PATHOLOGY

- HEALTH MAINTENANCE B

- AGEING AND ENDINGS A

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SPECIAL THANKS TO: VIDURANGA WIJERATNE'S NOTES

Exam structure

First, a rundown of the exam you're going to sit. Six questions in 30minutes, two booklets:

1. Histology (3 Questions, 1 Booklet)

Here you are given an unnamed slide from vSlides and asked to

a) label tissue-specific features

b) talk about their function

2. Pathology (3 Questions, 1 Booklet)

Here you are given an unnamed slide from vSlides and straight from the Prac Manual:

- case history
- accompanying test results (Liver Function Tests)

The questions can be anything like:

a) write a definitive diagnosis in one sentence (4 marks)

b) Write the abnormalities present in the slide (8 marks)

c) Why does symptom X (e.g. persistent oliguria) present? (4 marks)

d) What type of necrosis is present? (Coagulative, liquefactive, saponificiation)

e) What are cellular changes showing this? (coagulative = anucleate eosinophilic ghost outlines of cross-linked cytoplasmic protein)

f) How are these changes distributed? (Diffuse or focal lesion)

Study notes structure

Similarly, it is smart to organise your notes to suit the type of information you will be asked for each part of the exam.

1. Histology

Practise quickly sketching slides and labelling the bold items from the Prac Manual, then separately writing a quick few words about their function. e.g. 'simple columnar epithelium with microvilli (colonocytes) which are absorptive in function to solidify the faeces'.

Try and achieve a time of labelling main features and writing function for them, in under 3min.

2. Pathology

Identify abnormal histological **features** and relate them to the **signs and symptoms** as well as a **differential and provisional diagnosis**, possible **causes**, **complications** and further **investigations** to confirm a diagnosis. Prof. Velan loves to use **Adaptive Tutorial** content in the exams, so know these.

Write signs and symptoms, diagnostic features, possible investigations and causes in under 4min.

Exam technique

It is important in the exam to do the following:

General tips

1. Use your time well, have a watch with a timer so you can see if you have used all of 5minutes for each Question.
2. Invest in a highlighter, and highlight the important adjectives and nouns of the question, then number each question e.g.

> A 68 year-old man presented to his local doctor with a six-month history of episodic constipation and diarrhoea, associated with a feeling of incomplete evacuation following defaecation. On three occasions, he had noted bright red bleeding per rectum. Following investigation, a lesion at the rectosigmoid junction was removed surgically, and virtual slide 1 was prepared from the tissue thus obtained.
>
> a) On the basis of examination of virtual slide 1, a diagnosis was made of adenocarcinoma of the colon. List the features of virtual slide 1 that support this diagnosis (**Q1**).
>
> b) What investigations could have been done to identify a lesion (**Q2**) at this level?

DO NOT STRESS. As silly as this sounds, stressing and losing your centre will ruin your time management and self-confidence in the exam, making you panic and write down wrong answers. Stay cool, and try and quickly **figure out what tissue the slide is, what **features are in it**.**

1. Histology

1. **Quickly sketch what you are going to label, nothing else**, e.g. 'two functional areas of the slide' in the pancreas refers to Exocrine (lobules of acini) and Endocrine tissue (Islets of Langerhans). It is smart to quickly write the function of each type of tissue if the question asks, e.g. the type of epithelium in a colon slide is simple columnar with microvilli for absorption.

2. **Use** at least **half** of a whole **page to sketch** the image, as this makes labelling easier.

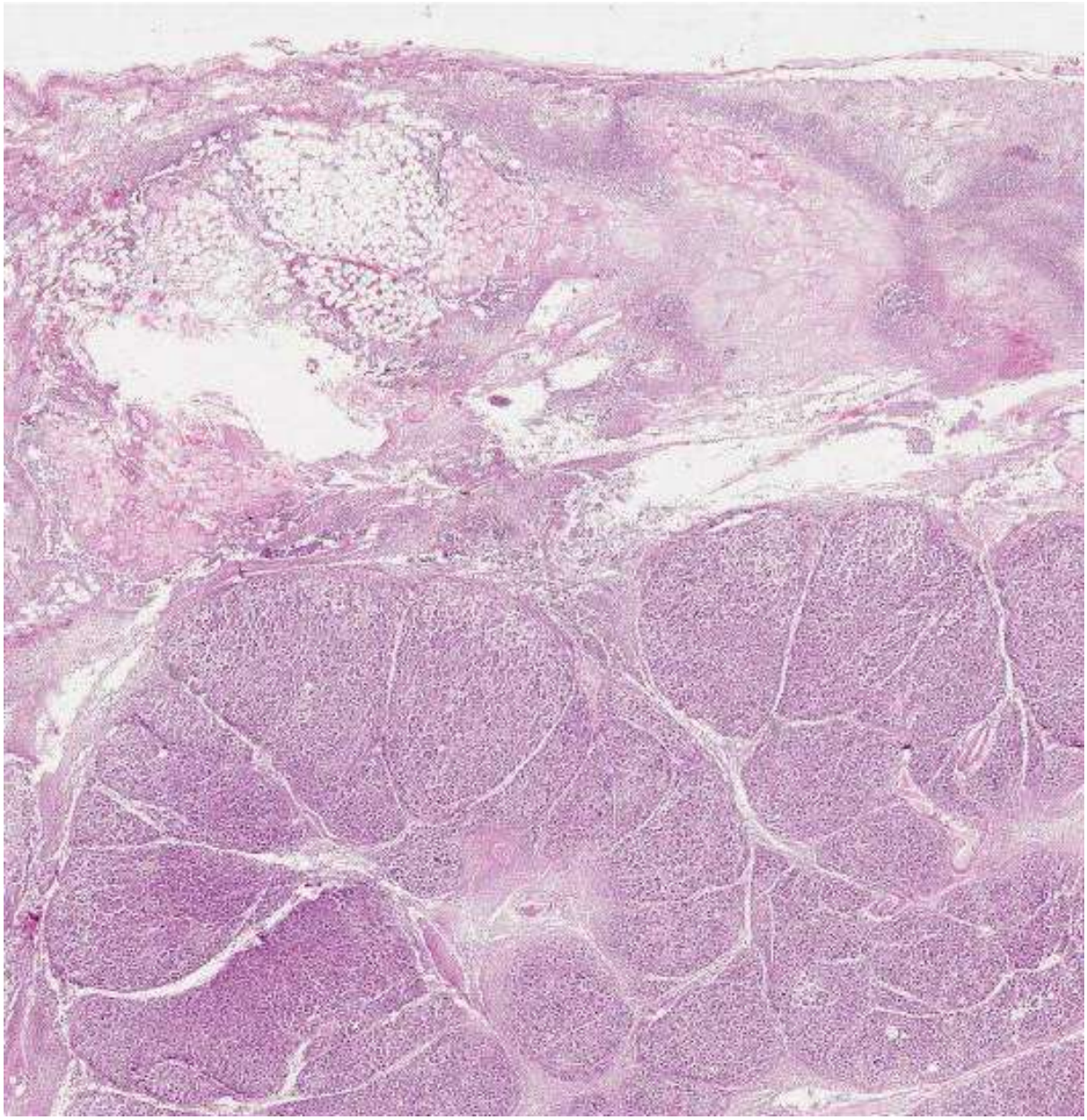
3. The **question** will **usually ask** for the **function** of **parts** of **tissue** e.g. 'name two products of each type of tissue, and the cells that make them'. This is best answered in a few lines labelled under 'Q1b)' but it is a good idea to label the location of these cells on the sketch.

2. Pathology

1. Understand what the question requires; **how many sub-questions**, **how many marks** each. This allows you to 'headshot the marks' and write concise statements targeting each mark.

2. There is **little time to write everything you know**, so write what you do know and **structure** your **answer in** the **order** of the question. If it asks for a diagnosis and THEN for tissue features supporting diagnosis, do it in that order.

Slide 1 (Acute pancreatitis) * Red indicate adaptive tutorial notes



Signs and symptoms

- 61yo woman
- abdominal pain gradual onset over 4hrs
    - **acute**
- severe localised to epigastrium, radiation to back
    - **typical of pancreatic disease**
- epigastric tenderness
    - guarding
    - rigidity
- no bowel sounds

        - **paralytic ileus (no peristalsis) - marker of peritonitis to prevent further damage. no absorption thus net loss of fluid through secretions (mostly water) → dehydration, fluid in bowel**
- became hypotensive with cold extremities
        - **hypovolemia from paralytic ileus**
- urea and creatinine elevated
        - **inadequate BP to drive GFR so urea, creatinine filtration high**
- amylase and lipase high
        - **released into blood as pancreatic acinar cells die**
- bicarbonate low
        - **used in buffering lactate produced by anaerobic respiration of cells with poor circulation**

Diagnosis

- Gallstones
        - **increased pressure in ampulla of vater → buildup of exocrine pancreas secretions → activation of enzymes → destruction of pancreas**
- alcohol
        - **damage to acinar cells → premature release and thus activation of enzymes**
- trauma
        - **damage to acinar cells → premature release and thus activation of enzymes**
        - **lipase → cell breakdown, elastase → blood vessels → haemorrhage**

Features

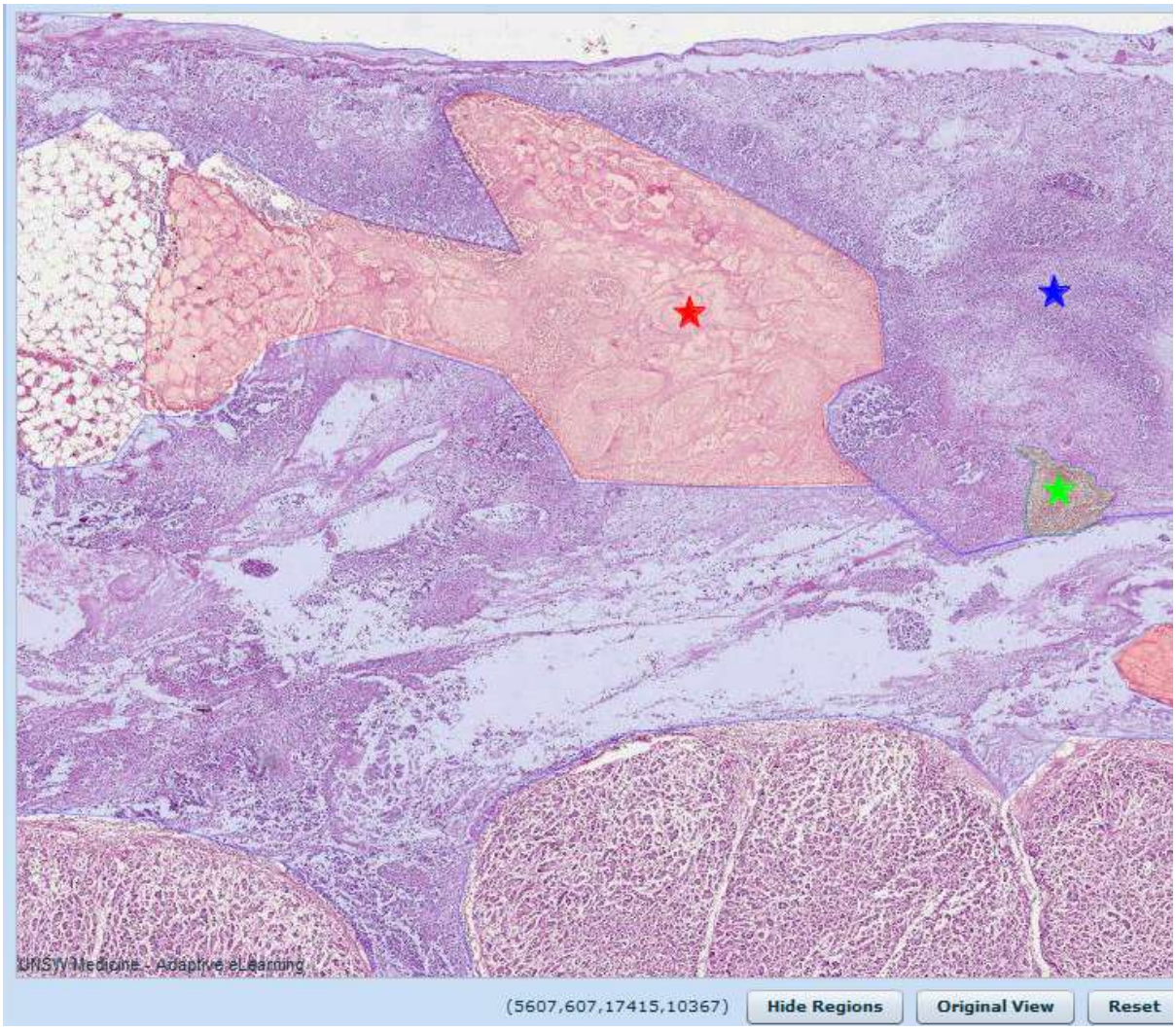
- acute inflammation
        - **enzymes → necrotic tissue → IL6 IL1 TNF released → oedema, neutrophils**
- saponification
        - **lipase breaks up adipose cells releasing fat, which binds with Calcium to form insoluble soaps**
- liquefactive necrosis
        - **cell membrane damage = phospholipase, proteolytic digestion, oxygen radicals released by neutrophils → destruction of pancreatic structure → liquefactive necrosis**
- preserved tissue
- haemorrhage
        - **elastase damages blood vessel walls**

Adaptive tutorial on Acute Pancreatitis

1. Drop a red star into a region of enzymatic fat necrosis.

Drop a green star into a region of hemorrhage

Drop a blue star into a region of acute inflammation and liquefactive necrosis.



The region of **enzymatic fat necrosis** is shaded **red**.

Fat necrosis is due to **digestion of fat by lipase**, liberating triglycerides and free fatty acids.

The region of **haemorrhage** is shaded **green**.

The **activation of pancreatic elastase** results in **damage to blood vessel** walls, leading to local **haemorrhage**.

The region of **acute inflammation and liquefactive necrosis** is shaded **blue**.

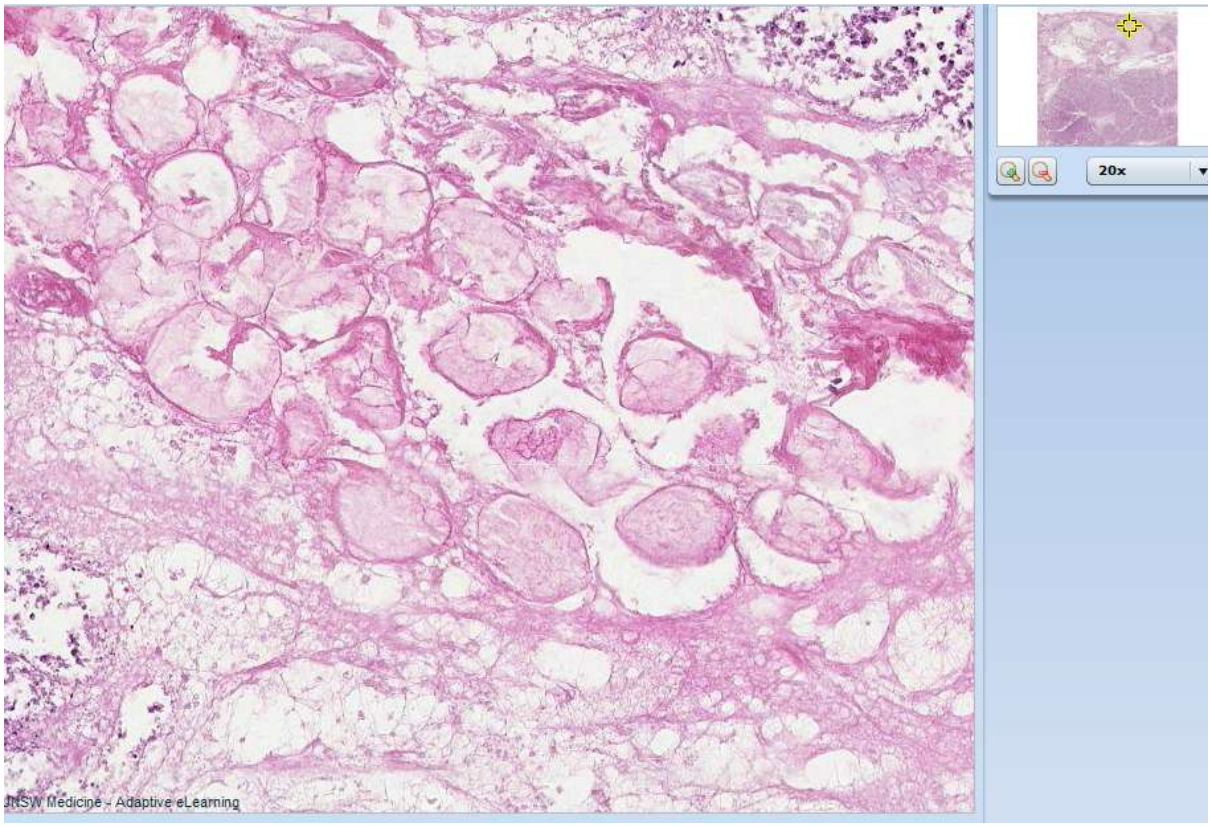
Injured tissues and leukocytes release proinflammatory cytokines including IL-1, IL-6, TNF. This, **together with release of lysosomal enzymes** from necrotic cells, **induces an acute inflammatory** response characterised by **oedema and infiltration by neutrophils**.

Parenchymal necrosis in pancreatitis is caused by:

1. **Enzymatic injury to cell membrane**s (**phospholipase**) and **proteolytic digestion (trypsin**, chymotrypsin); and

2. **Oxygen radicals and proteolytic enzymes** released **by neutrophils** as part **of the acute inflammatory** response.

The above processes **primarily result in liquefactive necrosis**, with potential loss of pancreatic structure, **although the pancreatic parenchyma (lower part of the section) is preserved in this case**.



Fatty acids, released as a result of enzymatic fat necrosis, combine with calcium to form insoluble salts. This gives the necrotic cells a **finely granular, basophilic appearance**.

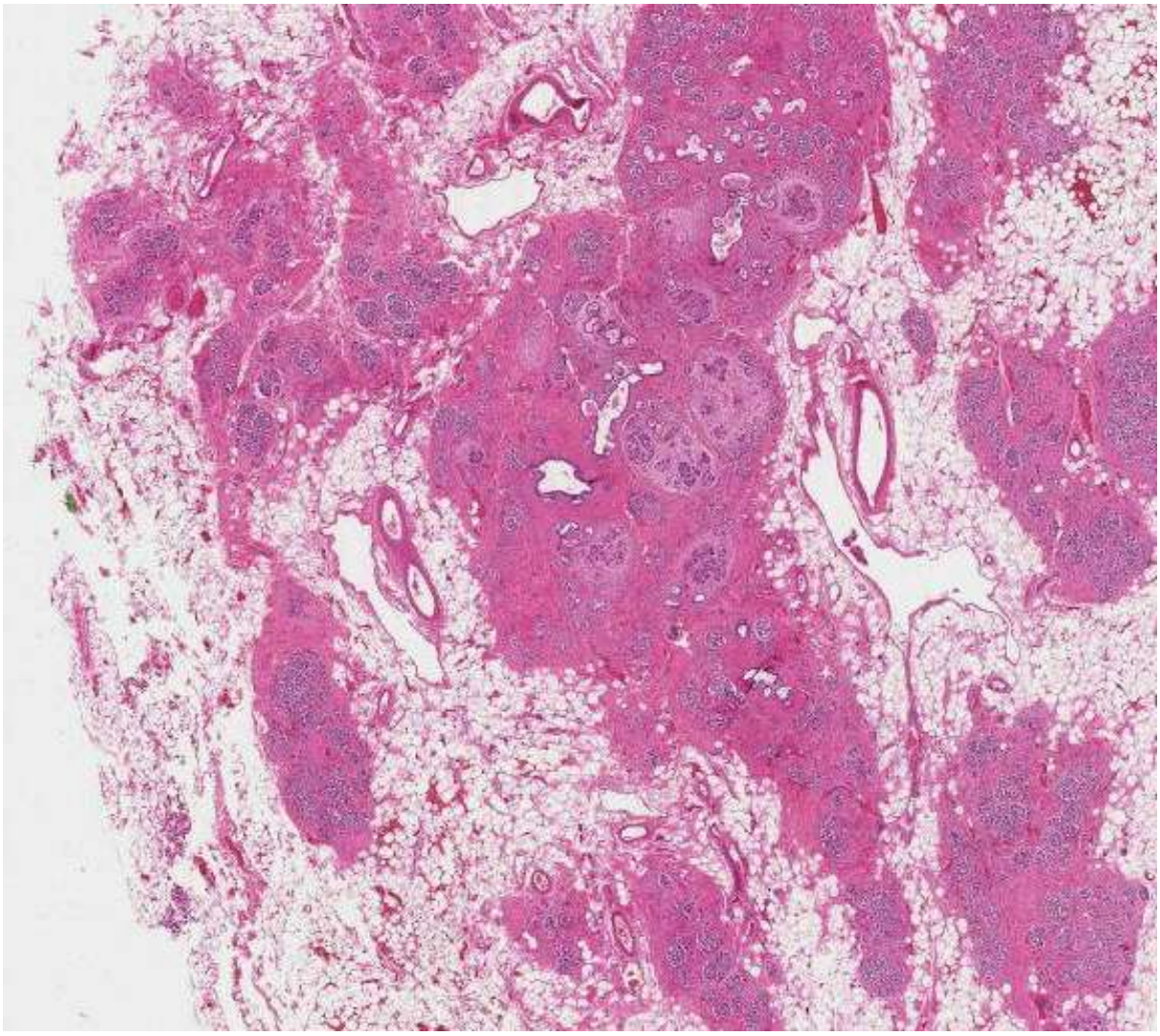
Gallstones impacted in the region of the ampulla of Vater result in **increased pressure** within the pancreatic ducts, accompanied by an **accumulation of enzyme-rich flui**d in the pancreatic intersititium. Amongst these enzymes are **lipase, which induces local fat necrosis**. The damaged tissue **triggers an inflammatory reaction**, and the **resulting oedema may increase tissue pressure sufficiently to impair perfusion, thereby producing a local ischaemic effect**. This results in injury to the acinar cells, leading to **release of zymogens**, which **are activated** within the pancreas by lysosomal enzymes, also released by injured cells.

Chronic alcohol consumption is known to result in the **production of protein-rich pancreatic fluid**, which can lead to the formation of **inspissated protein plugs and obstruction of pancreatic ducts**.

Alcohol can also be directly toxic to acinar cells, and can cause **defective intracellular transport**, whereby **zymogens are transported to lysosomes** (where the proenzymes are cleaved and activated), rather than being appropriately secreted into the acinar lumen.

Pancreatic cells can be injured via trauma, by **drugs** (e.g. sulfonamides, tetracycline, azathioprine), **infection** (mumps), **ischaemia** and excessive **alcohol** consumption. The release of pancreatic enzymes following trauma results in **autodigestion and acute inflammation**.

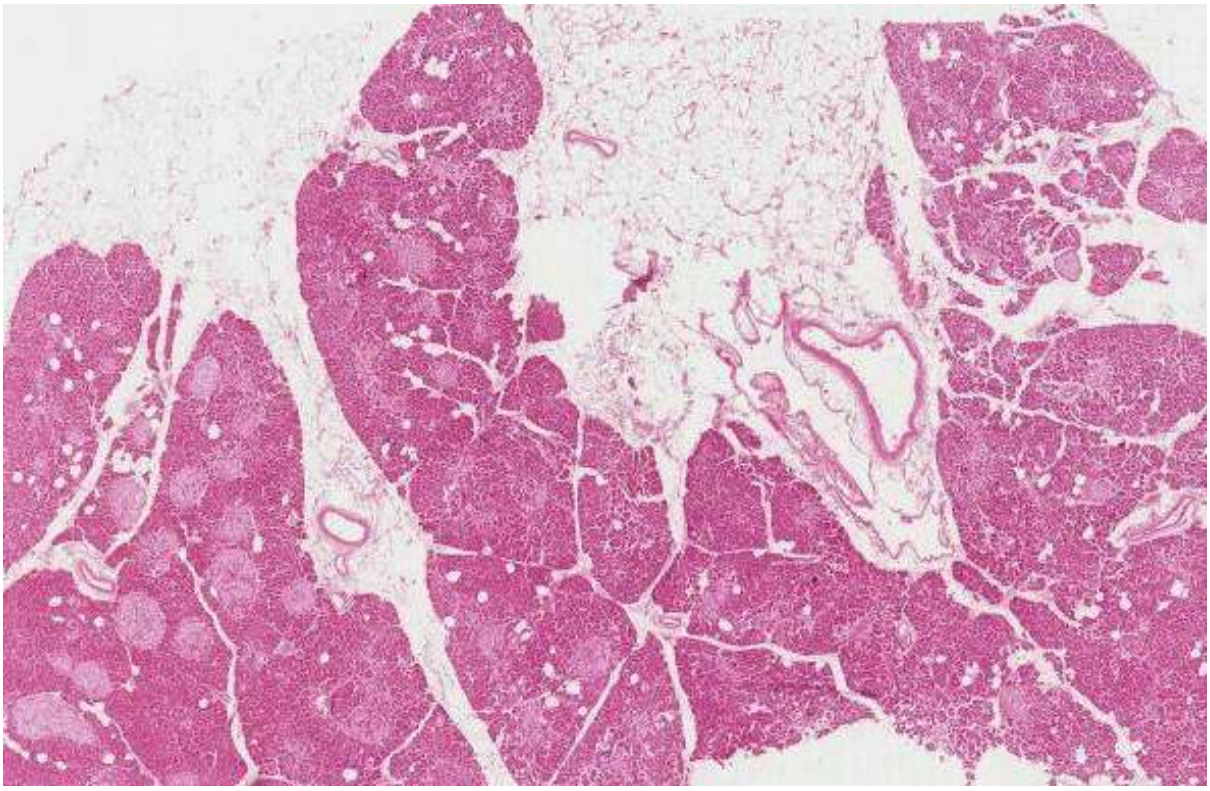
Slide 2 (Cystic fibrosis)



Features

- swivelling collagen throughout
    - **atrophied exocrine tissue replaced by collagen**
- extensive atrophy of exocrine tissue
    - **mucus (CFTR malfunction) blocks duct → blocks secretion → exocrine apoptosis**
- high presence of fat tissue
    - **fat that is normally in CT septa**
- preserved islets
- cystic duct enlargement
    - **thick mucus accumulation**

Slide 3 (Type 2 Diabetes)



Signs and symptoms

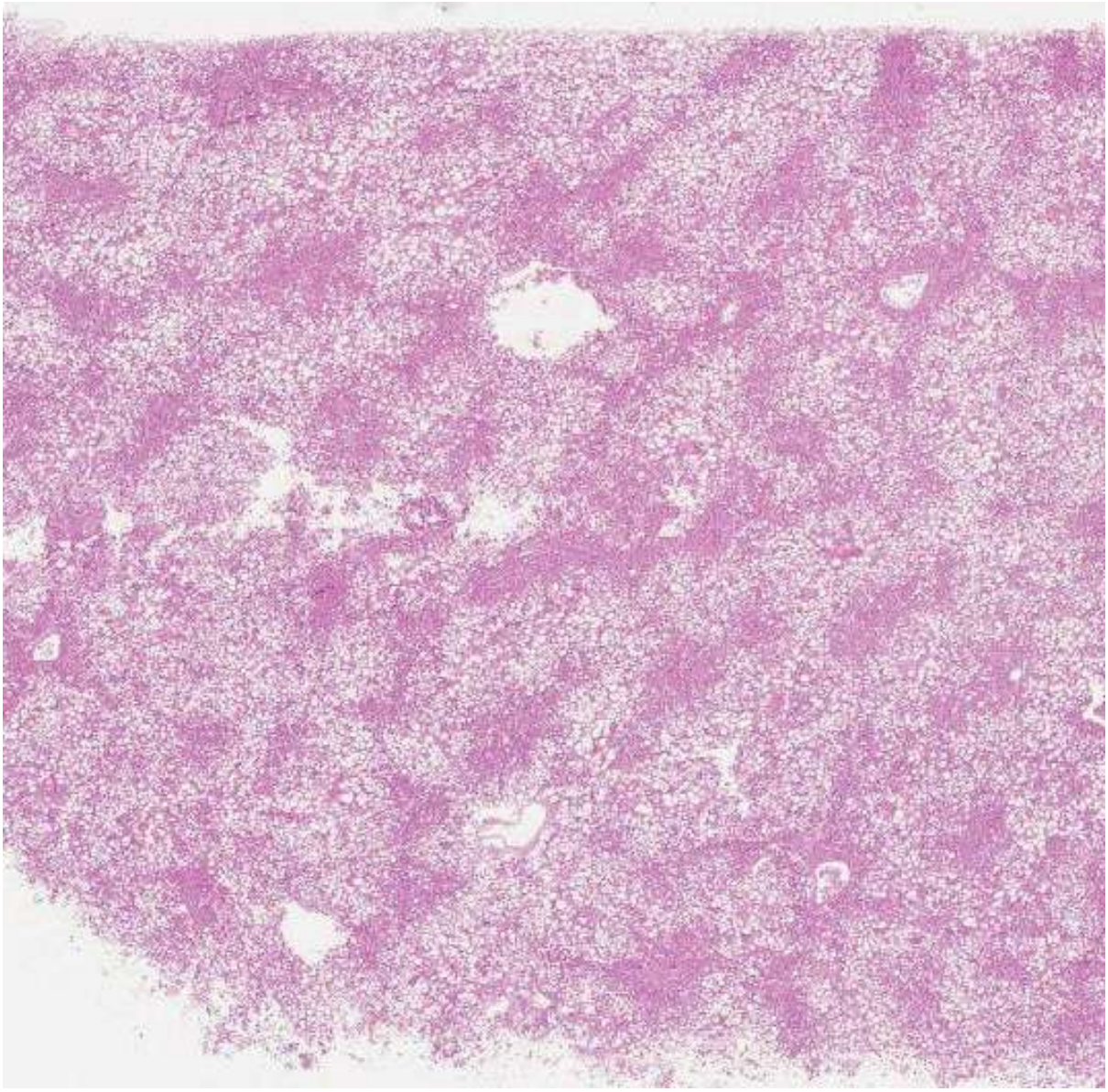
- 78yo man
- long-standing T2DM
- CKD
- peripheral neuropathy
- partial blindness
- died of recent MI

Diagnosis supported by Features

- amyloidosis
    - **amylin secreted with insulin in beta cells → increased beta cell activity due to peripheral insulin resistance → accumulation of pink amorphous amyloid with hyaline appearance → marked insulin decreased output**
- preserved exocrine tissue
- chronic kidney disease
    - **high plasma glucose → glycosylation of glucose + protein → advanced glycosylation end products → accumulate in BM of glomerulus → leaking of glomeruli + glomerulosclerosis → nephron loss → CKD + renal failure**
- peripheral neuropathy
    - **AGE deposition in blood vessels → interfere with blood nutrition supply to neurons → degeneration**

- partial blindness
    - **haemorrhaging and infarction of blood vessels → retinopathy**
- myocardial infarction
    - **increased plasma glucose → increased fat levels → sped up atherosclerosis in CA → MI**

Slide 4 (Fatty liver)



Features

- intracellular TAG accumulation (steatosis)
- occurs around central vein more than the portal vein

Signs and symptoms

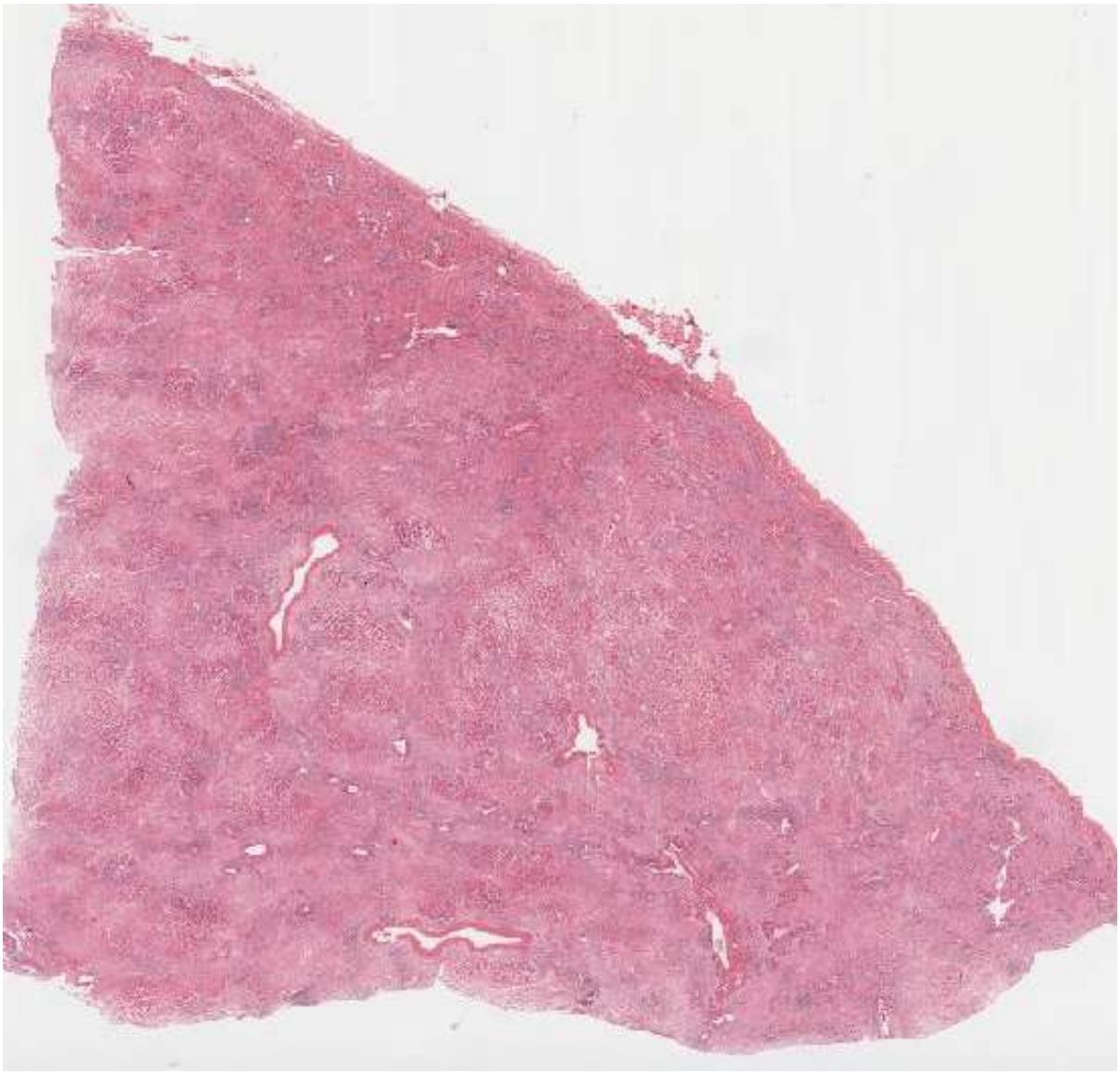
- none usually

- reversible response to injury
- rarely nausea

Causes

- alcohol
    - **blocks beta oxidation → TAG synthesis → accumulation in hepatocytes**
- hepatitis C
- obesity
    - **saturation with fat → high fat levels → high TAG synthesis**
- protein malnutrition
- drugs
- saturation with fat
    - **liver stores as TAG to send to peripheral fat stores with lipoproteins**

Slide 5 (Fulminant hepatitis)



Signs and symptoms

- 27yo female nurse
- gradually increasing anorexia, malaise
- jaundice = increased bilirubin
    - **disruption to hepatocyte conjugation + bile exit of bilirubin leading to jaundice of un+conjugated bilirubin**
- increased ALP and GGT
    - **disruption to bile flow - epithelial cell damage causes release of ALP and GGT**
- hugely increased AST and ALT
    - **high levels of hepatocyte death, high level suggests acute injury**
- normal protein and albumin
    - **suggests acute injury as albumin has a long plasma half life**

Physical examination

- tenderness
- enlarged liver
- jaundice
- arthritis (HBV/HCV)

Causes

- viral hepatitis
    - **HCV**
    - **HBV + HDV = high rates of fulminant hepatitis**
- alcohol
- drugs
- travel history
- hepatitis acquisition
- risky sexual activity

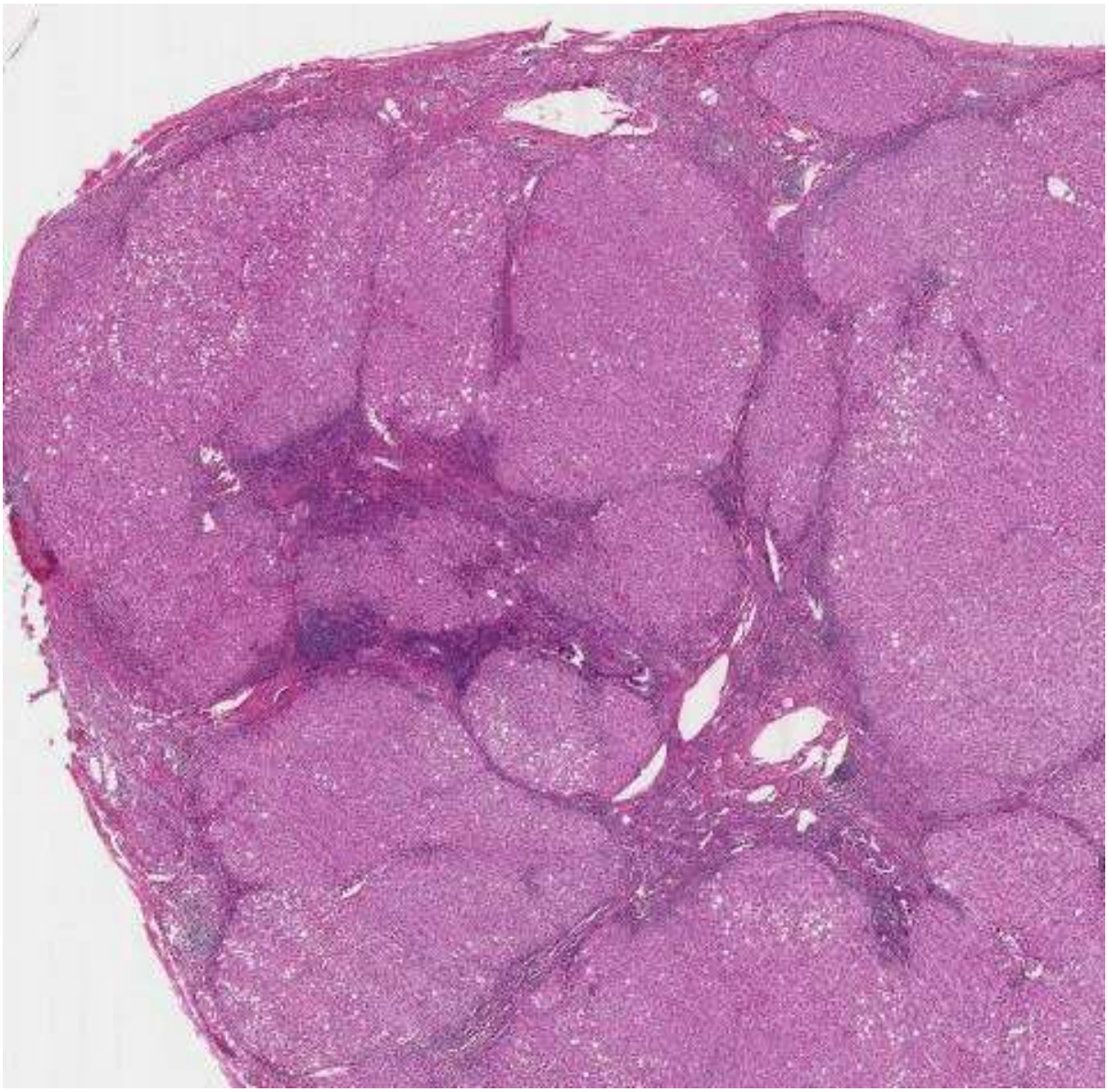
Diagnosis

- acute fulminant hepatitis

Features

- aggregations of lymphocytes
    - **gradual recruitment of lymphocytes into the tissue (not acute)**
- numerous biliary ductules
    - **collapse of liver parenchyma due to extensive injury to the tissue disrupts normal bile ductule structure and they are spread out (acute process)**
- irregular capsule shape
    - **collapse of liver tissue lobule structure (acute)**

Slide 6 (Chronic active hepatitis)



Signs and symptoms

- 45yo man
- IVDU
    - **risk factor for HCV infection**
- tiredness
- anorexia
- antibodies to HCV

Causes

HBV

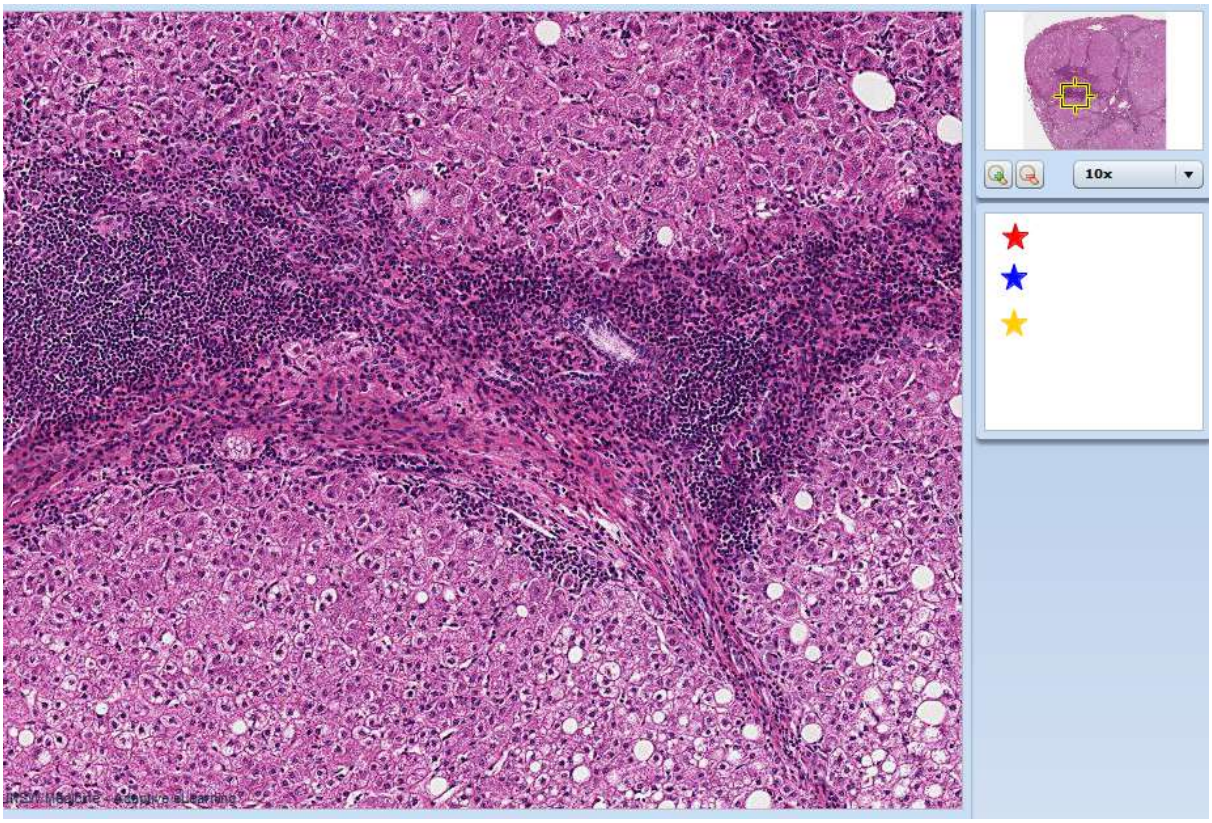
Features

- inflammatory cell infiltrate
    - **chronic hepatitis - predominantly lymphocytes with macrophages, plasma cells and occasional eosinophils.**
- interface hepatitis
    - **presence of chronic inflamm. cells in portal tracts, in which infiltrate extends into hepatic parenchyma resulting in hepatocyte apoptosis. if extensive damage obliterates hepatocytes between portal areas → confluent necrosis**
- deposition of fibrous tissue
    - **chronic liver damage. a response to parenchymal necrosis resulting from hepatic injury. fibrosis initially confined to portal tracts but as progresses, fibrous tissue expands forming portal-portal and portal-central septae imparting nodularity to the hepatic architecture**
- apoptotic hepatocytes
    - **appear shrunken with densely eosinophilic cytoplasm caused by cytotoxic T cells responding to viral antigens expressed on surface of hepatocytes**
- diffuse swelling of hepatocytes
    - **following injury, hepatocytes undergo ballooning degeneration with a vacuolated cytoplasm and eosinophilic fragments of organelles**

Complications

- Cirrhosis
    - **response to liver damage is 1 bile duct proliferation 2 fibrous portal septa bridging 3 hepatocyte regeneration**
- Hepatic Cellular Carcinoma
- Portal hypertension
    - **perisinusoidal fibrosis → increased resistance to blood flow through liver**
    - **Portal-systemic anastamoses → oesophageal varices → massive haematemesis → hepatic encephalopathy**
- Liver failure
    - **once liver drops below 5% of normal function**

Adaptive tutorial



1. A biliary ductule is highlighted in **red**.

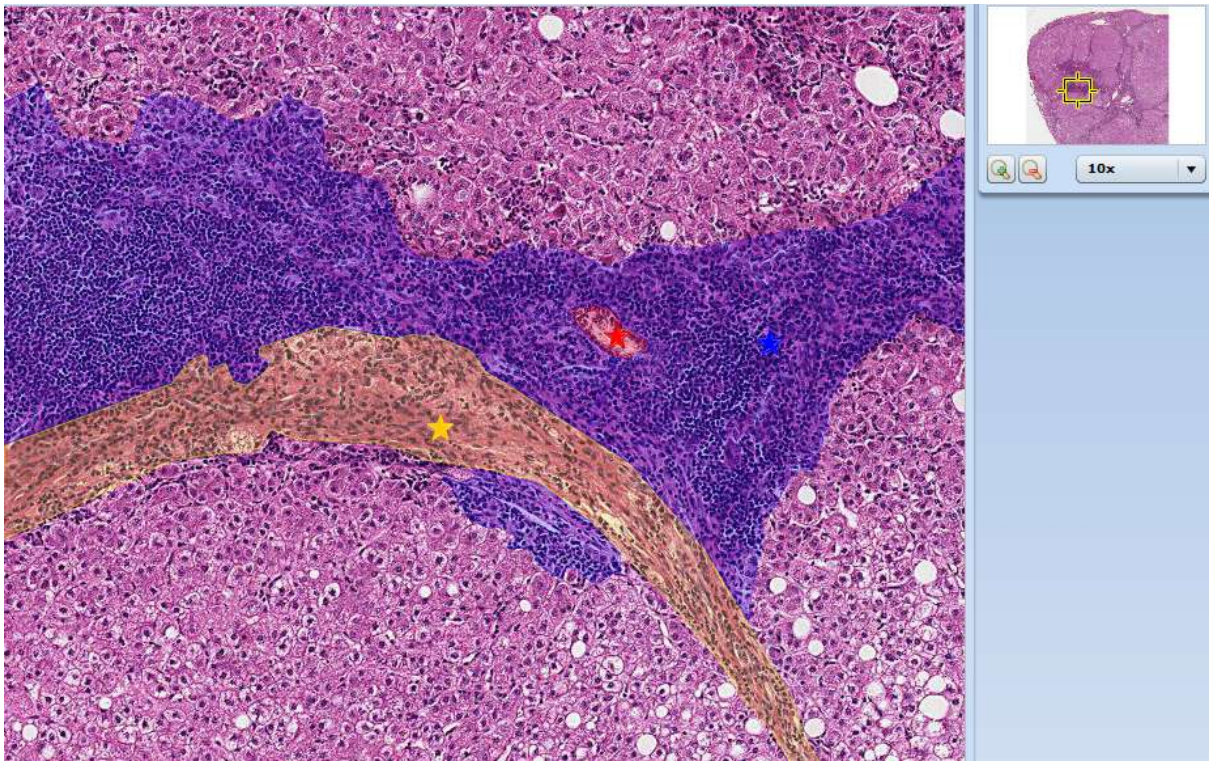
2. The inflammatory cell infiltrate is highlighted in **blue**.

3. The region of fibrosis is highlighted in **yellow**.

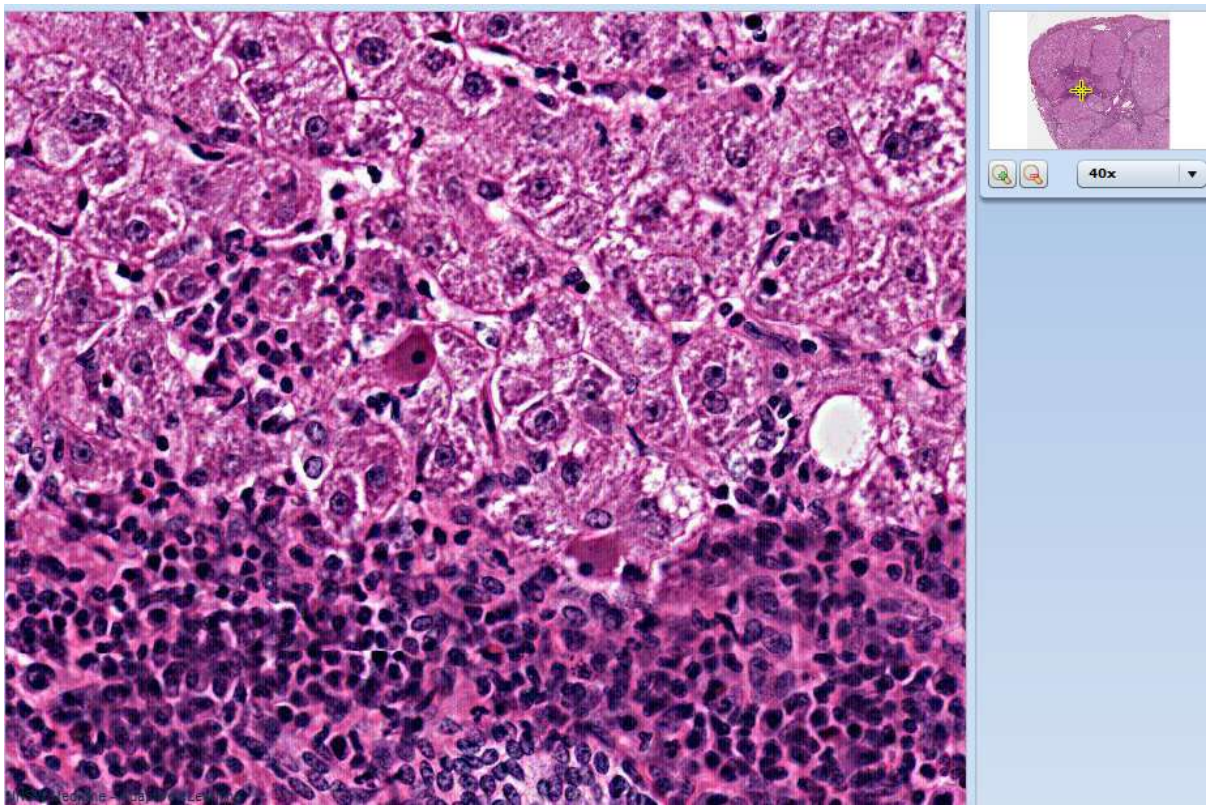
Biliary ductules are lined by simple cuboidal epithelium, and occur within the portal areas.

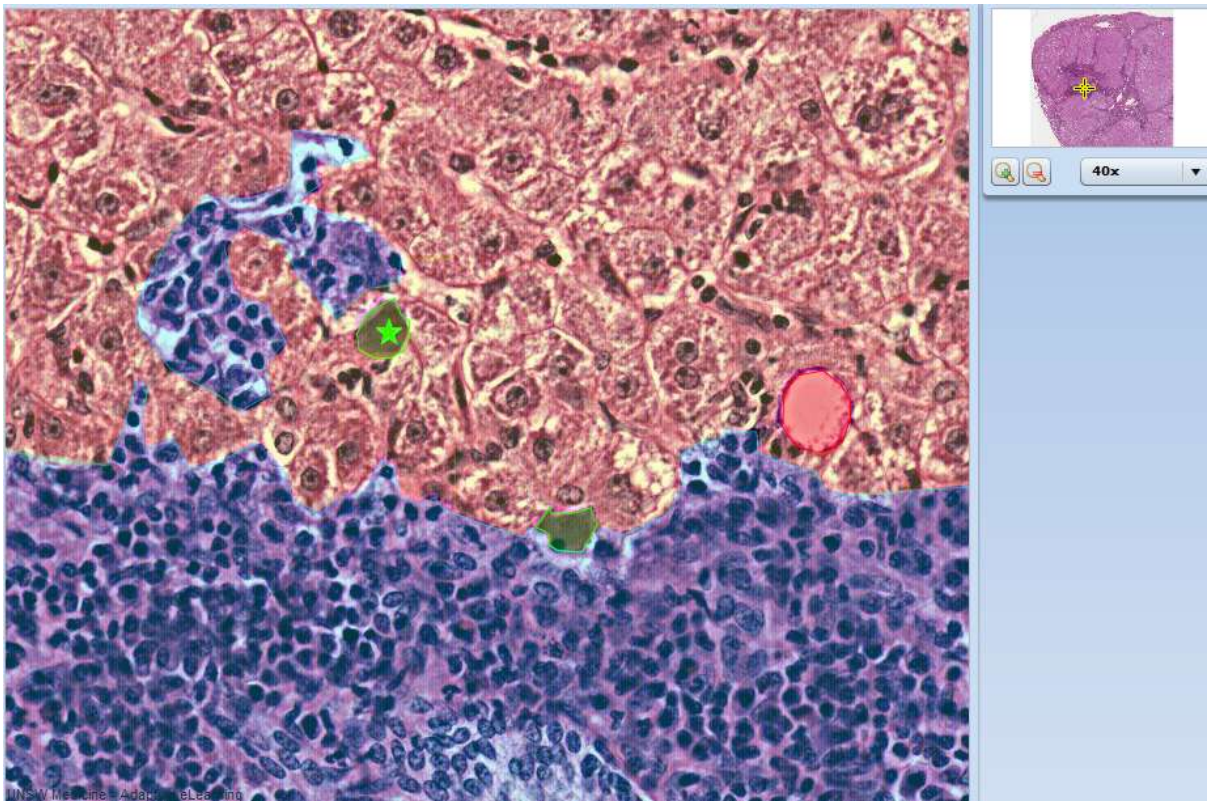
The **inflammatory cell infiltrate in chronic hepatitis** consists **predominantly of lymphocytes**, with **macrophages, plasma cells, and occasionally eosinophils**. In **milder** cases of chronic hepatitis, the inflammation is **limited to the portal areas**. **Interface hepatitis refers to the presence of chronic inflammatory cells in the portal tracts**, in which the inflammatory infiltrate **extends into the hepatic parenchyma** (ie at the interface of hepatic parenchyma and portal tract) **resulting in apoptosis of hepatocytes.** In more **severe** cases, the damage to hepatocytes may be so **extensive as to obliterate hepatocytes between portal areas, resulting in confluent necrosis.**

A defining feature of **chronic liver damage is the deposition of fibrous tissue**. This is the response to **parenchymal necrosis,** which results from hepatic injury. Initially, the **fibrosis is confined to the portal tract**s, but as the chronic hepatitis progresses, **fibrous tissue expands and extends to form portal-portal, and portal-central septae**. Please view the section at lower power: Notice the **fibrous septae imparting a nodularity** to the overall architecture of the hepatic tissue.



Following injury, hepatocytes may undergo diffuse swelling, otherwise called “ballooning degeneration”. The cytoplasm is vacuolated and contains scattered eosinophilic fragments of organelles.





1. The apoptotic hepatocytes are highlighted in **green**.

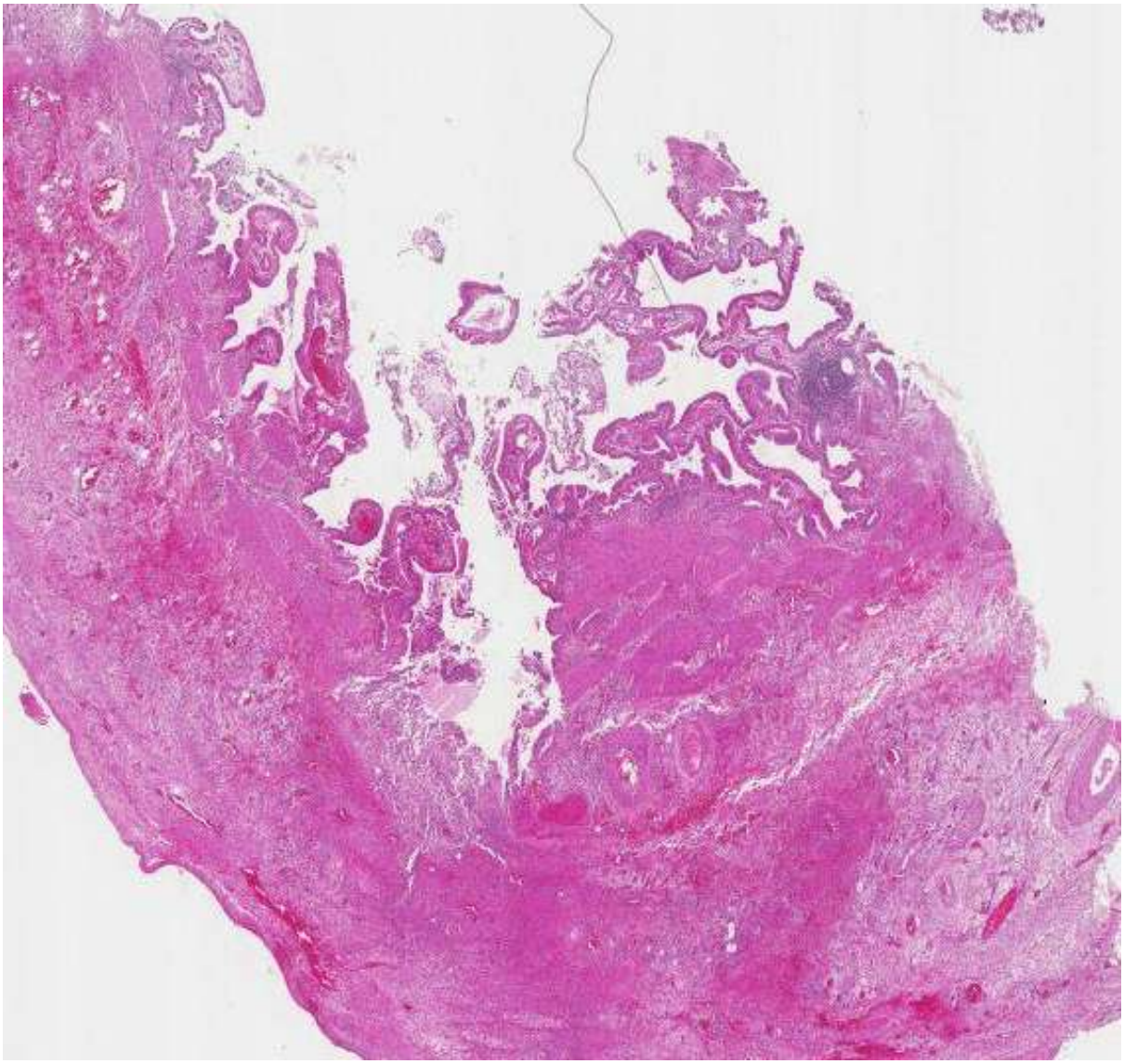
2. Chronic inflammatory cell infiltrate is highlighted in **blue**.

2. Fatty change is highlighted in **red**.

3. Degenerating but still viable hepatocytes are highlighted in **yellow**.

Apoptotic hepatocytes appear shrunken and have densely eosinophilic cytoplasm. The nuclei in this image are small and dense, but they may also appear fragmented. Apoptosis in this case is caused by cytotoxic T cells, which are responding to viral antigens expressed on the surface of infected hepatocytes.

Slide 7 (Acute cholecystitis)



Signs and symptoms

- 51yo obese f
- eight hours of severe upper abdominal pain radiating to back
    - **pressure on pain nerves**
    - **inflammatory mediators**
    - **ischemia**
- associated nausea and vomiting
- mildly jaundiced (elevated bilirubin), elevated GGT and ALP
    - **normal AST and ALT so extrahepatic obstructive jaundice.**
- tachycardia
- fever
    - **systemic effects of inflammation**
- tenderness in upper right quadrant of abdomen

- past history of episodic epigastric pain which on one occasion was accompanied by jaundice
    - **acute presentation of a chronic problem**

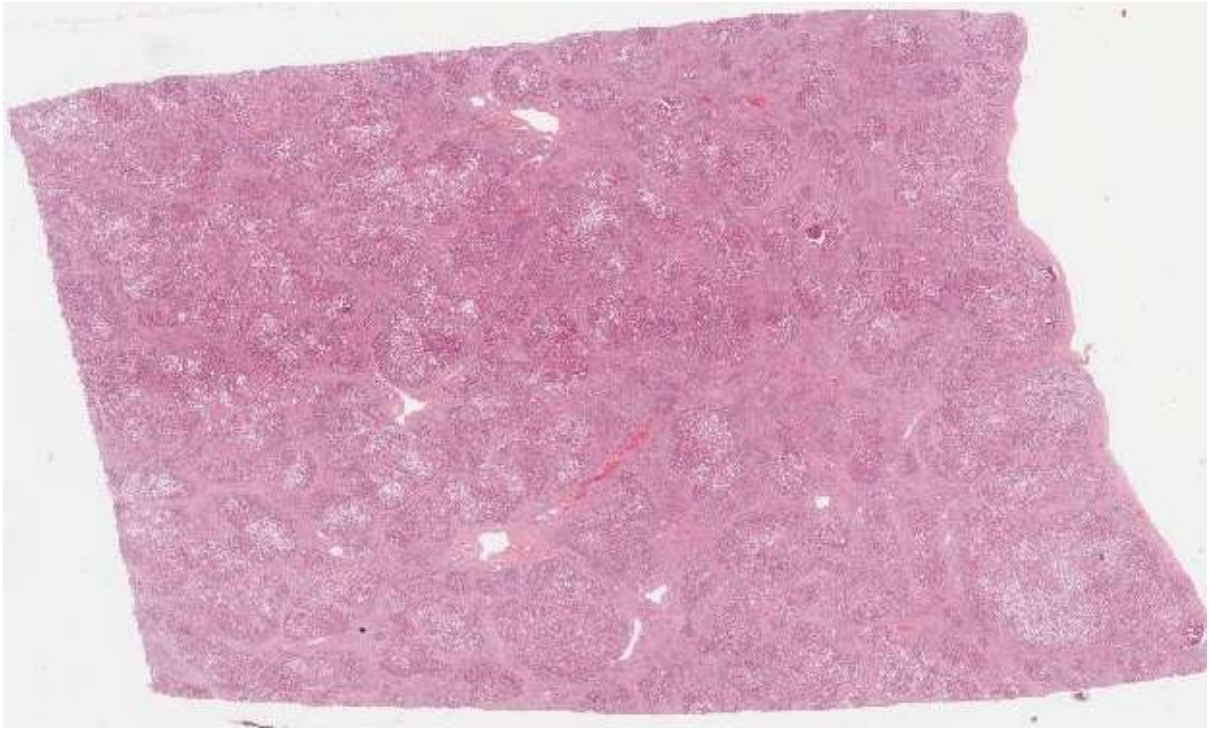
Features

- lymphocyte follicle presence
    - **indicates an underlying chronic problem**
- thickened wall from tissues from sub-serosal layer
    - **response to increased pressure in the gallbladder - hypertrophy in chronic inflammation**
- pus on ulcerated surface
- muscle layer degradation
    - **necrotic process will continue until wall is ruptured → perforation. bile, neutrophils and oedema reduces the blood supply and causes more necrosis - gb only has one artery and vein for blood supply.**
- scarring/fibrosis
    - **response to chronic inflammation → fibrosis**
- fat filled macrophages

Complications

- gall bladder perforation
    - **if not removed, necrosis would continue and perforate gallbladder wall releasing bacteria and bile into the abdominal cavity → acute peritonitis**
- inflammation of serosal surface
    - **causing adjacent tissue to adhere to GB → inflammatory spread contained locally by adherence**
- infection
    - **may travel from bile up the biliary tree → cholangitis, obstructing bile flow from liver**
- acute pancreatitis
    - **can obstruct head of pancreas**

Slide 8 (Cirrhosis, micronodular)



Signs and symptoms

- 59yo m
- weakness, tiredness
- increasing abdominal distension
- >100g alcohol/day
    - **alcoholic hepatitis → fatty change (mild and reversible) → cirrhosis (severe and irreversible)**
- looks older than stated age
- pale with tense ascites
    - **ascites = fluid entering peritoneal cavity, up to 5L in abdomen.**
    1. **hypoalbuminemia = reduced colloid osmotic pressure → water in abdomen**
    2. **portal hypertension = increased resistance by perisinusoidal fibrosis**
    3. **exudate/transudate**
    4. **renin-angiotensin system = loss of BV into preitoneum → stimulate RAS → aldosterone → increases water retention**
- liver and spleen not palpable
- elevated bilirubin, ALP, GGT
    - **bilirubin has to be above 90 before significant. implies cholestasis (bile flow stopped)**
- elevated AST, ALT
    - **not significant hepatocellular necrosis occurring**
- decreased Albumin, total protein

- **hypoalbuminemia indicates low protein synthetic function of the liver**
  - **chronic liver problems**
  - **protein malnutrition**

Features

- fibrous septa
  - **dense, eosinophilic collagenous bands containing blood vessels and lymphocytes - characteristic of cirrhosis. key cirrhotic pathogenic processes:**
    1. **hepatocyte death**
    2. **extracellular matrix deposition**
    3. **vascular reorganisation**
  - **proliferation + activation of stellate cells responsible for fibrosis.**
- bridging fibrous bands linking portal tracts
- nodules of regenerating hepatocytes
- proliferation of bile ductules
  - **induced by intrahepatic obstruction of biliary outflow**
- perisinusoidal fibrosis
  - **increases resistance to flow in portal venous system**

Diagnosis

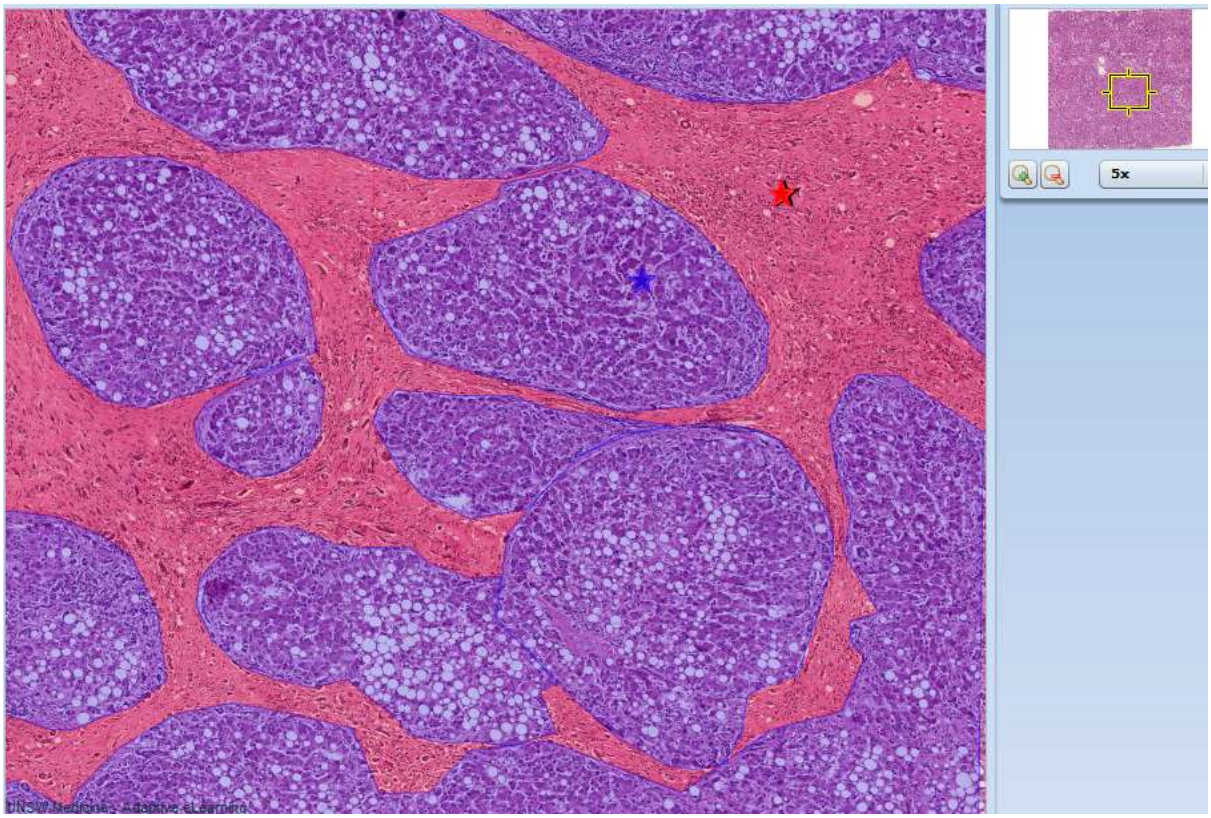
indicative of high alcohol consumption leading to liver cirrhosis and liver failure.

Complications

- Cirrhosis
  - **response to liver damage is 1 bile duct proliferation 2 fibrous portal septa bridging 3 hepatocyte regeneration**

1. Hepatic Cellular Carcinoma
2. Portal hypertension
   - **perisinusoidal fibrosis → increased resistance to blood flow through liver**
   - **Portal-systemic anastamoses → oesophageal varices → massive haematemesis → hepatic encephalopathy**
3. Liver failure
   - **once liver drops below 5% of normal function**

Adaptive tutorial



The regions highlighted in **purple** are nodules of hepatic parenchyma.

The regions highlighted in **red** are fibrous septa.

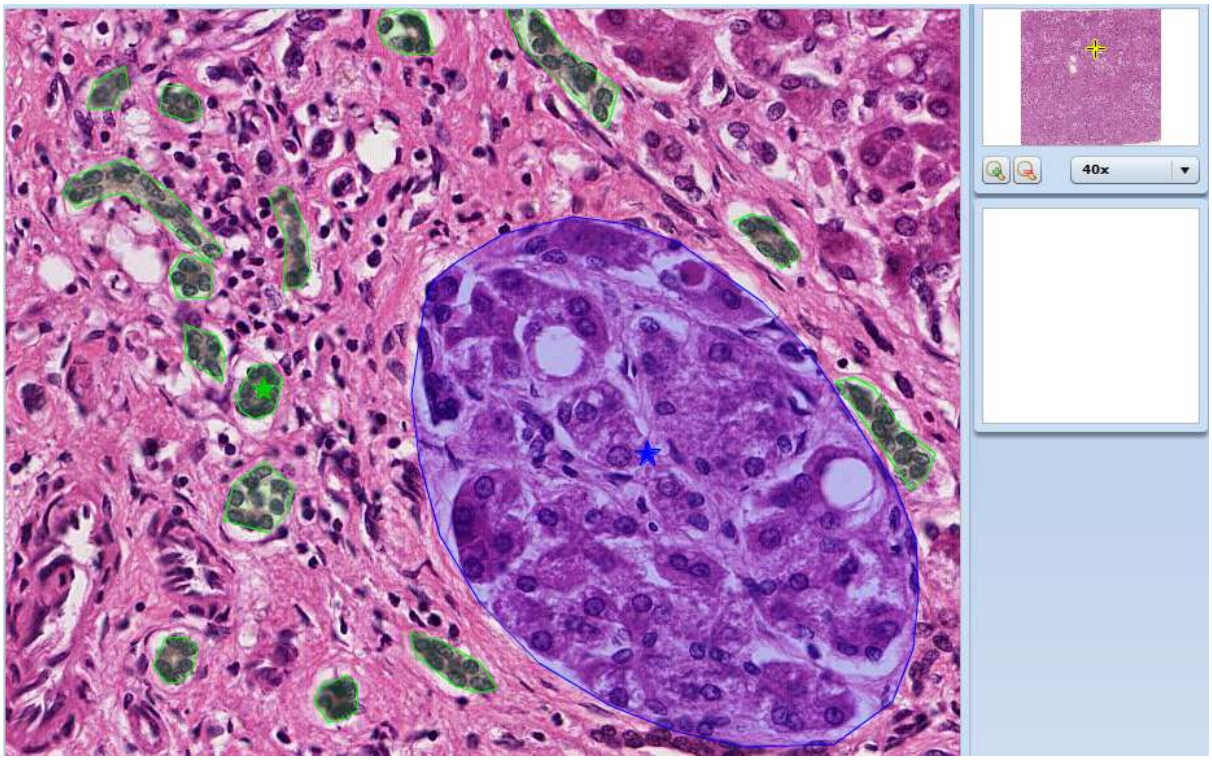
The **fibrous septa** are composed of **dense, eosinophilic, collagenous bands**, and are characteristic of **cirrhosis**. The **key pathogenic processes in cirrhosis are**

1. **hepatocyte death,**
2. **extracellular matrix deposition,**
3. **vascular reorganisation**.

Proliferation and activation of hepatic stellate cells are primarily **responsible** for the **fibrosis**. As the disease progresses, **bridging fibrous bands link portal tracts to portal tracts**, and **portal tracts to hepatic veins**. The fibrous bands surround **nodules of hepatocytes, which undergo regeneration**.

Cirrhosis is the final common pathway for a number of chronic hepatic diseases. The most common causes in our society are

- **alcohol**
- chronic viral hepatitis (**HBV and particularly HCV**)
- **chronic biliary obstruction** eg. primary biliary cirrhosis
- **metabolic disorders** eg. **haemochromatosis**
- **cryptogenic** (some of these might be related to non-alcoholic fatty liver disease)



1. The biliary ductules are highlighted in **green**.

2. The regenerative nodule of hepatocytes is highlighted in **blue**.

In cirrhosis, there is **intrahepatic obstruction of biliary outflow**. This **induces proliferation of ductular epithelial cells, forming twisted cords of ductules** in portal areas.

Surviving hepatocytes proliferate and are arranged in **multiple layers rather than single plates** of cells.

The **eosinophilic material surrounding the nodule is fibrous tissue**, **containing blood vessels** and **lymphocytes**.

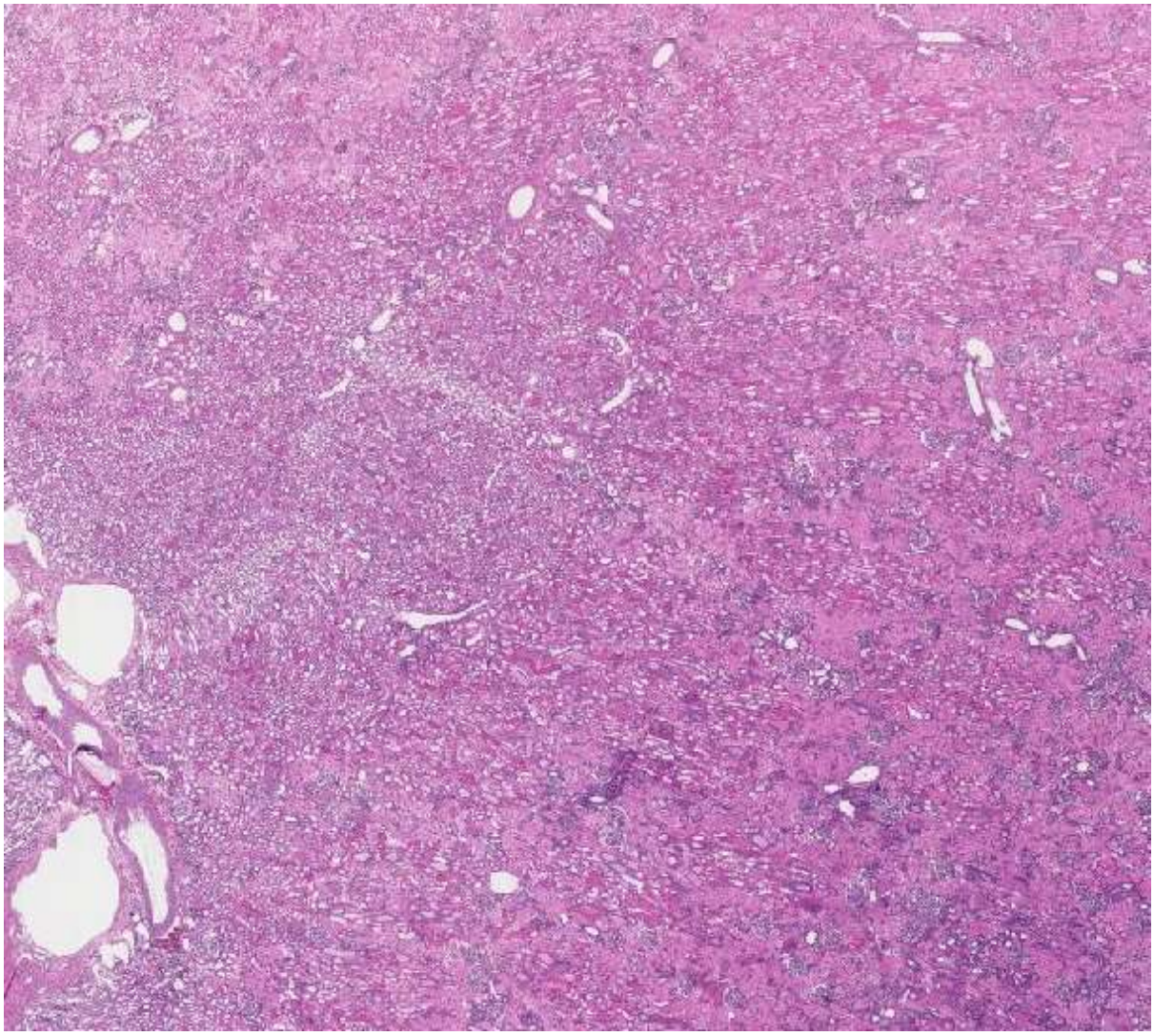
Perisinusoidal fibrosis directly increases resistance to flow in the portal venous system, thereby contributing to portal hypertension.

Obstruction of hepatic veins contributes to portal hypertension in settings other than cirrhosis (eg. Budd-Chiari syndrome).

Biliary ductular proliferation has no effect on portal venous flow.

Hepatic arteriolar disease is not implicated in cirrhosis, and therefore would not contribute to portal venous hypertension.

Slide 9 (Acute tubular necrosis)



Signs and symptoms

- 22yo man
- trapped under motorbike wreckage for 5hrs
- pale and sweating profusely
- considerable pain from compound fracture of right femur
    - **bone breaks the skin → massive blood loss, esp. femoral artery**
    - **infection risk**
- heart rate 130/min and blood pressure 80/50 returning to normal in two hours
    - **hypovolemic shock. sympathetic nervous system response → tachy, pale, sweating**
    - **tachycardia = increase tissue blood flow**
- urine output of 150ml/24hrs even after fluid replacement + orthopaedic management
    - **proteinaceous casts obstruct urine flow, prevent urination.**
    - **glomerular filtrate leaks into renal interstitium**

        - **inadequate Na reabsorption causes RAS activation which constricts afferent arterioles → reduced blood flow → reduced urine output + PCT necrosis**
- sodium decreased, potassium increased, chloride decreased, bicarbonate decreased
        - **hypovolemic so GFR reduced, no reabsorption of Na, Cl, HCO3**
- urea and creatinine increased
        - **GFR does not proceed so urea, creatinine not eliminated**
        - **possibly skeletal muscle necrosis contributing to extremely high amount of creatinine**

Features

- tubules lack nuclei
        - **coagulative necrosis - anucleate, eosinophilic ghosts filled with denatured cross-linked cytoplasmic protein**
        - **tubular damage is selective to most metabolically active parts → straight PCT and aLH. Thus some tubules are intact and this is a focal lesion.**

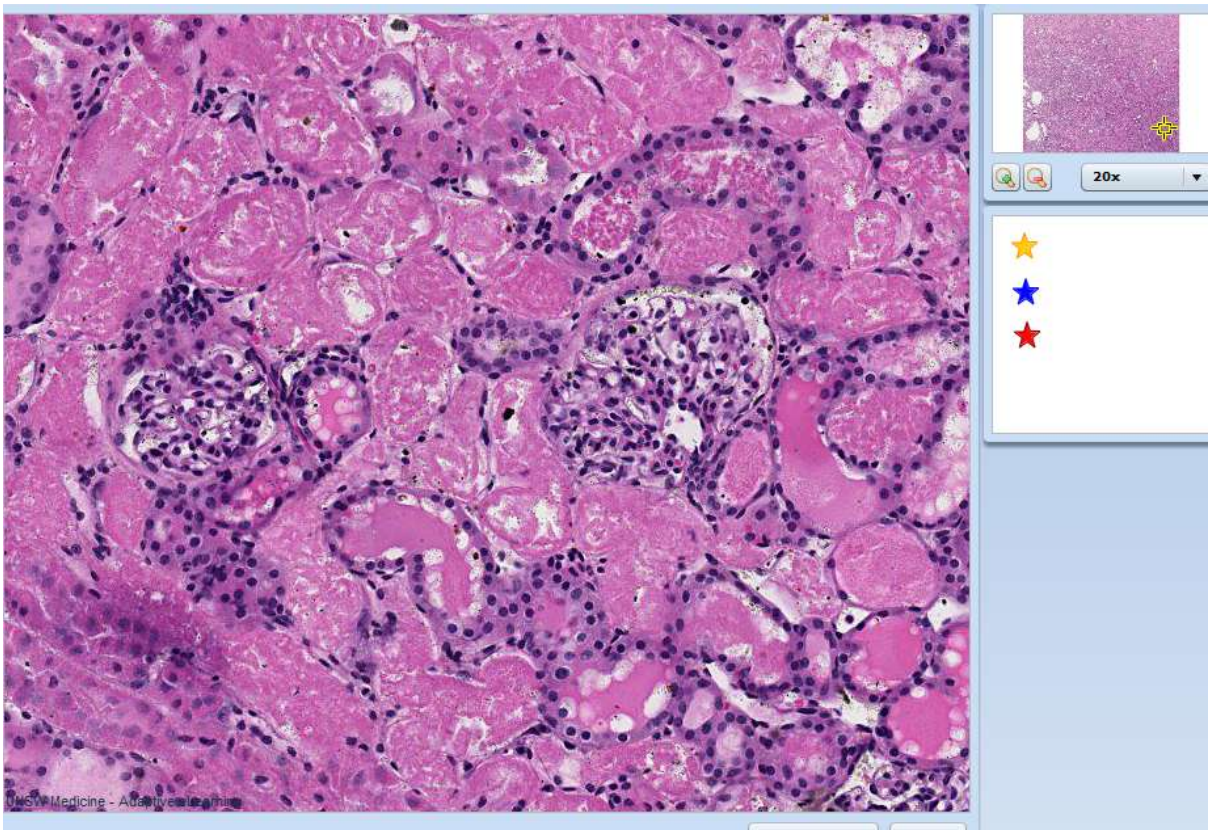
Diagnosis

Acute tubular necrosis due to hypovolemic shock.

Complications

- polyuria
        - **Dialysis required for a few weeks while kidneys repair damage until lining of tubules regenerate. reabsorption will be inadequate resulting in polyuria until epithelial regeneration complete**

Adaptive tutorial



1. The necrotic tubules are highlighted in **red**.

2. The glomeruli are highlighted in **blue**.

3. The viable tubules are highlighted in **yellow**.

The **tubular epithelial cells exhibit coagulative necrosis**, and are recognisable as **anucleate, eosinophilic ghosts, filled with denatured, cross-linked cytoplasmic protein**.

Acute kidney injury (previously known as acute tubular necrosis) is most commonly caused by **ischaemia**. The **tubular damage is focal**, **preferentially affecting the most metabolically active parts** of the nephron: the **straight portion of the proximal convoluted tubule**; and the **ascending thick limb of the loop of Henle**. This explains the presence of **intact tubules (primarily distal convoluted tubules)**, between the necrotic areas.

Irreversible injury to tubular epithelium

Tubular epithelial cells may be injured by ischaemia associated with **hypotension** (e.g. blood loss, burns, septic shock, pancreatitis). The molecular mechanisms underlying this include **ATP depletion** (leading to cellular swelling); **loss of cell membrane integrity**; **accumulation of intracellular calcium**; **activation of proteases**; and **activation of endonucleases**.

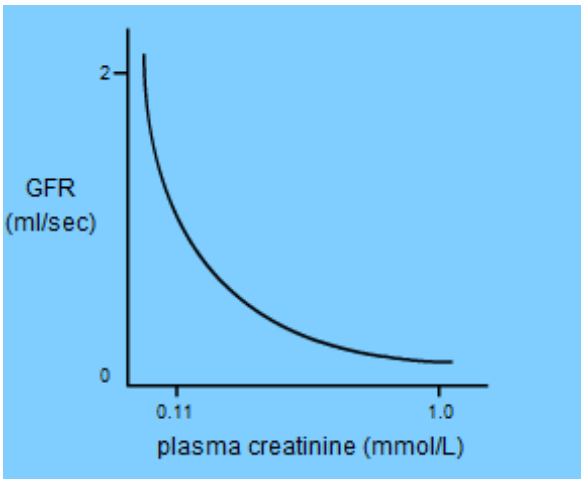
Tubular epithelial cells may also be **injured by toxins** (radiocontrast agents, aminoglycoside antibiotics, heavy metals, chemotherapeutic agents, myoglobin).

Disturbances to nephronal blood flow

In addition to **ischaemic damage**, **acute kidney injury** (AKI) **causes intrarenal vasoconstriction** affecting afferent arterioles. This vasoconstriction may be **mediated by the renin-angiotensin** system, or by **sublethal endothelial injury** which leads to the **release of the vasoconstrictor substance, endothelin**. The result is reduced glomerular blood flow and a reduced oxygen delivery to the tubular epithelium. These disturbances **explain persistent oliguri**a despite intact glomeruli.

Blockage of tubules by proteinaceous debris

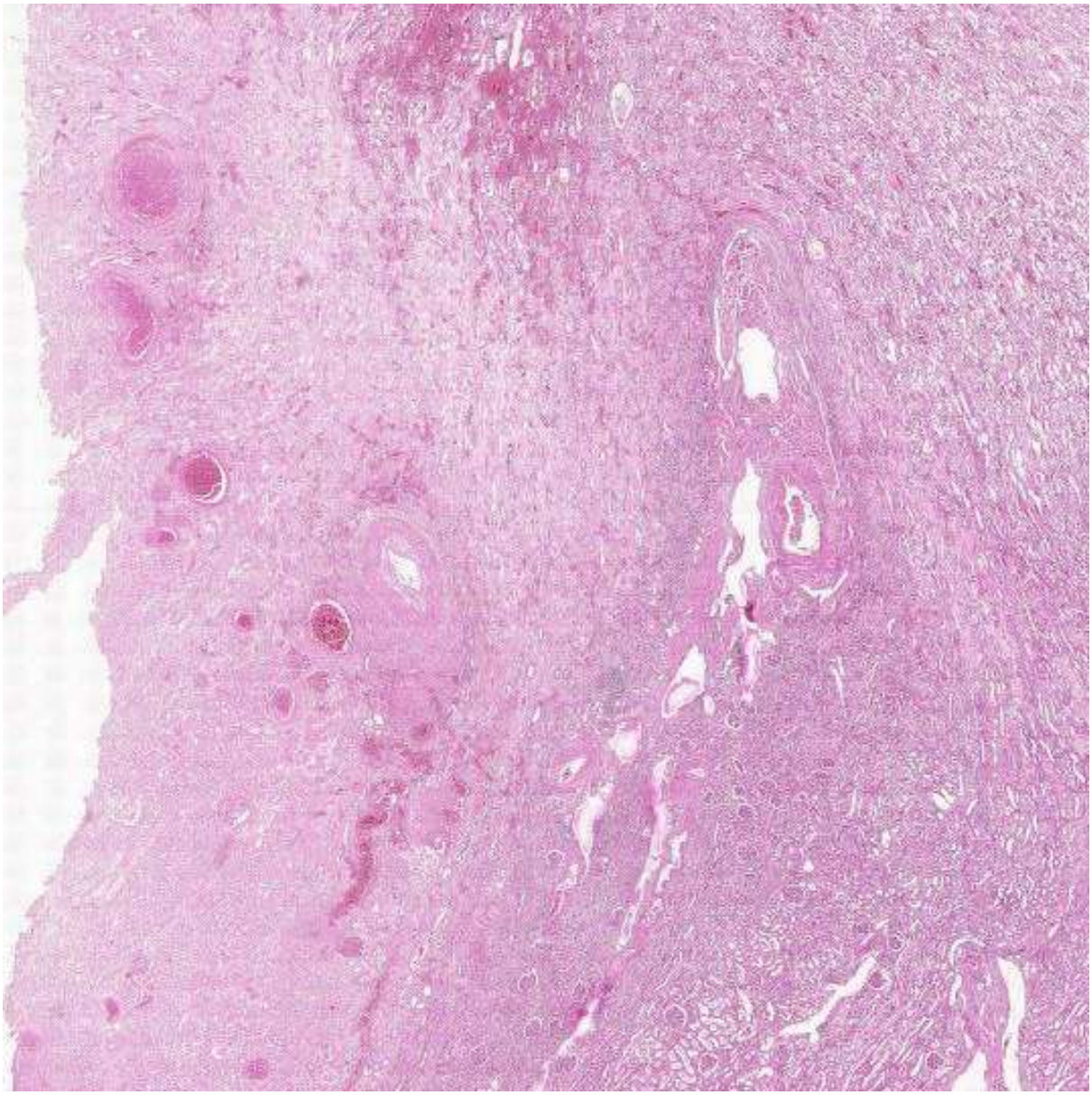
Epithelial cell debris can form proteinaceous casts (as seen in the viable tubules in this field), which can prevent any glomerular filtrate from reaching the renal collecting system.



An **increase in plasma creatinine concentration** is **typically the first biochemical sign of renal impairment,** even though most patients with subnormal

GFR (0.6-1.3mls/sec) still have plasma creatinine levels within normal limits. **Thus, in the early stages of chronic kidney disease, a small change in plasma creatinine can be a marker for a large change in renal function.**

Slide 10 (Renal infarct by embolism)



Signs and symptoms

- 72yo man
- recent onset of loin pain and haematuria, 2wks after MI
- 1 day later prolonged episode of retrosternal chest pain, cardio-resp arrest → death

Features

- coagulative necrosis
    - **all tissues instead of just selectively in the PCT and aLH (metabolically active)**
- dilated blood vessels
    - **indicative of inflammation**

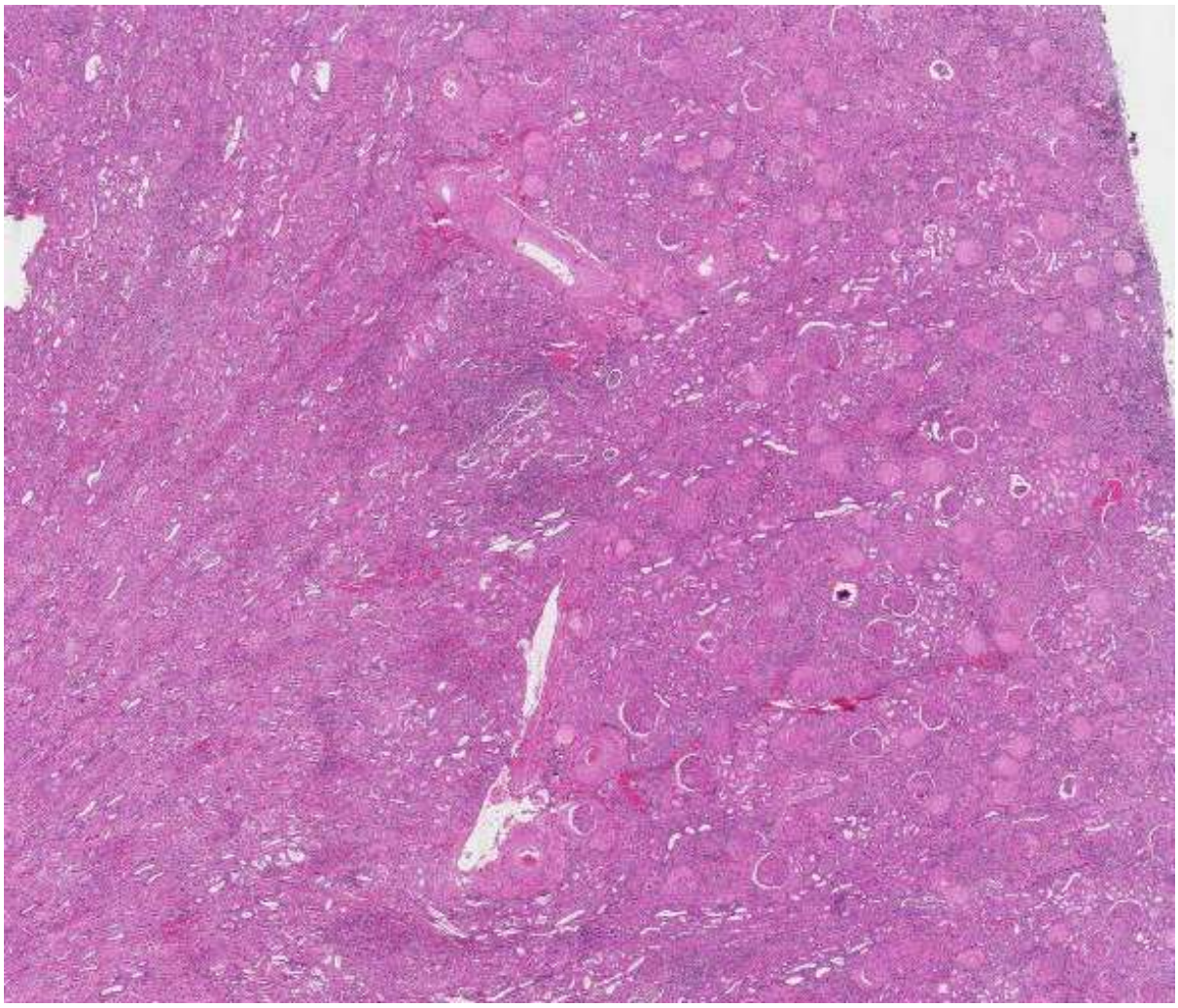
Diagnosis

- thromboembolus
    - **MI → necrotic LV muscle tissue → thrombus form → break off → impact renal artery**
- acute
    - **older thrombus (48hrs+) would result in acute inflammation + attempts at healing and regeneration**

Complications

- Emboli
    - **brain**
    - **spleen**
    - **lower limbs → peripheral gangrene**
    - **heart**
    - **intestines**

Slide 11 (Diabetic glomerulosclerosis)



Signs and symptoms

- 78yo man
- T2DM long standing
- CKD
- glomerular lesions
- renal vascular lesions
- pyelonephritis
- partial blindness
- peripheral neuropathy

Features

- nodular regions of dead glomeruli
    - **capillary BM thickening = advanced glycosylation end products in BM of glomeruli interfere with barrier to protein loss → proteinuria**

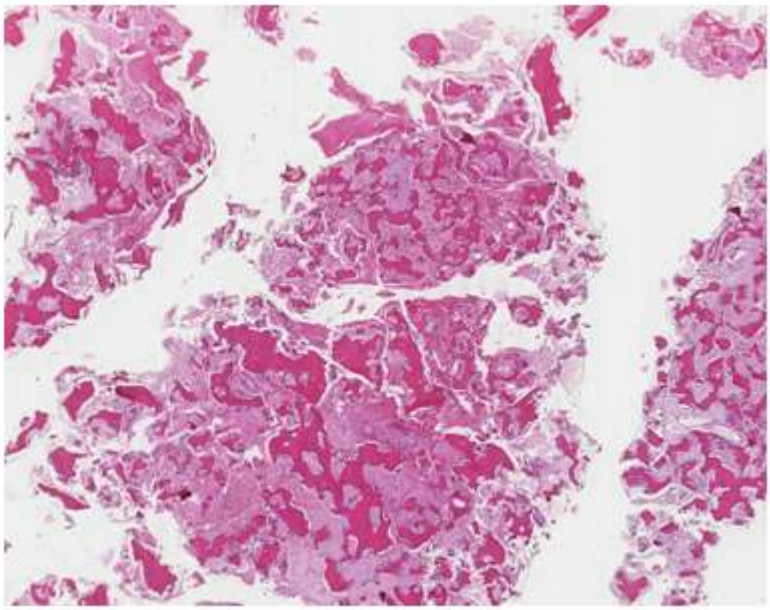
1. diffuse mesangial sclerosis = as sclerosis increases, capillary loops have no space → CKD
2. nodular glomerulosclerosis = distincitve ball-like deposits in periphery of glomerulus
3. hyaline sclerosis of arterioles

- renal atheroscleros s+ arteriolosclerosis
    - **hyaline changes within afferent/efferent arterioles → obstruction → ischaemic injury to nephron → CKD**
- presence of lymphocytes
    - **hyperglycaemia → interfere with neutrophils, macrophages → increased risk of infections → acute pyelonephritis (present lymphocytes)**

Investigations

- urinalysis
    - **proteinuria = casts**
    - **albuminuria = leaked through glomeruli**

Slide 12 (Paget's disease)



Signs and symptoms

76yo man

increase in bone mass, decreased tensile strength

Features

- mosaic pattern of bone matrix (disorganised)
    - **frantic attempt to lay down bone after osteoclastic activity of Paget's disease**
- increased numbers of osteoclasts and at bigger size with more nuclei
    - **showing higher level of activity**
- marrow is fibrosed with hypervascularisation due to high metabolic activity
- presence of woven bone
    - **immature without remodelling**

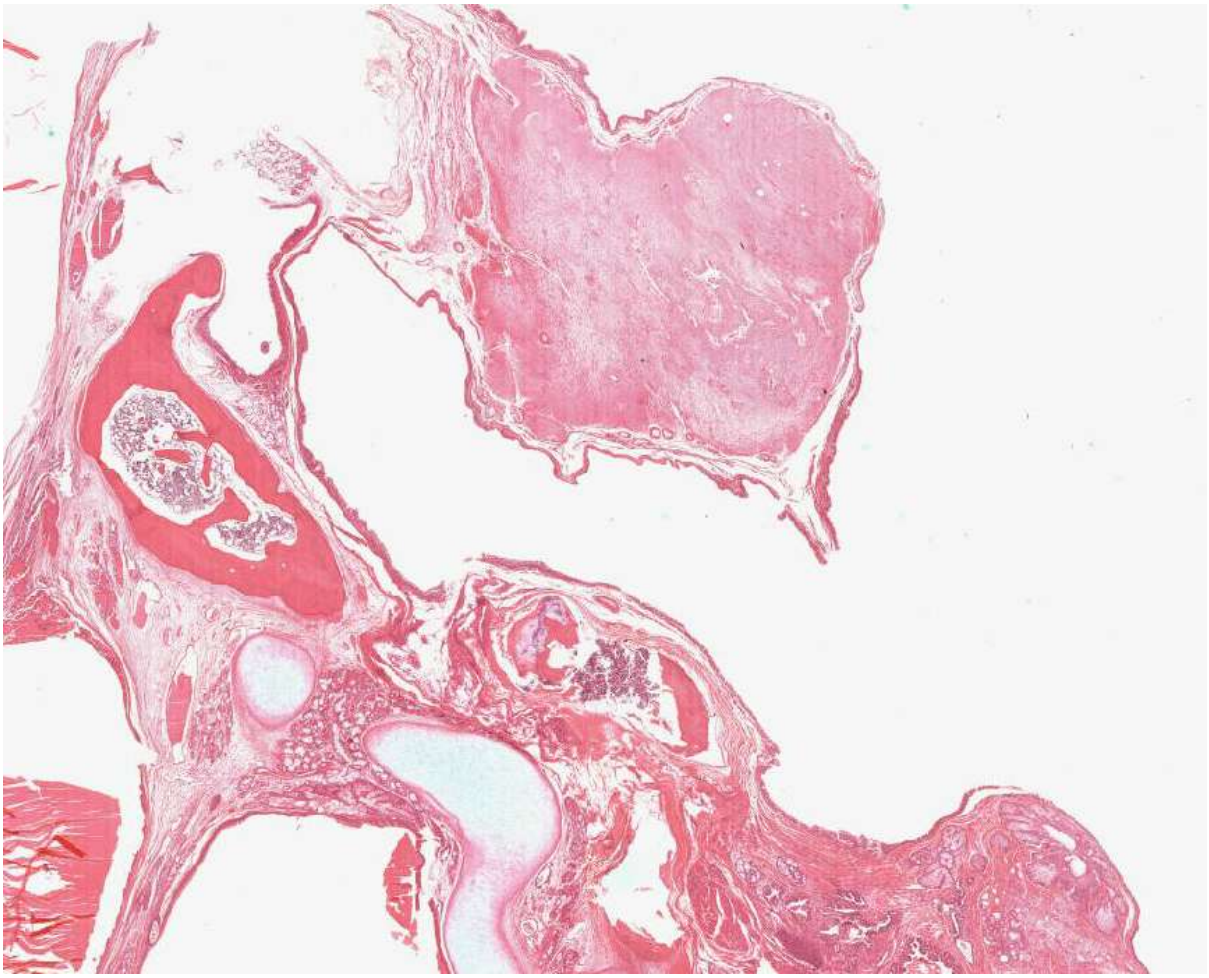
Diagnosis

- Paget's disease
    - **osteolytic phase = increased osteoclast activity → bone breakdown**
    - **mixed phase = increased osteoblast activity → mosaic pattern bone rapidly put down with no structure**
    - **sclerotic phase = osteoblasts lay down more bone than is lost resulting in excess bone with little strength due to lack of structure**

Complications

- high output congestive heart failure
    - **increased demand for blood to supply new increased mass of bone = increased load on heart = heart failure**
- neurology due to compression of brain and foramen
    - **sensorineural deafness in 50%**
- rheumatological
    - **osteoarthritis due to improper gait**
    - **gout due to hyperuricaemia due to increased bone turn over and thus DNA turnover**
- osteosarcoma
    - **high turnover of cells at old age = cancer likely**

Slide 13 (Teratoma, dermoid cyst)



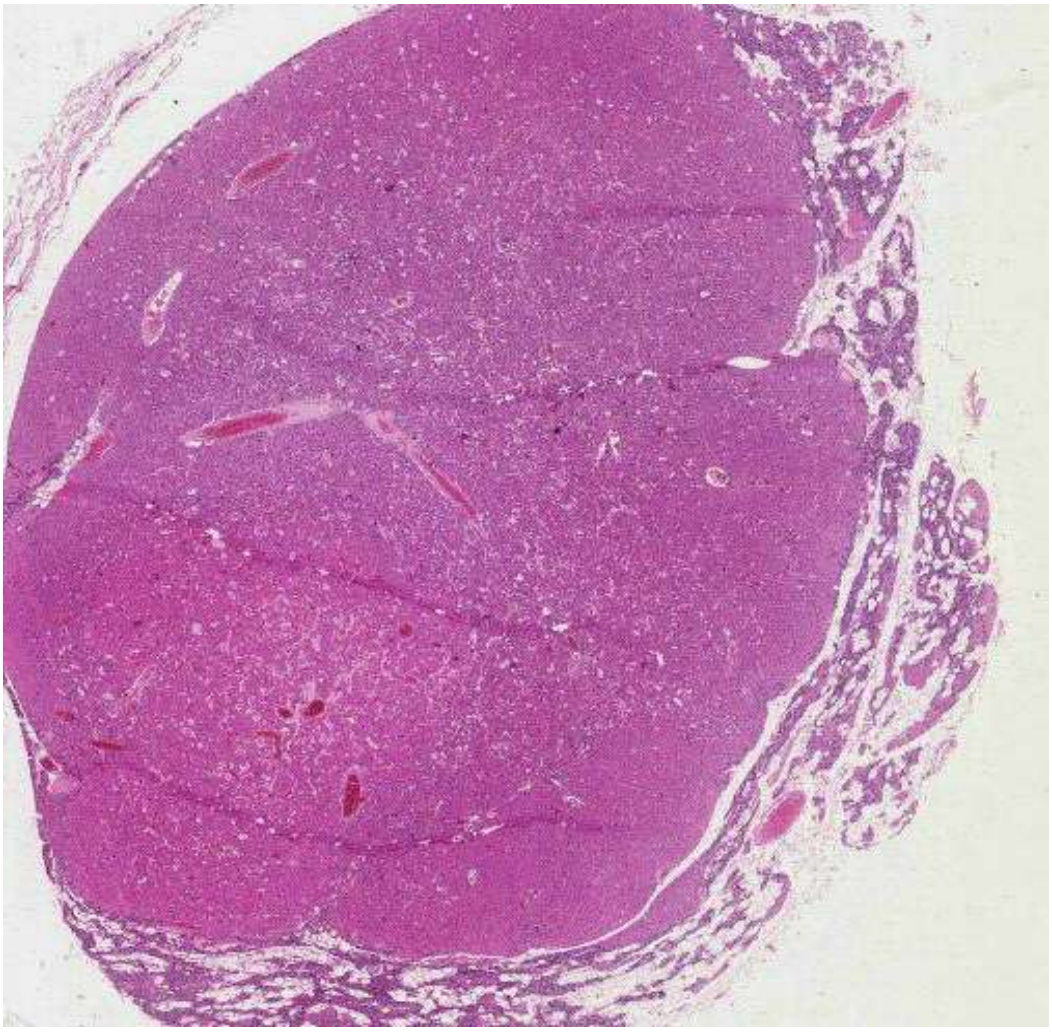
<u>Signs and symptoms</u>

- 32yo woman
- gradually worsening pain and swelling in left iliac fossa
- ultrasound shows large complex cystic lesion of left ovary

Features

- teratoma (three germ layer derived tissues)
    - **glial cells, bone, cartilage, bone marrow, respiratory epithelium, hair follicles, teeth, skin, thyroid gland**
    - **totipotent tumour mainly forming dermis/epthelial (ectoderm) structures but all three layers evident**
- benign
    - **not malignant as well differentiated and limited in growth (expansile not invasive)**
    - **unlikely to become malignant; testis more likely. also well circumscribed with good differentiation showing it is not aggressive.**

Slide 14 (Parathyroid adenoma)



Signs and symptoms

- metabolic bone disease
- decreased calcium in bone

    - **increased bone resorption via osteoclasts as a result of PTH increased levels**
- renal calculi
    - **increased serum calcium likely to precipitate as calculi**
- pancreatitis
- peptic ulcers
- neurological disturbances
- abnormal heart rhythms

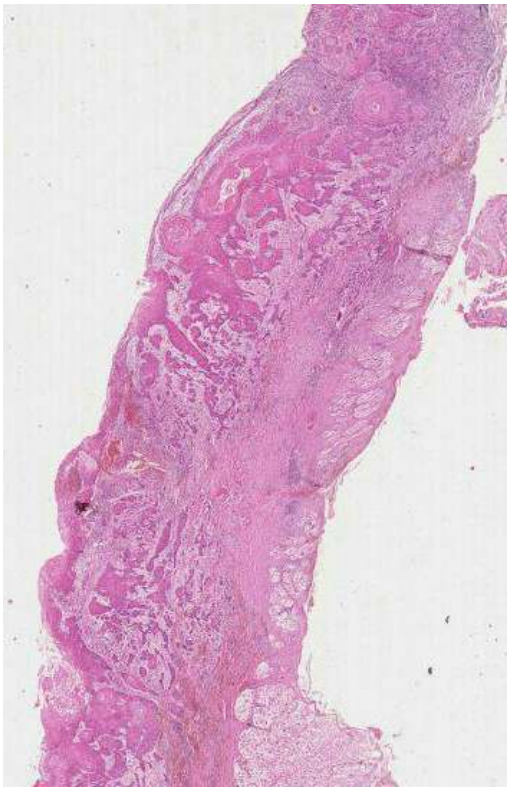
Features

- well circumscribed
- remains encapsulated
- monomorphic cells and highly differentiated, similar to chief cells
- N:C ratio is not too high

Investigations

- Tc-99m scan
- surgery
    - **cut out all four PT glands and compare to see if hyperparathyroidism or parathyroid adenoma**

Slide 15 (Squamous cell carcinoma, Tongue)



Signs and symptoms

- 65yo man
- smoked heavily, imbibed alcohol to excess for many years
    - **smoking, alcohol are known carcinogens**
- painless ulcer in tongue

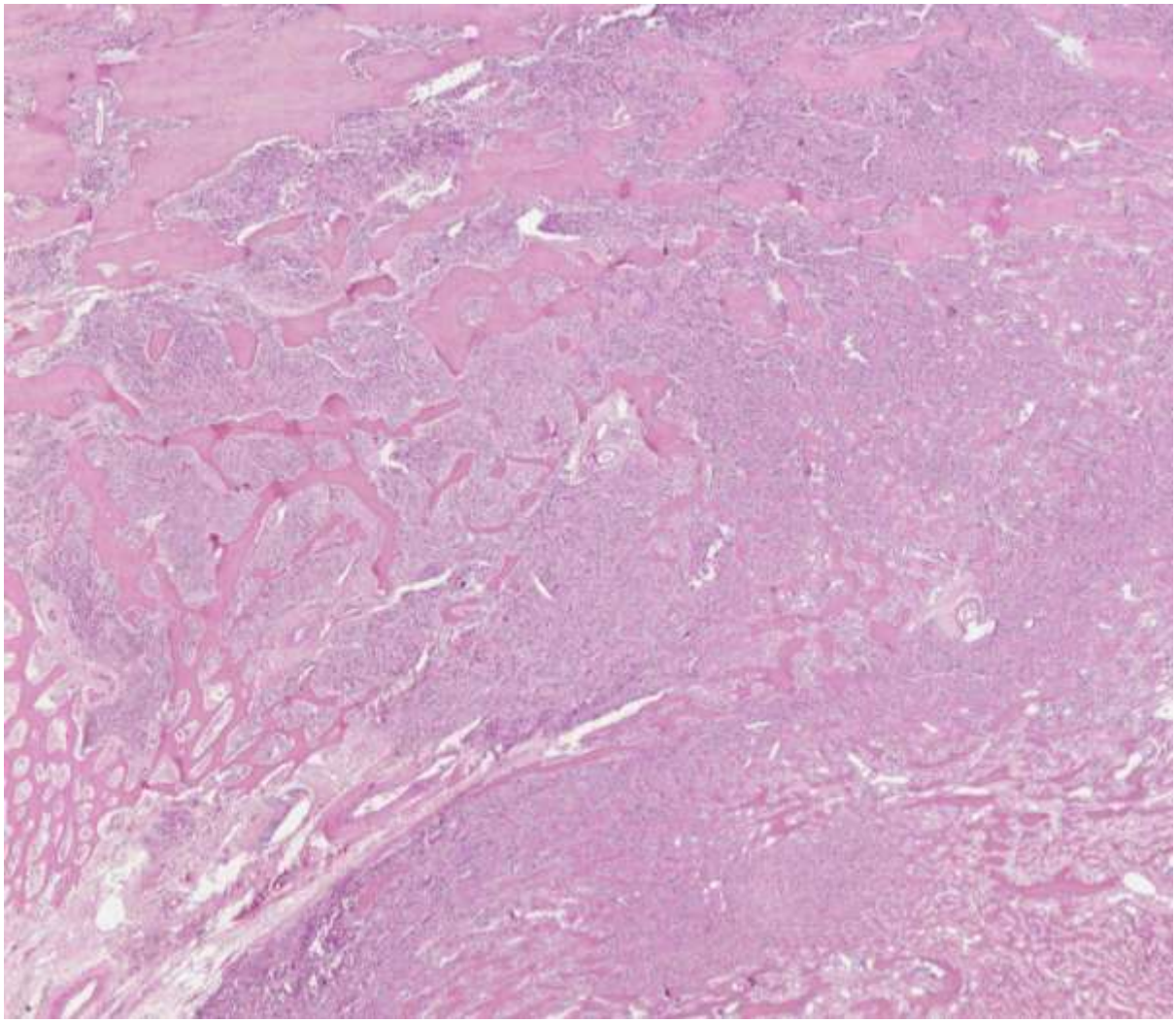
Features

- tumour islands
    - **central basopihilic cell → mitosis → matures forming keratin → lose nucleus → apoptose**
    - **swirly, pink and eosinophilic due to high keratin content**
    - **differentiation of cells is better in the middle section, worst in the top section**
- desmoplasia
    - **angiogenesis and fibroblastic activity producing collagen → firm mass**
- squamous cell carcinoma
    - **pattern of growth is forming bands/cords not ducts with lumen thus SCC not adenocarcinoma**
- high N:C ratio
    - **with many mitotic figures indicating mitoses**
- malignant
    - **cells invaded beyond muscularis mucosa**
- pleomorphism evident
    - **cells are unlikely to match their neighbours**

Complications

- local spread
    - **spread through oral cavity**
    - **aspiration of necrotic tissue into lung**
- metastatic
    - **lymphatics → submandibular lymph nodes**

Slide 16 (Osteosarcoma, Tibia)



Signs and symptoms

- 13yo boy
- 3wk history of intermittent ache in left lower leg
- tender swelling on anteromedial aspect of midshaft of left tibia

Features

- loss of bony spicules in trabecula
- **collagen, osteoid and cartilage formation**
- multipotent osteoprogenitor cell
- mesenchymal origin
- no distinct cell-cell adhesion
- non-descript cells form proliferative mass
- elongated

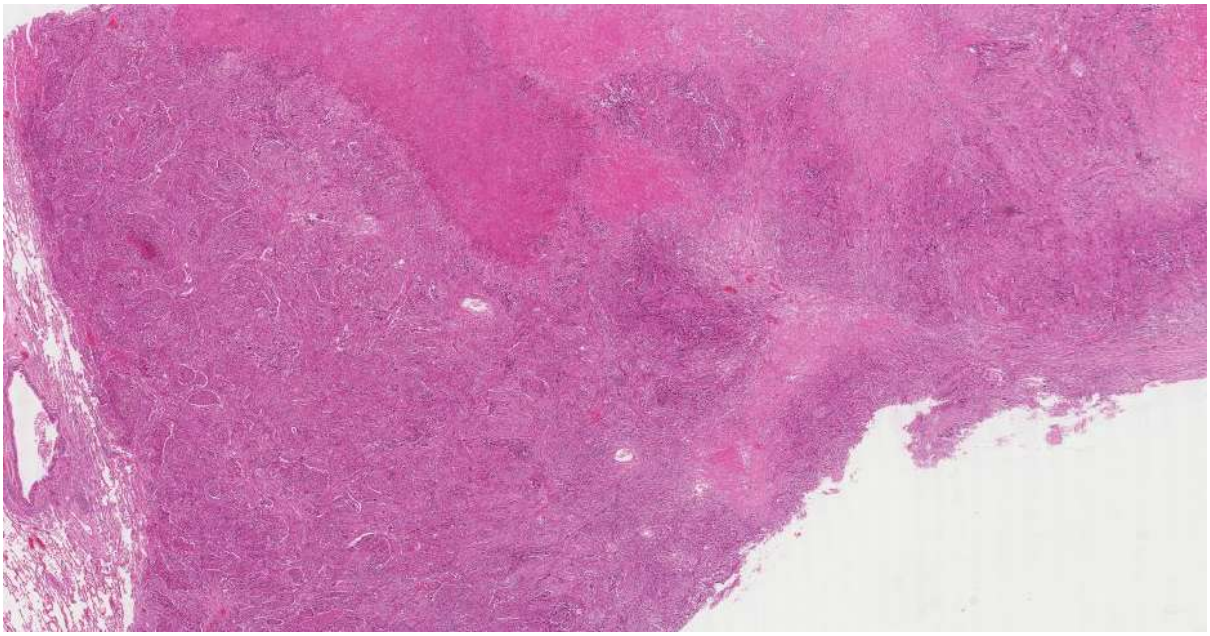
Complications

- local spread
    - **through bone**
- metastatic spread
    - **lymphatic spread**
    - **haematogenous spread (most common)**
        - **bone, brain, lung, liver, kidney, adrenal**

Investigations

- X-ray
    - **codman's triangle**
    - **halo around swollen bone**
    - **calcified tissue in mass (new bone)**
    - **reactive bone formation in periosteum**
- bone scan
- full blood count

Slide 17 (Leimyosarcoma, Lung metastasis)



Signs and symptoms

- 55yo post-meno woman
- intermittent bleeding per vagina
- hysterectomy to rid leiomyosarcoma
- 6m later, haemoptysis associated with weakness and weight loss
- 3m later, dies

Features

- elongated in loose bundles
    - **vaguely appear like smooth muscle cells with immunohistochemical staining revealing actin + desmin filaments → likely leimyosarcoma metastases to the lung**
- coagulative necrosis
- with nuclear fragments and cellular debris
    - **result of increased tissue pressure → central ischaemic regions → infarction → coagulative necrosis**
- malignancy due to
    - pleomorphism
    - abnormal mitotic figures
    - multinucleated tumour giant cells
        - **characteristically pleomorphic, clumped chromatin and located peripherally.**
    - high nucleus:cytoplasm ratio
    - disordered pattern of growth
    - quadripolar mitosis
        - **malignant neoplasms exhibit large no. of mitoses, often atypical and multipolar as chromosomal instability and polyploidy of proliferating neoplastic cells**

Adaptive tutorial

The cells within the lesion exhibit **cytological features of malignancy**

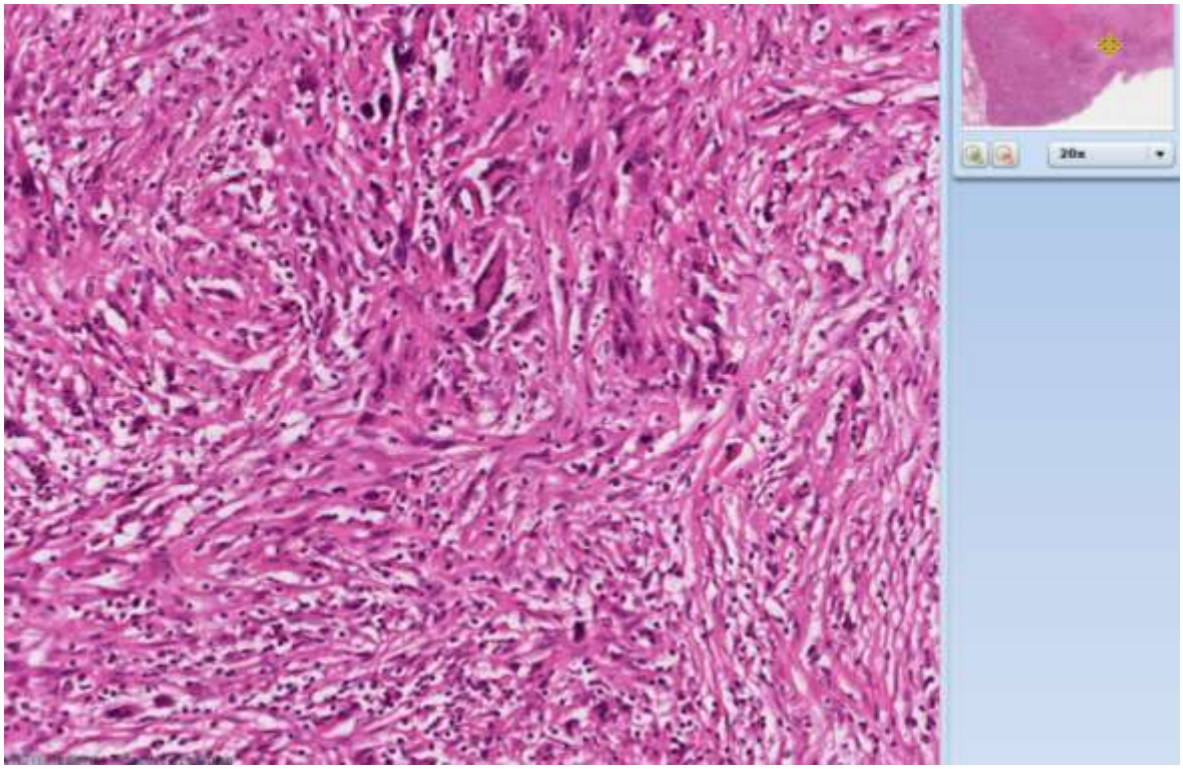
The proliferating cells of this **neoplastic growth exhibit marked pleomorphism** of nuclei with regard to size and shape, as well as **hyperchromasia**. There are also numerous **abnormal mitotic figures** and **multinucleated tumour giant cells** (**caused by nuclear division without cytoplasmic separation**). Many cells have a high **nucleus:cytoplasm** ratio.

The lesion contains a **central zone of coagulative necrosis**

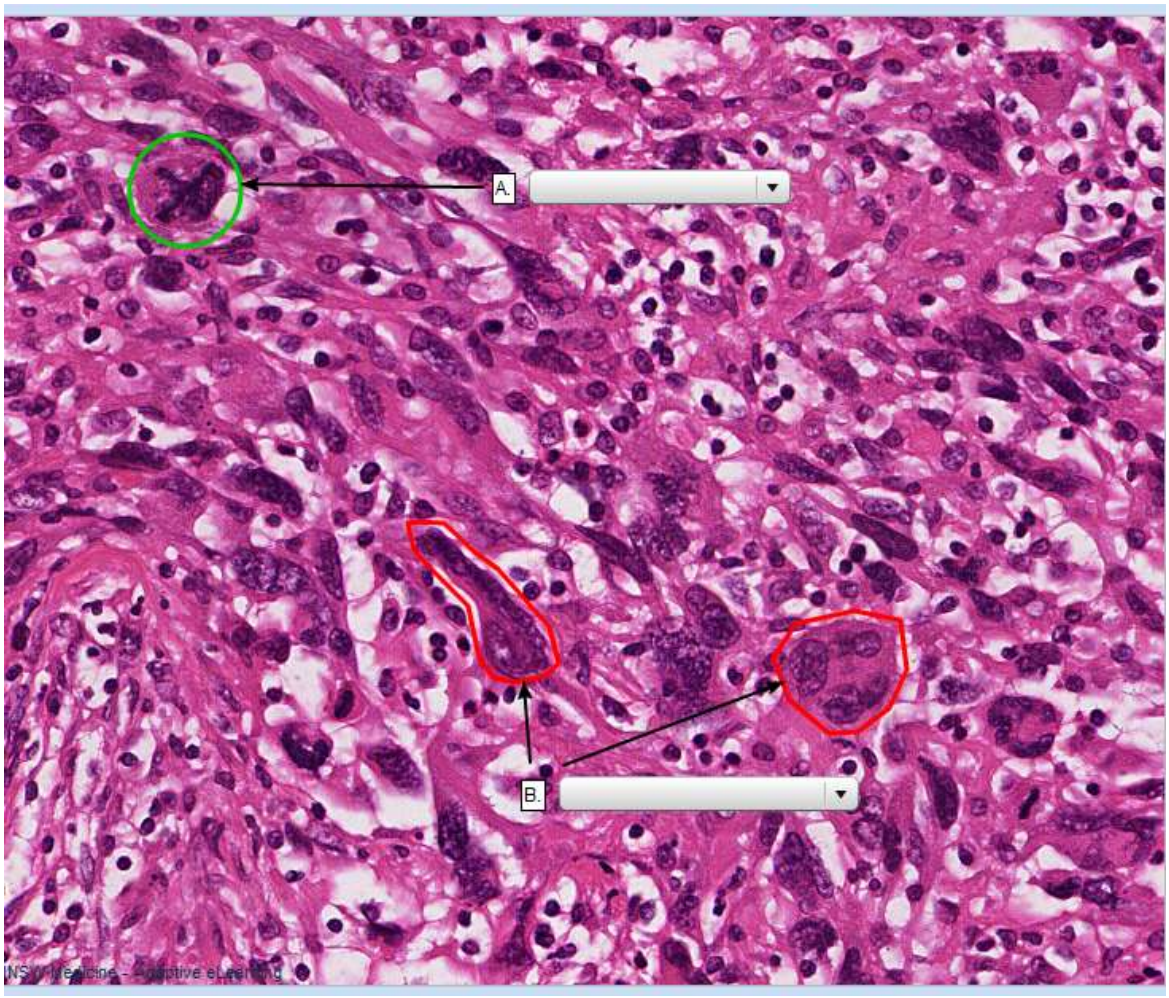
The necrotic areas within this lesion are characterised by **eosinophilic regions containing nuclear fragments and cell debris**. The **necrosis occurs as a result of increased tissue pressure** in the centre of the tumour mass, caused by **rapid cellular proliferation** (more likely in malignant than in benign lesions). As a consequence, **ischaemic regions in the centre of the tumour undergo infarction**, with **resultant coagulative necrosis**.

The **disordered pattern of growth**

A **disordered pattern of growth is characteristic of malignant neoplasms**.



Neoplasms exhibiting mesenchymal differentiation characteristically comprise elongated cells loosely arranged in bundles, rather than in coherent sheets or nests as is the case with neoplasms that exhibit epithelial differentiation. The **cells of this neoplasm vaguely resemble smooth muscle** cells, and **immunohistochemical staining revealed cytoplasmic actin and desmin filaments**. Therefore **this malignant tumour is classified as a leiomyosarcoma** (in this case, metastatic to the lung from a primary uterine leiomyosarcoma)



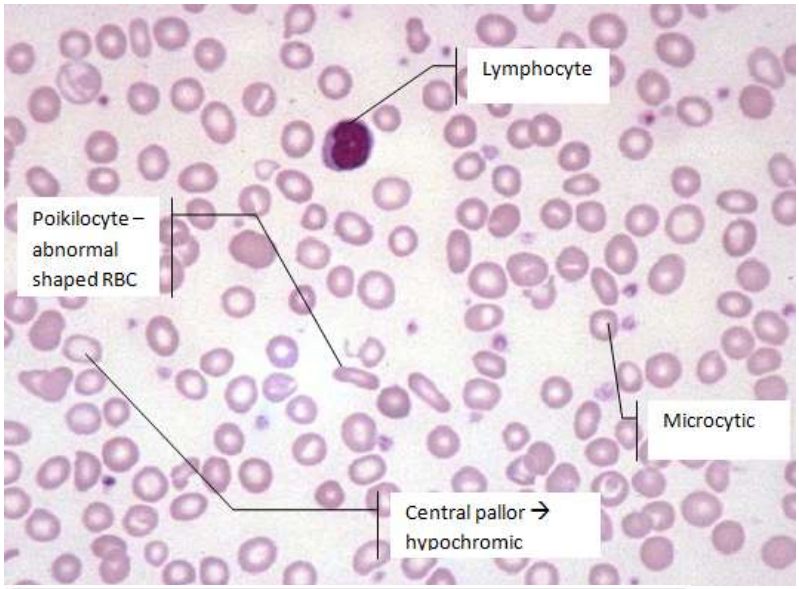
A quadriploar mitosis

Malignant neoplasms can exhibit large numbers of mitoses. These mitoses are often atypical and are frequently multipolar, reflecting chromosomal instability and polyploidy of the proliferating neoplastic cells.

Tumour giant cells

The nuclei of malignant cells are **characteristically pleomorphic**, showing a **variation in size and shape**. The **chromatin is clumped**, and **peripherally located**. **Multinucleated tumour giant cells**, of which these are examples, often feature in **poorly differentiated neoplasms**.

Case 18 (iron deficiency anaemia, microcytic w platelet increase)



Full Blood Count			
Haemoglobin (g/L)	**100**	**130-180**	*
RCC (x 10^{12}/L)	4.0	4.5-6.5	*
PCV	0.35	0.40-0.54	*
MCV (fL)	72	80-100	*
MCH (pg)	25	27-32	*
MCHC (g/L)	286	300-350	*
WCC (x10^9/L)	**6.5**	**4.0-11**	
Neutrophils	4.3	2.0-7.5	
Lymphocytes	1.8	1.5-4.0	
Monocytes	0.3	0.2-0.8	
Eosinophils	0.1	0.04-0.4	
Platelets (x10^9/L)	**452**	**150-400**	*
Blood Film ++ microcytes, ++ poikilocytes, no polychromasia			

Signs and symptoms

- 61yo m
- NSAIDs for hip OA
    - **common side effect = stomach ulcer → bleeding = iron loss**
- 6wk increasing weakness, fatigue, dyspnoea on exertion
    - **signs of anaemia**
- conjunctival pallor and sinus tachycardia
    - **signs of anaemia**
- PR haemoccult-positive faeces
    - **indicating occult bleeding**
- lowered Hb
    - **diagnostic of anaemia**
- lowered MCH, MCHC
    - **indicating hypochromasia**
- lowered MCV
    - **microcytic anaemia**

- lowered Packed Cell Volume/Haematocrit
- Raised platelets
    - **suggests iron deficiency over Thalassemia as platelets could be clotting a bleed**
- reduced RCC

Features

- Microcytic
    - **RBC are smaller than the lymphocyte next to them**
- Central pallor
    - **indicates hypochromasia**
- poikilocyte
    - **abnormally shaped RBC**

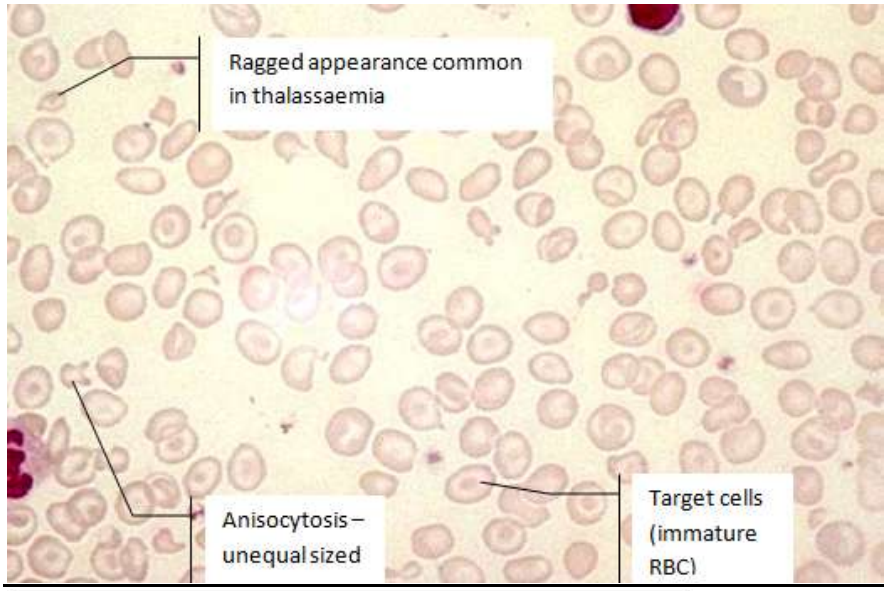
Diagnosis

Iron deficiency anaemia due to bleeding from a stomach ulcer caused by NSAID use.

Investigations

- Iron studies
    - **ferritin (low)**
    - **serum iron (low)**
    - **transferrin (high)**
    - **transferrin saturation (low)**
- colonoscopy/gastroscopy
    - **to exclude bowel cancer**
- Iron tablets
    - **replenish iron stores**
- replace NSAIDs
    - **with paracetamol**

Case 19 (Thalassemia, microcytic)



Full Blood Count			
Haemoglobin (g/L)	**92**	**115-165**	*
RCC (x 10^{12}/L)	3.69	3.8-5.8	*
PCV	0.31	0.37-0.47	*
MCV (fL)	68.5	80-100	*
MCH (pg)	25	27-32	*
MCHC (g/L)	297	300-350	*
WCC (x10^9/L)	**10.0**	**4.0-11**	
Neutrophils	7.5	2.0-7.5	
Lymphocytes	2.1	1.5-4.0	
Monocytes	0.2	0.2-0.8	
Eosinophils	0.2	0.04-0.4	
Platelets (x10^9/L)	**315**	**150-400**	
Blood Film ++ microcytes, ++ anisocytosis, + hypochromasia			

Signs and symptoms

- 28yo f chinese
  - **ethnic risk factor for thalassemia**
- antenatal clinic, 10wks during first pregnancy
  - **pregnancy often results in anaemia as fetus needs more iron via blood**
- mild conjunctival pallor, low Hb
  - **anaemia**
- low RCC
- low PCV
- low MCV
  - **microcytic anaemia = iron deficiency or thalassemia minor**
- low MCH, MCHC
  - **hypochromasia**

Features

- Hypochromasia

- **central pallor**
- anisocytosis
  - **unequally sized. abnormal globin chain (DNA problem can't make proper globin chain)**
- ragged appearance
  - **common in thalassemia**
- Microcytes
- tear drops

Diagnosis

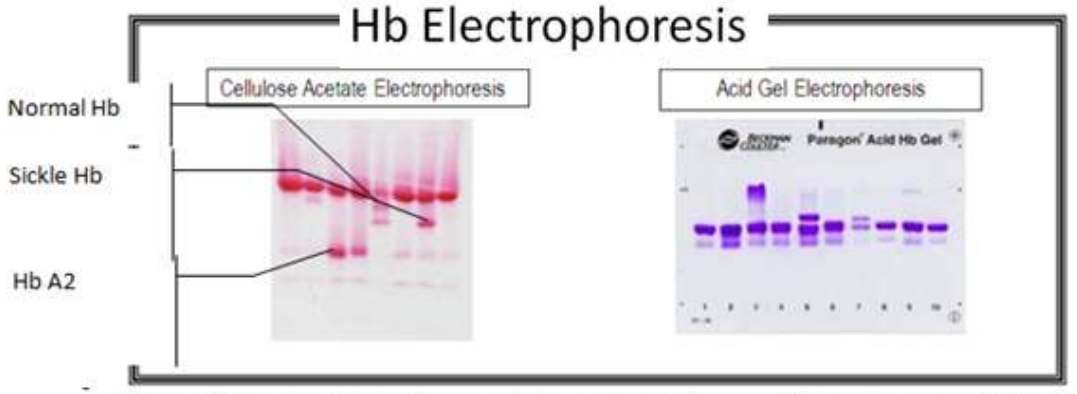
- Microcytic Anaemia (Low MCV)
- Iron Deficiency
  - **Iron deficiency = NORMALLY occurs later (late 2nd –early 3rd)**
- OR Thalassemia
  - **Ethnic = may carry thalassemia**
  - **NB: NOT having thalassemia Major (transfusions always needed)**
  - **Could have the minor version → exacerbated by pregnancy (may need blood transfusion → the bone marrow can NOT keep up with demand)**
  - **NB: in pregnancy, increase blood volume (BUT do NOT make as many RBC, so the "concentration" decreases → why anemia, have made a lot of RBC)**

Complications

- Thalassemia
  - **Implications on fetus**
  - **Compromised growth of baby**
  - **Baby could have full thalassemia (must check if the partner is also a carrier)**
  - **Check if alpha or beta**

Investigations

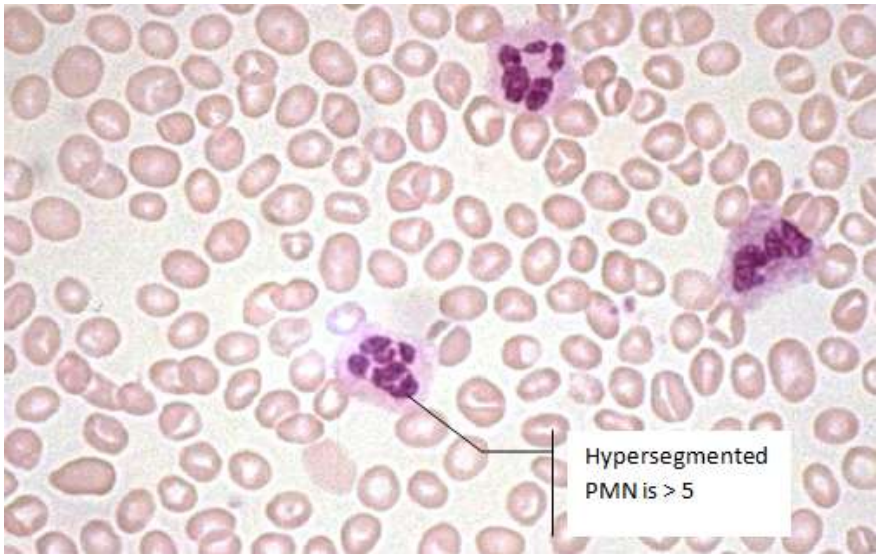
- Hb electrophoresis
  - **see which type of Hb floats out. HbA = thal, HbS = sickle cell**



- Hb Electrophoresis / HPLC → look at Hb to determine if normal globins or altered protein or if less of a certain Hb protein
- Iron studies

- **ferritin (low)**
- **serum iron (low)**
- **transferrin (high)**
- **transferrin saturation (low)**

Case 20 (B12/folate deficiency, macrocytic)



Full Blood Count			
Haemoglobin (g/L)	**87**	**130-180**	*
RCC (x 10^{12}/L)	2.6	4.5-6.5	*
PCV	0.29	0.40-0.54	*
MCV (fL)	110	80-100	*
MCH (pg)	33	27-32	*
MCHC (g/L)	300	300-350	
WCC (x10^9/L)	**6.2**	**4.0-11**	
Neutrophils	4.1	2.0-7.5	
Lymphocytes	1.8	1.5-4.0	
Monocytes	0.3	0.2-0.8	
Eosinophils	0.1	0.04-0.4	
Platelets (x10^9/L)	**154**	**150-400**	
Blood Film	++ oval macrocytes, ++ target cells, + hypersegmented neutrophils		

Signs and symptoms

- 48yo alco dependent homeless male
- weakness, confusion
- poor nutrition, atrophic glossitis
- pallor of conjunctivae and palm creases
- sensory peripheral neuropathy
- low Hb
    - **anaemia**
- low RCC
- low PCV
- high MCV

    - **macrocytic anaemia = B12/folate deficiency**
    - **B12/folate required for DNA synthesis → reduced leading to oval macrocytes and hypersegemented neutrophils**
    - **>5 nuclei PMN**
    - **possibly pancytopenia as no cells can be made without proper DNA**
- raised MCH
    - **hyperchromasia**

Features

- hypersegmented PMN
    - **>5 nuclei due to immature production of DNA**
- oval shaped macrocytes
- target cells
    - **signifying a decrease in Hb**

Diagnosis

- Macrocytic megaloblastic anaemia
    - **with oval macrocytes**
- Chronic liver disease
    - **round not oval macrocytes**
- myelodysplastic anaemia
- macrocytic anaemia in pregnancy due to reticulocyte production
- hypothyroidism
- B12/folate (provisional)

Causes

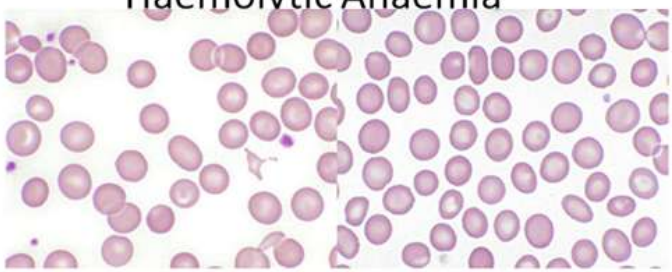
- Pernicious anaemia
- antibody to intrinsic factor so failure of B12 absorption, requiring injections
- gastrectomy
- celiac disease
- vegetarian/vegans
- alcohol interferes with folate absorption
- lack of green leafy vegetables

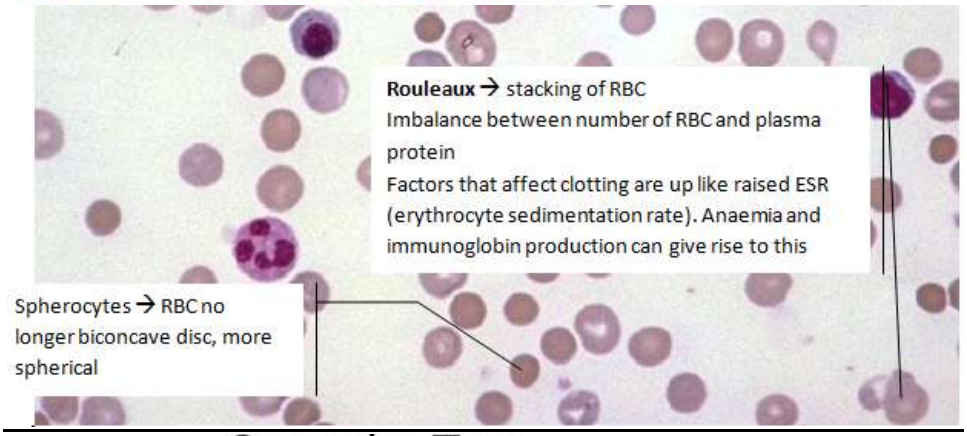
Investigations

- serum B12/folate
- cell folate, Red Cell Folate
    - **RCF good indicator of long term folate status**

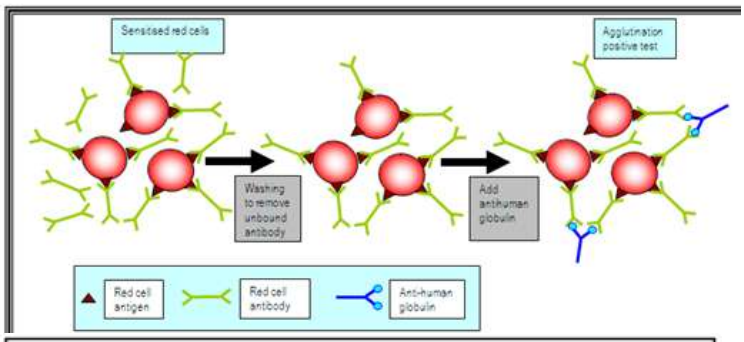
Case 21 (Haemolytic anaemia, normocytic)

Haemolytic Anaemia





Coombs Test



Full Blood Count			
Haemoglobin (g/L)	**90**	**115-165**	*
RCC (x 10^{12}/L)	2.8	3.8-5.8	*
PCV	0.26	0.37-0.47	*
MCV (fL)	95	80-100	
MCH (pg)	32	27-32	
MCHC (g/L)	346	300-350	
WCC (x10^9/L)	**4.7**	**4.0-11**	
Neutrophils	2.8	2.0-7.5	
Lymphocytes	1.5	1.5-4.0	
Monocytes	0.3	0.2-0.8	
Eosinophils	0.1	0.04-0.4	
Platelets (x10^9/L)	**172**	**150-400**	
Reticulocytes (x 10^9/L)	**420**	**10-90**	*
Blood Film +++ polychromasia, ++ spherocytes, ++ rouleaux			

Signs and symptoms

- 35yo f
- 1wk headaches, weakness, palpitations and light headedness
- pale and tachycardic
    - **symptoms of anaemia**
- spleen palpable just below left costal margin
    - **activation of reticuloendothelial system to a high level causing splenomegaly**
- low Hb
    - **anaemia**
- low RCC
    - **low RBC count**
- low PCV
    - **low haematocrit**
- high Reticulocytes
    - **bone marrow working hard to restore RBC levels, yet low RCC, indicating high turnover rate**

Features

- spherocytes
    - **no longer biconcave disc, more spherical**
- Rouleaux
    - **stacking of RBC**

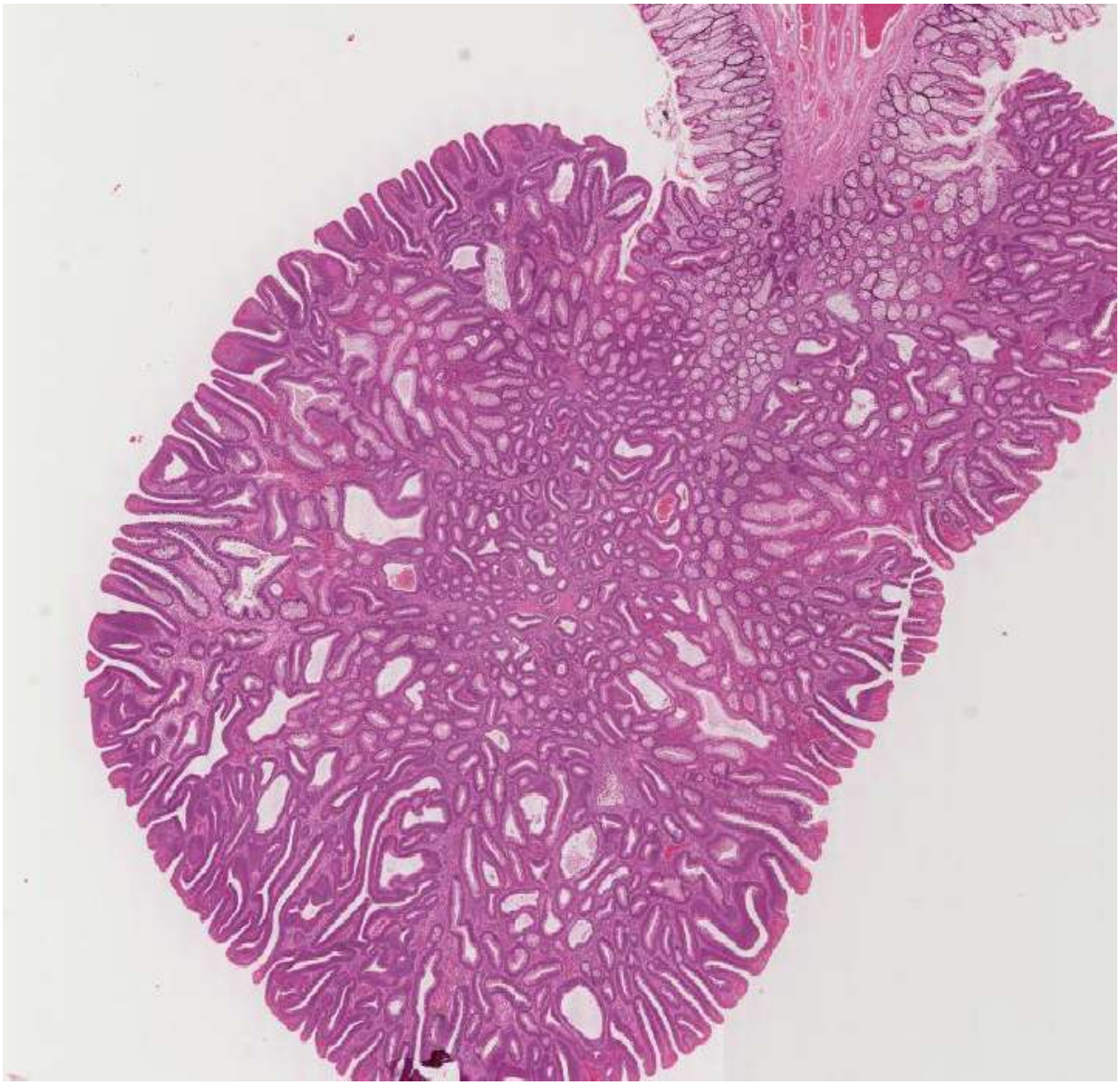
Diagnosis

- Normocytic anaemia (provisional)
    - **immune or non-immune haemolysis**
- (Differential) haemorrhage
    - **massive blood loss**
    - **anaemia of chronic disease**
    - **bone marrow failure**

Investigations

- Haemolysis testing
    - **bilirubin levels = unconjugated bilirubin will be high with haemolysis**
    - **LDH = muscle ischaemia or kidney damage will lead to increased LDH levels**
- haptoglobins
    - **these stick to broken RBC and remove from circulation to prevent damage to kidneys**
- Coombs test for type of haemolysis

Slide 22 (Tubular adenoma, Colon)



Signs and symptoms

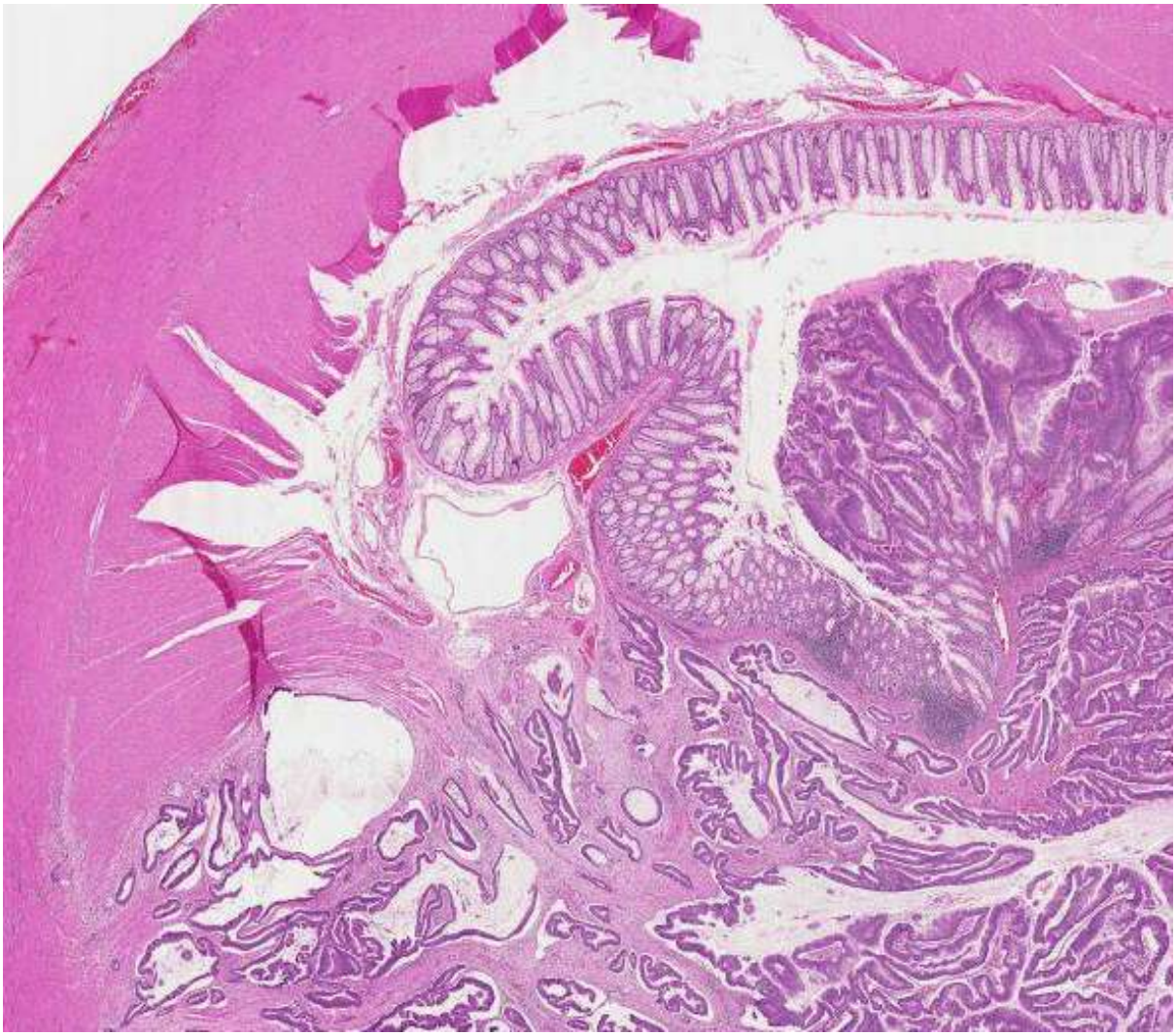
- possible occult bleeding
    - **requires FOBT**
- bowel twisting (location dependent)
- mucus diarrhoea
    - **villus adenoma increasing secretions of mucin**

Features

- Tubular adenoma
    - **smooth surface, with stalk**
    - **pedunculated**
- benign
    - **not broken the muscularis mucosa layer**

- **tubular unlikely to become malignant, villous more likely**
- **N:C ratio is slightly increased**
- **mitotic figures present**
- **loss of differentiation**
- **architectural atypia**
- **abnormal epithelium yet normal lamina propria**
- **longer cells with overlapping nuclei**
- **basal orientated nuclei with less mucin production**

Slide 23 (Villous adenocarcinoma, Colon)



Signs and symptoms

- 68yo f
- insidious onset of weight loss, lethargy and dyspnoea
- FOBT abnormal
    - **indicating occult bleeding and thus likely to have a right sided lesion.**

- lowered Hb, pale skin and conjunctivae
    - **anaemic**
- lowered RCC
- lowered MCV
    - **microcytic anaemia → either iron deficiency or thalassemia. likely to be iron-deficiency anaemia due to occult bleeding**
- lowered MCH, MCHC
    - **hypochromia due to lower concentration of Hb so paler RBC**
- increased platelet

Features

- residual adenoma
    - **lacks desmoplasia**
    - **invaded**
    - **more organised**
- abnormal mass in lower screen
    - **invades into the muscularis mucosa**
- bottom middle screen inner circular muscle invaded
    - **desmoplasia - granulation tissue**

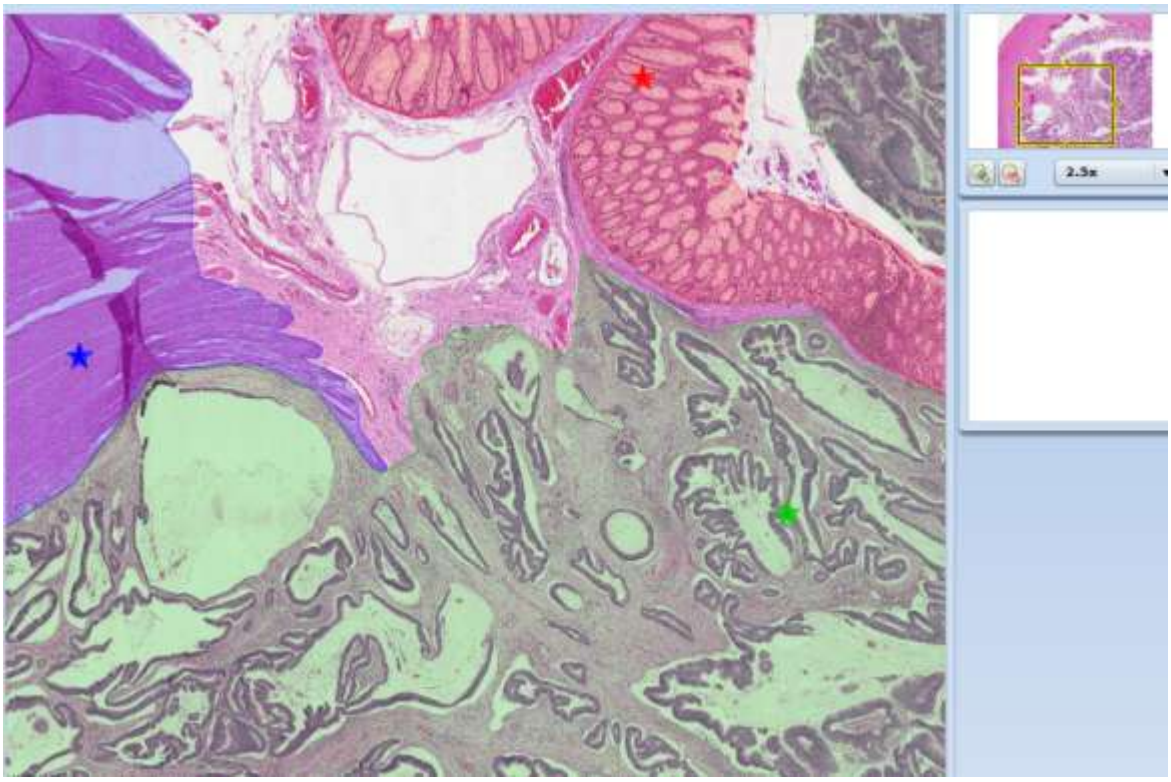
Diagnosis

Iron-deficiency anaemia due to occult bleeding caused by a likely right sided colon cancer in the ascending colon/cecum.

Investigations

- Iron storage
    - **ferritin = decreased**
    - **transferrin = increased**
    - **transferrin saturation = decreased from 30% to 10% likely**
    - **total iron binding capacity = increased**
- colonoscopy → observe growths and abnormalities

Adaptive tutorial



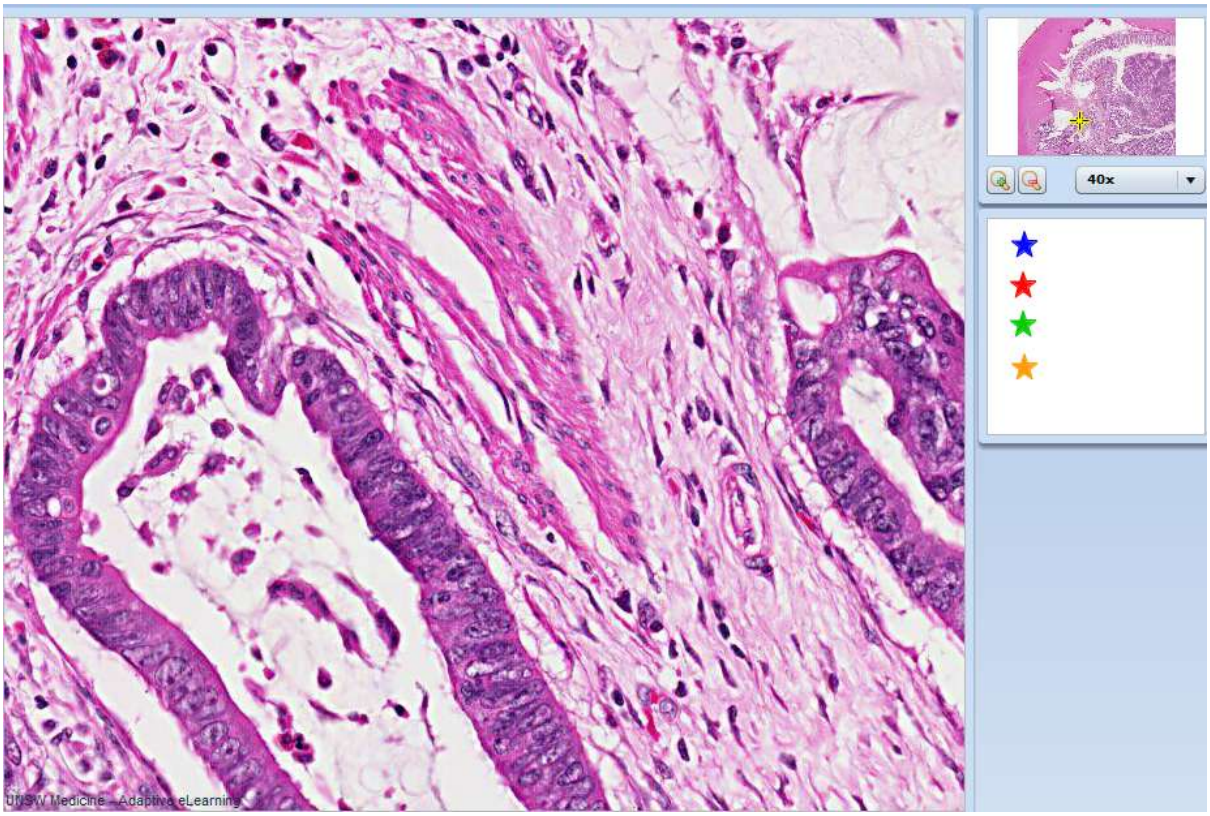
The **muscularis propria (externa)** is highlighted in **blue**.

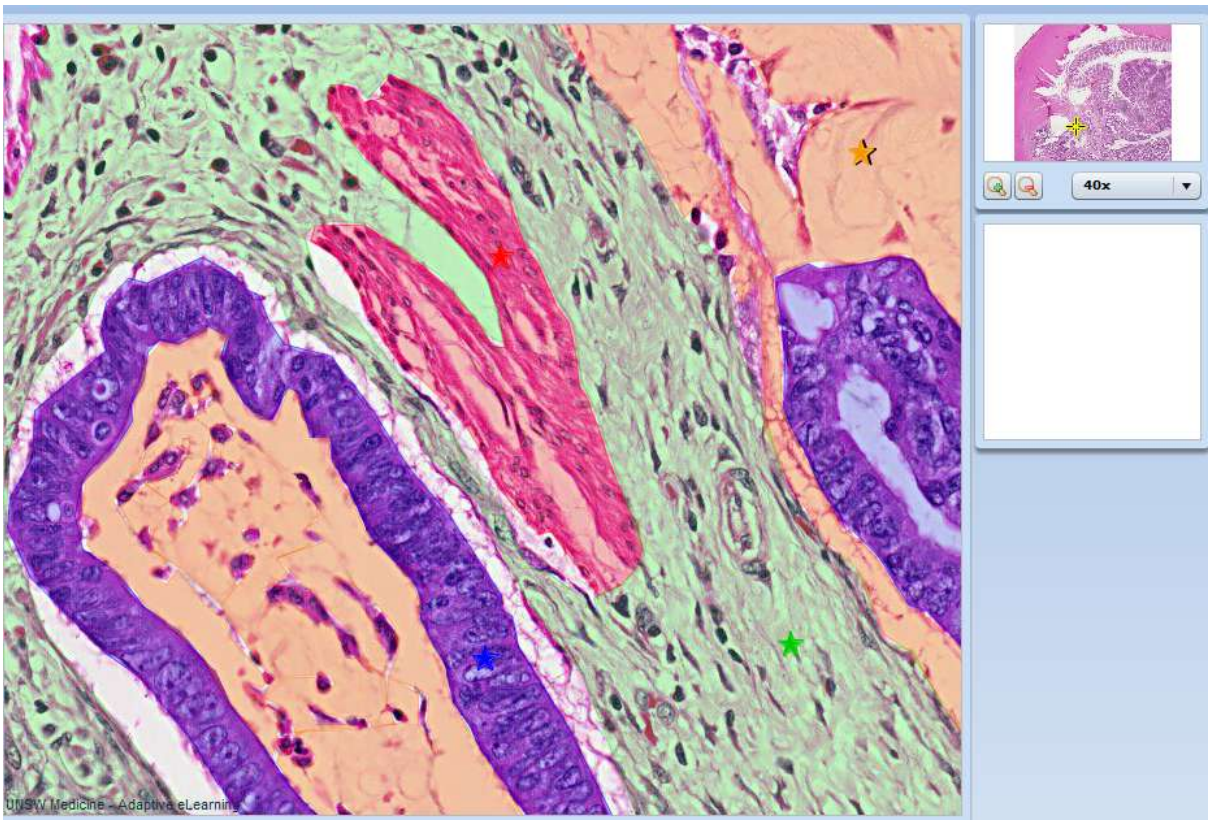
The non-**neoplastic colonic mucosa** is highlighted in **red**. This layer **incorporates epithelium, lamina propria, and muscularis mucosae**.

The region of **malignant neoplasia** is highlighted in **green**. A malignant neoplasm arising from colonic epithelium has **penetrated through the submucosa, to invade the muscularis propria (externa).**

The **neoplastic cells in this lesion are polygonal in shape and form coherent structures**, thereby **displaying epithelial differentiation**. The **tubular structures formed by the neoplastic** cells, as well as their **secretory function (indicated by lakes of mucin) indicate glandular differentiation**. This lesion **must be malignant**, **given its invasion into the colonic wall**. Therefore the **correct nomenclature is an adenocarcinoma of the colon**.

The **depth of invasion is important for staging**, which is the **most important prognostic indicator**. In the **absence of metastases, this example would be at least Stage I - invasion into muscularis propria** (T2), but not beyond. Stage II involves invasion beyond the outermost edge of the muscularis propria (T3 or T4), but without involvement of lymph nodes. Stage III involves metastasis to local lymph nodes. Stage IV involves distant metastases, e.g. to the liver. You should revise the AJCC staging system.





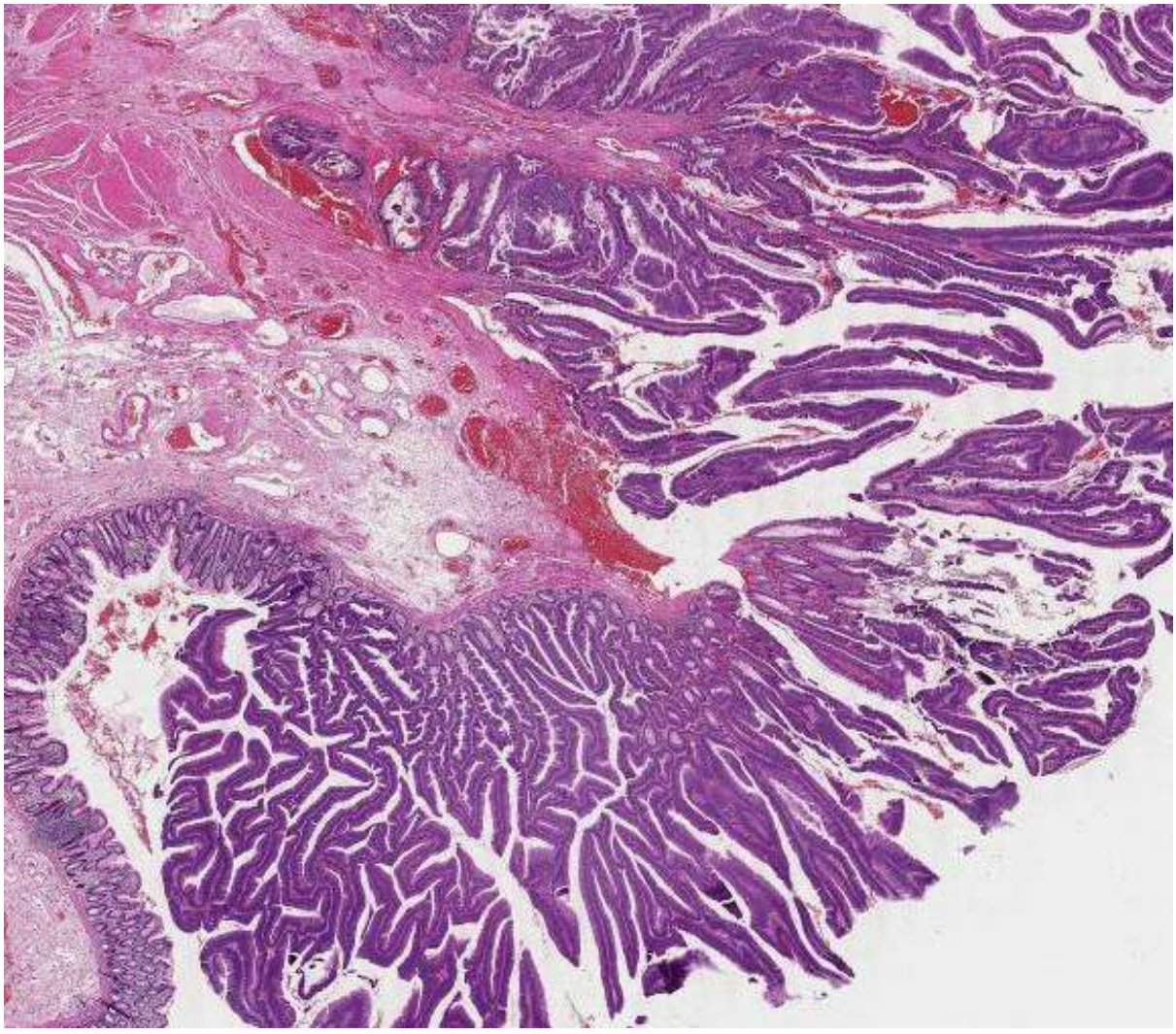
The invasive **neoplastic cells exhibiting epithelial differentiation** are highlighted in **blue**. This **consists of cells exhibiting differentiation to form glandular columnar epithelium** with a high **nucleus:cytoplasm ratio. The nuclei are palisaded and are irregular in shape**.

The **region of smooth muscle is highlighted** in red. These are spindle-shaped cells with elongated eosinophilic cytoplasm, and small regular nuclei. They represent **residual fragments of the muscularis propria (**externa), into which the tumour has invaded.

The **reactive stroma is highlighted** in green. This is the **non-neoplastic connective tissue which provides the structural framework and blood supply (via angiogenesis) essential for the growth and evolution of the tumour.**

The region of **extracellular mucin** is highlighted in orange. The **mucin is produced by the tumour cells, and can dissect through the adjacent tissue planes, forming large pools.**

Slide 24 (Villous adenoma, Colon)



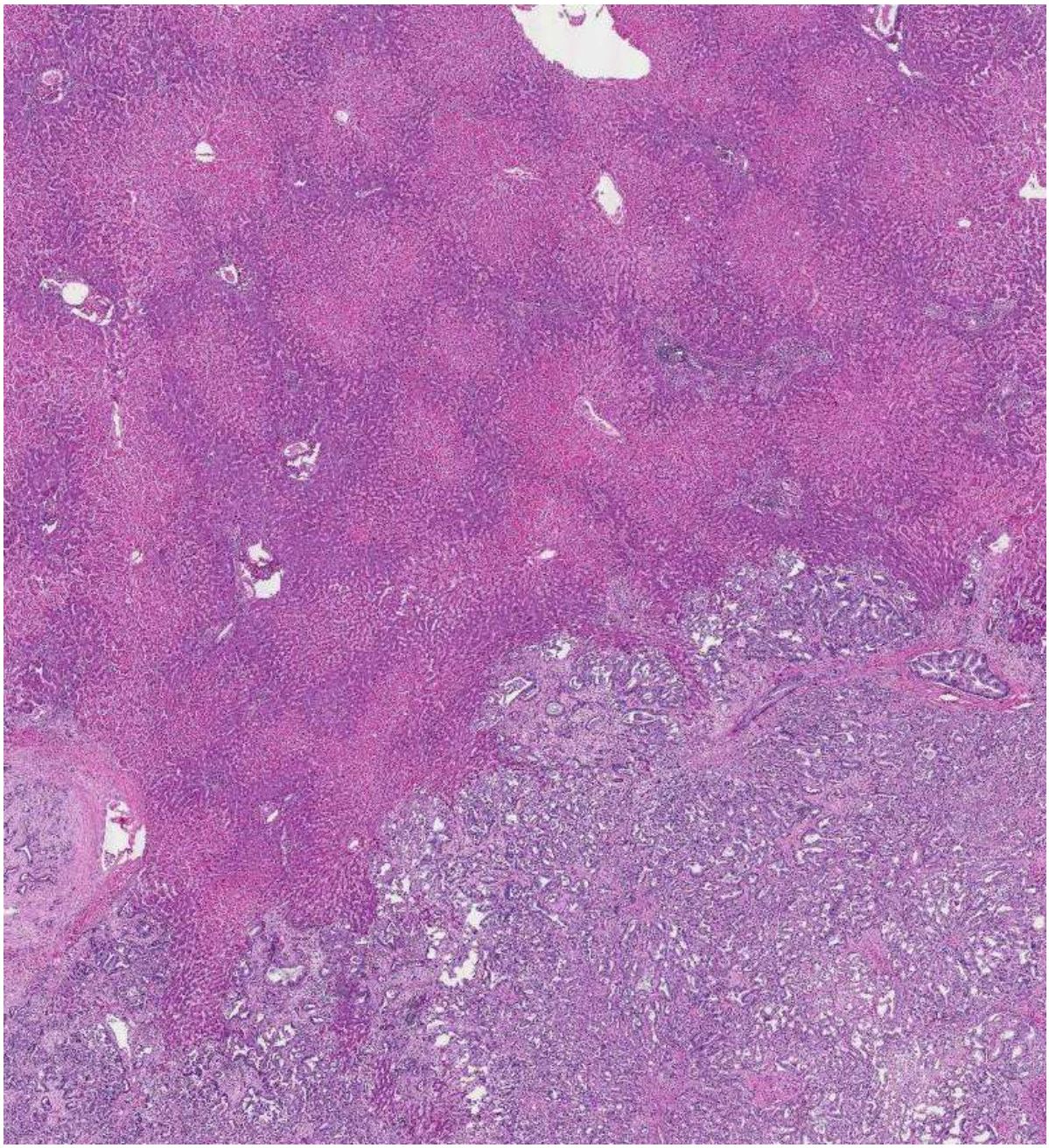
<u>Features</u>

- Sessile, polypoid lesion
    - **muscularis mucosa intact**
- thus it is benign
    - **angiogenesis in the submucosa**
- healthy tissue surrounding

Benign v Malignant

- has not invaded muscularis mucosa
    - **artefact of tissue breaking off gives the appearance of malignancy but there is no invsaion**

Slide 25 (Adenocarcinoma metastasised to the Liver)



Signs and symptoms

- 12m later
- increasing weakness
- swelling and discomfort in RU quadrant of abdomen

- shortness of breath
- slight cough → gradually worsened
- coughed a small amount of blood stained sputum

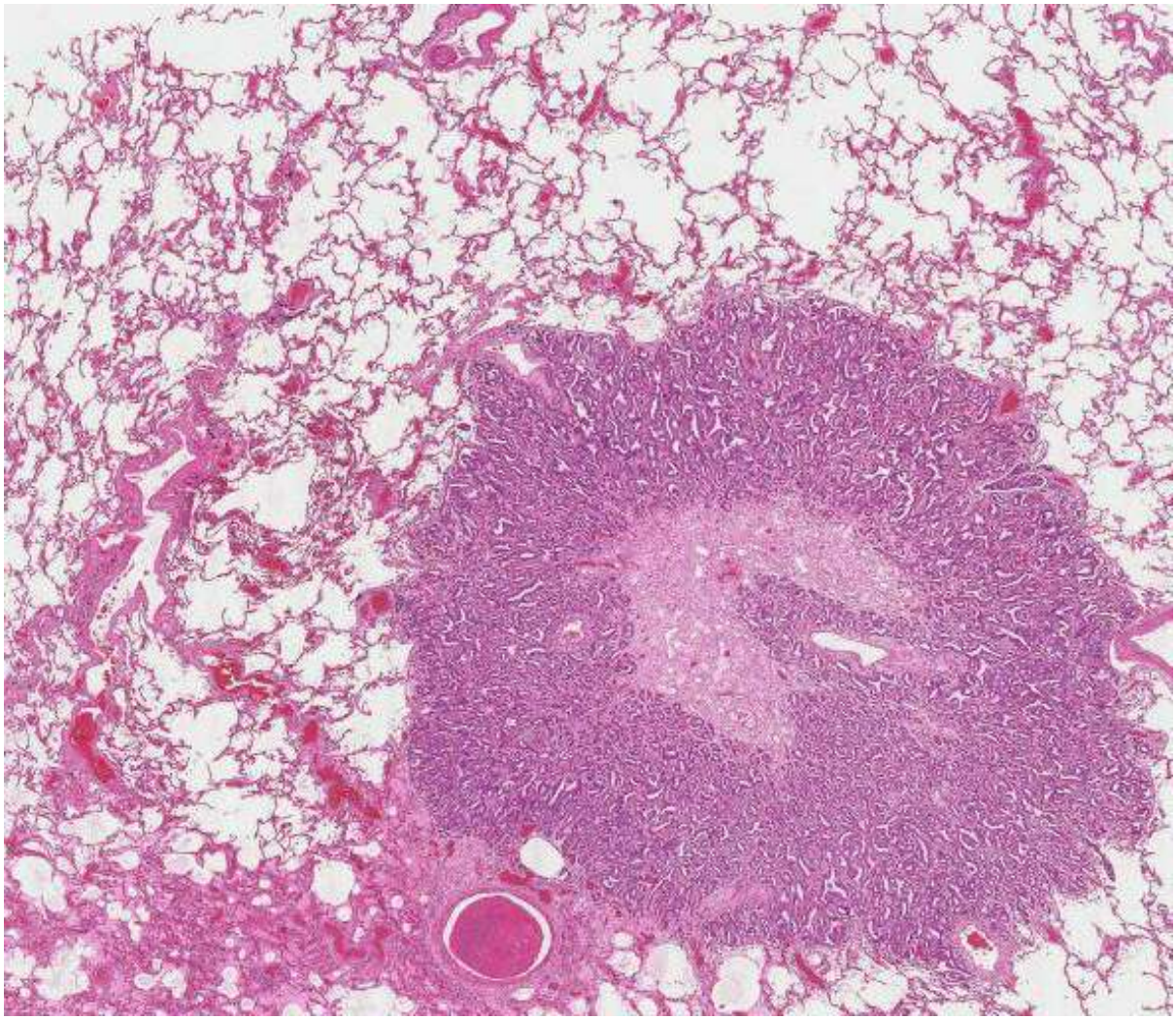
Features

- normal tissue at top
    - **invading along sinusoids of liver**
- circumscribed metastatic mass
    - **forming glandular structures with mucin production**
    - **high N:C ratio**
    - **pleomorphism**
    - **irregular chromatin**
    - **mitotic figures**

Investigations

- Liver function tests
    - **expect to reveal high rates of AST and ALT and some GGT and ALP elevation too**
    - **protein should be in the normal range**
- expect to see
    - **lung metastases**
    - **liver metastases**
    - **abdominal metastases**
- chest x-ray
    - **for lung metastases**

Slide 26 (Adenocarcinoma metastasised to the Lung)



Features

- normal alveoli surrounding
- glandular structure metastatic deposit
    - **high N:C ratio**
    - **pleomorphism**
    - **irregular chromatin**
    - **nuclear polarity decreased**

Investigations

- expect to see
    - **lung metastases**
    - **liver metastases**
    - **abdominal metastases**
- chest x-ray
    - **for lung metastases**