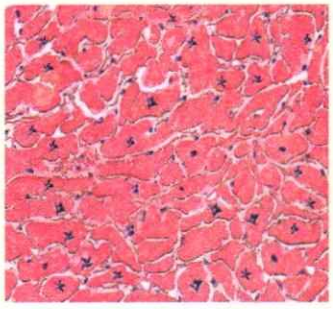
To diagnose a MI <12hours old. Lack of dehydrogenase activity leads to pale staining.



In Rheumatic heart disease, Ascoff bodies can be seen → Anhischow cells / caterpillar cells with areas of fibrinoid necrosis.



Ninja star nuclei seen in dilated cardiomyopathy due to Titin gene mutation.

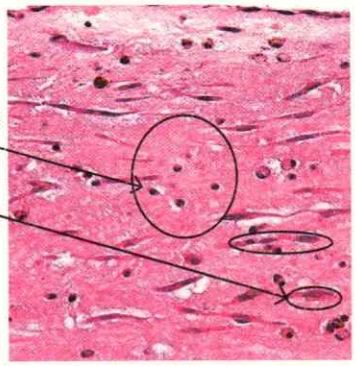


Ninja star nuclei

Active space

MC cardiac tumor in adults : Myxoma.

Stellate cells/myxoma cells seen.



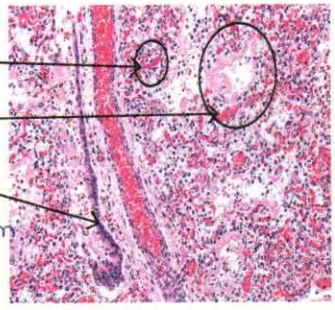
Cardiac myxoma

Lungs

00:12:58

Hyaline membrane disease is seen in ARDS.

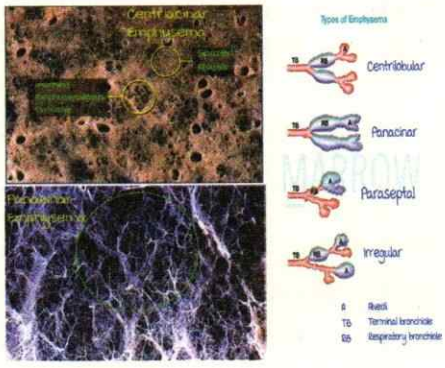
COVID -19 lung biopsy shows Hyaline membrane deposition & thickening of alvioli.



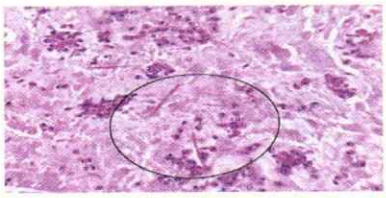
Centriacinar emphysema - Some acini are affected (dilated), some are normal. Smoking history present.

Panacinar Emphysema - All acini are damaged (dilated). History of Alpha 1 Antitrypsin deficiency present.

PAS positive lobules seen in liver.



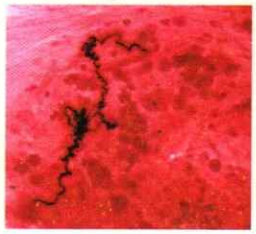
Charcot leyden crystals are composed of Eosinophillic membrane proteins - Galactin 10.



Charcot leyden crystals

Active space

Curshman spirals are whorled mucus plugs.

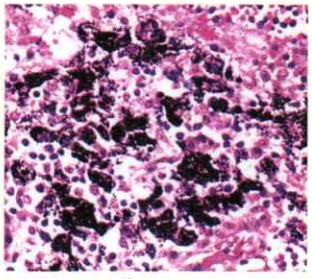


Curshman spirals

2 causes of bronchiectasis :
Obstruction & infection.
Can lead to Amyloidosis (AA).

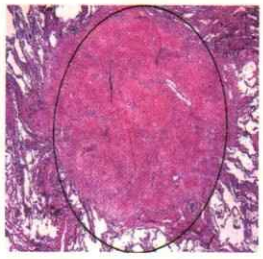
Bronchiectasis

Anthracosis shows black pigmentation (carbon deposition) on lymph node biopsy.



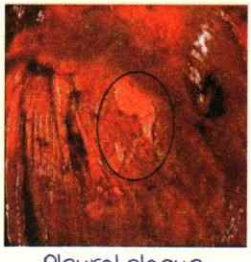
Anthracosis

Collagen nodule is usually seen in Silicosis.
silicosis – MC occupational lung disease.
Xray shows egg shell calcification.

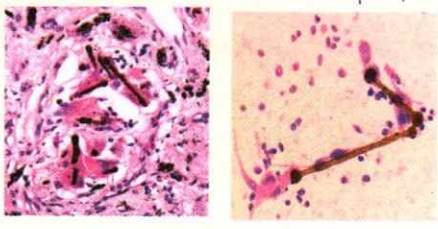


Collagen nodule

Asbestosis : yellow coloured plaque – pleural plaque seen on lungs.
Asbestos fibres : Sepentine & amphibole (more carcinogenic).
Feruginous bodies / Asbestos bodies – Beaded, Fusiform, Dumb bell shaped ; Asbestos fibres coated with iron.



Pleural plaque



Asbestos bodies

Active space

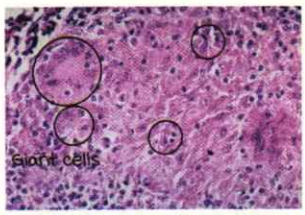
Sarcoidosis :

Epitheloid cells (Activated macrophages surrounded by a collar of lymphocytes) have slipper shaped nuclei.

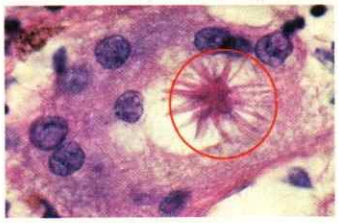
Non- caseating granuloma (naked - abscence of lymphocytic collar) is seen in Sarcoidosis.

Asteroid body is star shaped inclusion in the giant cell.

Schauman body (composed of calcium) appears basophillic in the giant cell.

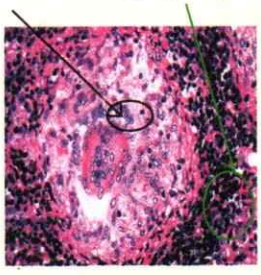


Giant cells & epitheloid cells

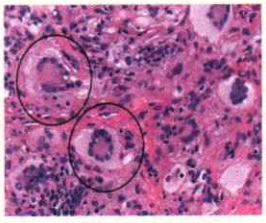

Asteroid body

TB produces caseating granuloma (mostly).

Epitheloid cells surrounded by lymphocytic collar.

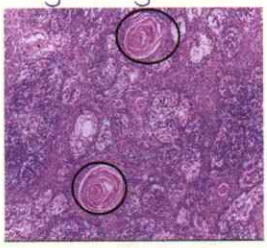


Langerhan giant cells with necklace/ horse shoe shaped arrangement of nuclei are seen in TB.

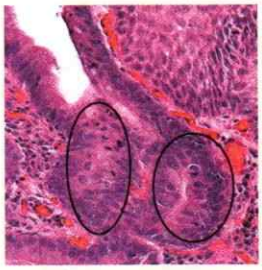

Langerhan giant cells

Squamous cell Carcinoma shows Keratin pearls (pink in colour) & Desmosomes (on high power).

Immunohistological marker _ _ _ _ _ _ _ _

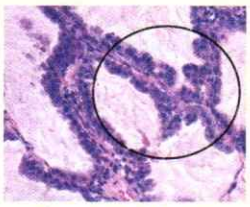

Keratin pearls

Adenocarcinoma shows glands lined by pleomorphic cells.


Adenocarcinoma

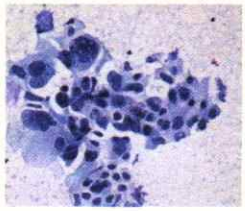
Active space

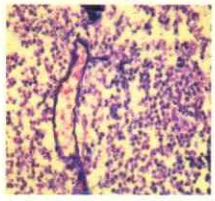
Bronchio-alveolar Cancer shows Filigree/ Lepidic / Butterflies on a fence pattern.
Bronchio-alveolar Cancer is also known as adenocarcinoma in situ.


Filigree pattern

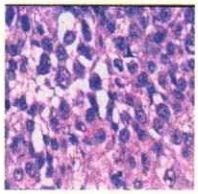
Small cell lung cancers shows Nuclear moulding & azzopardi effect.
History of smoking & paraneoplastic syndromes present.
Small cell lung cancer has poor prognosis.
Basophillic staining of vessel wall - Azzopardi effect.
Markers :

- Neuron specific enolase.
- Synaptophycin.
- Chromogranin.


Nuclear moulding in small cell lung cancer

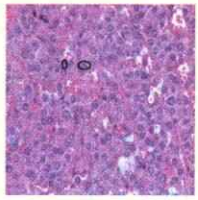

Azzopardi effect

Large cell carcinoma - highly pleiomorphic cells


Large cell lung cancer

Carcinoid syndrome - salt & pepper chromatin in nuclei (seen in all neuroendocrine tumors).
Markers :

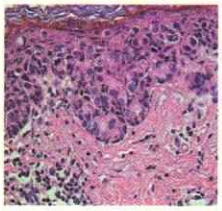
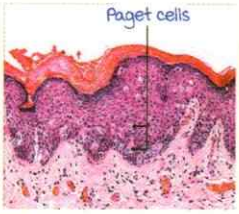
- Neuron specific enolase.
- Synaptophycin.
- Chromogranin.


Salt & pepper chromatin

Breast

00:35:03

Paget cells show perinuclear halo.
Pagets disease is also seen in vulva.
Paget's disease in breast implies malignancy.
DD : Eczema (B/L) ;
Biopsy is required for confirmation.

Paget cells

Active space

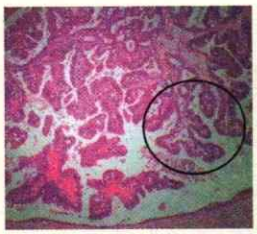
Ductal carcinoma in situ :

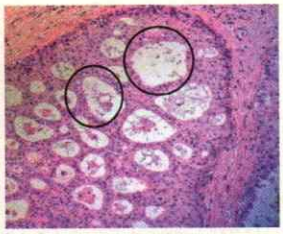
Comedo pattern – Central area of necrosis with proliferation of ductal epithelial cells.

worst prognosis.

Papillary pattern

Cribriform pattern

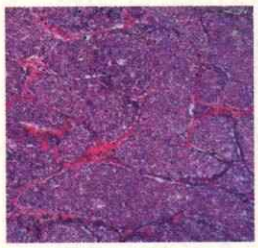




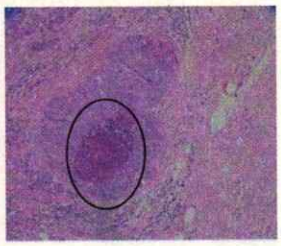
Cribriform pattern – Cookie cutter like spaces / seive like pattern seen.

Solid pattern – the ducts are full of cells.

Papillary pattern / micropapillary (small sized papillae).



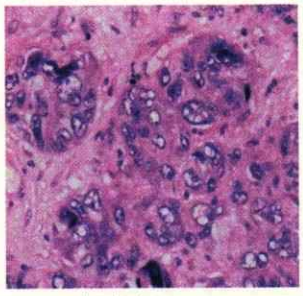
Solid pattern



Comedo pattern

Ductal cancer –

Ducts lined by pleiomorphic cells.

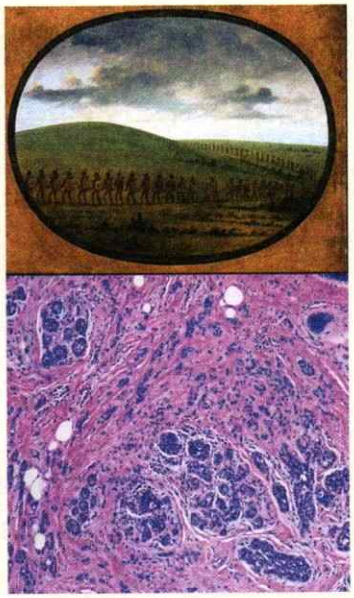


ductal cancer

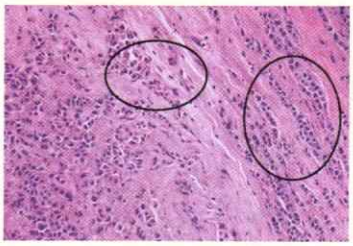
Invasive lobular cancer –

Morphology : Histologic hallmark → dyscohesive infiltrating tumor cells, often arranged in single file or in loose clusters or sheets → Indian File Appearance.

Pathology – CDH1 Gene mutation → loss of E Cadherin (Also seen in diffuse type of gastric Ca).

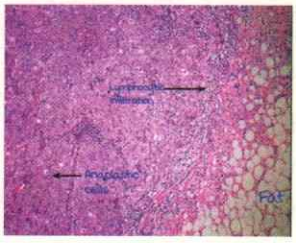


Active space

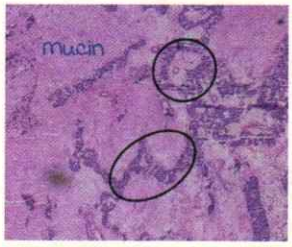


Single file appearance

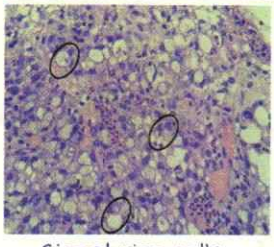
medullary carcinoma of breast - Sheets of pleomorphic cells.
BRCA I positive cancers usually have medullary like features.



Mucinous Ca breast - cells floating in pools of mucin.

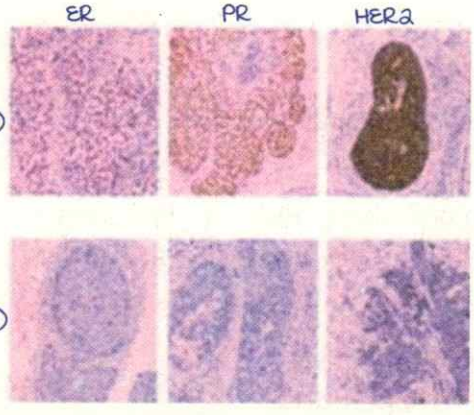


Intracellular mucin forms Signet ring cells.

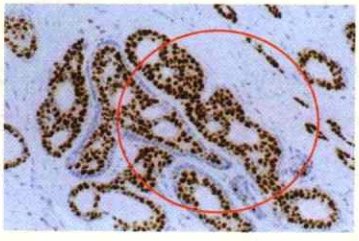


Signet ring cells

Any IHC marker if positive will produce brown colour on a breast tru cut biopsy.

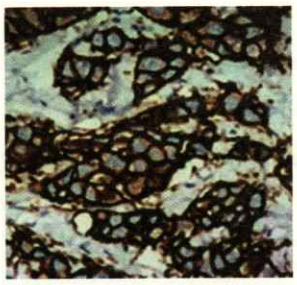


ER & PR are nuclear receptors, hence the nuclei is stained brown. Patient responds to Tamoxifen.



Active space

HER2 Neu is a membranous receptor, hence membrane stains brown (positive).
patient responsive to Trastizumab / Herceptin.

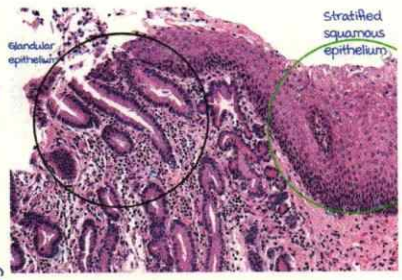


HER2 Neu positive

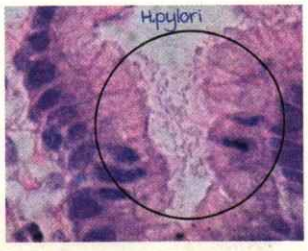
GIT

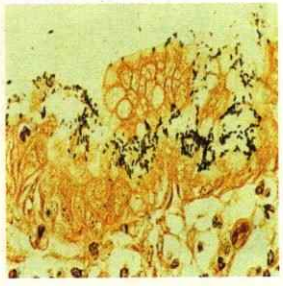
00:45:59

Metaplasia seen in Barret's esophagus.
Glandular epithelium & stratified squamous epithelium both are seen.
Barret's esophagus leads to increased of adenocarcinoma of esophagus.
Stained by Alcian blue.
Histopathology – Intestinal metaplasia & goblet cells containing mucin.
Silver stain is usually done for Barret's esophagus.



H.Pylori – Gram negative bacilli.
Cannot penetrate gastric wall; seen floating over mucosa
Pathogenic factors :
Cag A & Vac A.
Usually invades pyloric antrum & hence antral biopsy is required.
Lesions :
chronic gastritis.
marginal lymphoma/ maltoma.
Gastric adenocarcinoma.
H.pylori can be seen on warthin's starry silver stain.
Modified Giemsa stain can also be used.

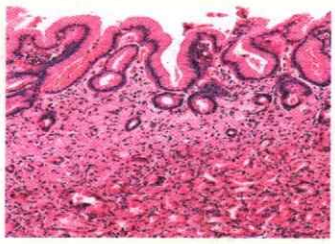




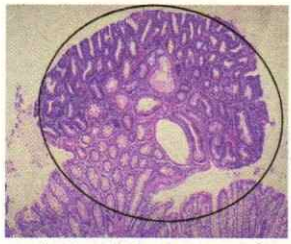
Warthin's starry silver stain

Active space

Gastric adenocarcinoma –
Glands lined by malignant cells.
Diffuse variety of gastric ca :
Signet ring cells seen (associated with CDH1 gene mutation).

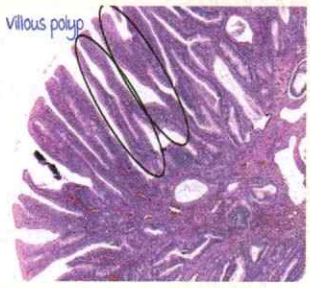


Polyp – protrusion of mucosa.
Glands /Tubules seen in tubular adenoma.
Tubulo-villous type of polyps also present.



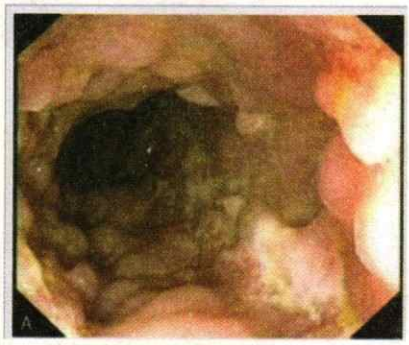
Tubular adenoma

Villous polyp – Finger like projection.
It is most malignant type of polyp.



Skip lesions are seen in Crohn's disease (IBD).
Features of crohn's disease :

- Cobblestone appearance of mucosa.
- Deep knife ulcers.
- Skip lesions.
- Transmural involvement.



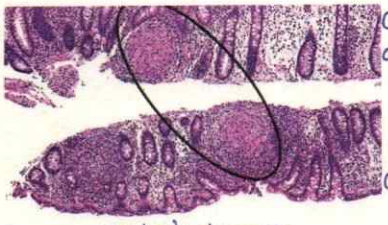
p-Anca positive Crohn's disease.
Histopathology : Crohn's disease shows Non caseating granuloma (not seen in UC).

Active space

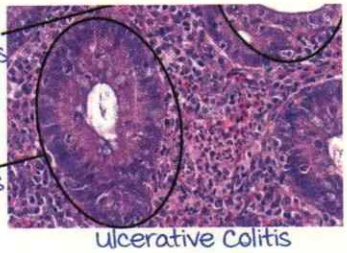
Ulcerative colitis –

Cryptitis & Crypt abcesses seen.

Anti Saccharomyces cerevisiae antibodies are positive.



Crohn's disease

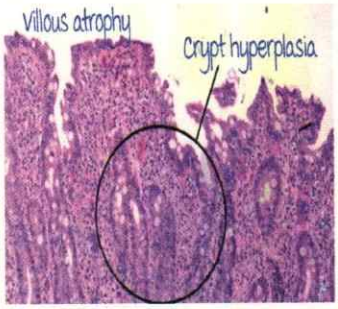


Ulcerative Colitis

Celiac disease :

Marsh scores –

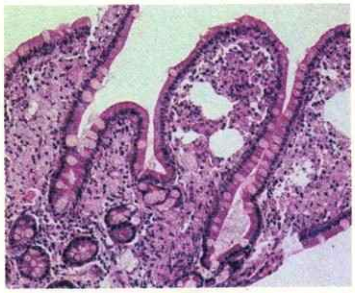
- Villous atrophy (Blunting of villi) seen.
- Crypt hyperplasia.
- Increased number of Intraepithelial lymphocytes.



Patient has Gluten sensitive enteropathy.

Skin disorder – Dermatitis Herpetiformis.

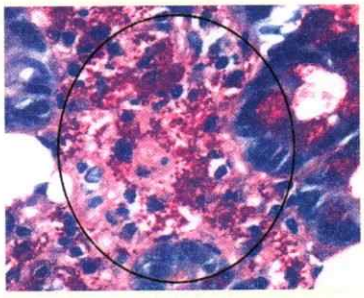
Lymphoma – enteropathy associated T cell lymphoma.



Whipple's disease –

Lamina propria infiltrated with foamy macrophages (filled with trophyrima whipplei).

PAS positive diastase resistant granules seen.

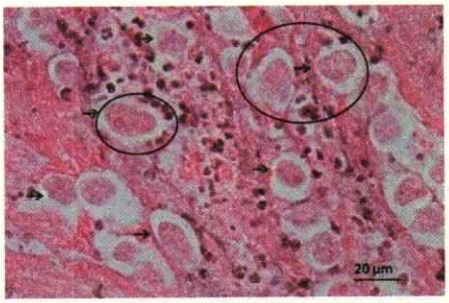


Whipple's disease

Amoebiasis :

Entamoeba histolytica can be seen.

Anchovy sauce pus in liver/ flask shaped ulcer present in history.



Entamoeba histolytica

Active space

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