Primary Cast Episode 14 - Gastrointestinal Pathology

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Hepatobiliary Pathology

1. **Alcoholic Liver Disease**

Describe the pathological features of the liver in alcoholic liver disease

There are four stages

- Hepatic steatosis - fatty change, perivenular fibrosis
- Hepatitis - liver cell necrosis, inflammation, mallory bodies, fatty change and fibrosis
- Cirrhosis - extensive fibrosis, hyperplastic nodules, derangement of liver perfusion with portal hypertension
- Hepatocellular carcinoma

Which of these features are reversible?

Steatosis and hepatitis.

What changes occur at a cellular level in alcoholic hepatitis?

- Hepatocyte swelling and necrosis, accumulation of water, fat and protein
- Mallory bodies - eosinophilic cytoplasmic inclusions in degenerting hepatocytes
- Neutrophilic reaction - neutrophils accumulate around degenerating hepatocytes
- Fibrosis - via activation of sinusoidal stellate cells and portal tract fibroblasts

Aside from alcohol, what are other causes of cirrhosis?

- Viral hepatitis
- Biliary diseases
- Primary haemochromatosis
- Wilson disease
- Alpha-1 antitrypsin disease
- Idiopathic
- Drug induced
- Cardiac disease

What are the possible sequelae of cirrhosis?

- Portal hypertension
- GIT bleeding from varices
- Liver failure → coagulopathy
- Hepatocellular cancer
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Encephalopathy
- Infection

2. **Portal HTN**

What are the causes of portal hypertension?

- Prehepatic - portal vein thrombosis or narrowing
- Hepatic (the most important) - cirrhosis, massive fatty change, schistosomiasis, granulomatous disease i.e. sarcoid or TB
- Post hepatic - constrictive pericarditis, hepatic vein occlusion

What are the clinical consequences of portal HTN?

- Ascites - with potential for infection
- Porto-systemic shunts - varices, haemorrhoids, spider naevi
- Congestive splenomegaly - thrombocytopaenia/pancytopaenia
- Hepatic encephalopathy

What mechanisms are involved in the formation of ascites?

- Sinusoidal hypertension - from starling forces - there is an increase in pressure and a decrease in albumin.
- Increased formation of hepatic lymph which exceeds the capacity for the thoracic duct ad percolates into the peritoneum
- Splanchnic vasodilation with a decrease in BP
- Renal retention of sodium and water due to secondary hyperaldosteronism

3. **Hepatitis A**

What is the causative agent of hepatitis A?

Hepatitis A virus - small non enveloped single stranded RNA virus

How is it transmitted and what is the clinical course?

- Faecal oral route - shellfish from sewage contaminated seawater
- Incubation period 2-6 weeks
- In childhood, mild symptoms or asymptomatic
- Adults: febrile illness with nausea, vomiting, lethargy, dehydration
- Rarely develop serious hepatitis, but acute disease more severe if superimposed on another chronic hepatitis i,e chronic hep B

How do the clinical outcomes differ between hepatitis A and B?

- A is a self limiting illness with no carrier state and no chronic state
- Does not cause hepatocellular Ca
- Rarely leads to fulminant disease
- Low fatality rate of 0.1%

How is hepatitis A diagnosed serologically?

Acutely, anti-HAV IgM, followed by the appearance of anti-HAV IgG which rises over months and lasts for years

There is also an acute rise in faecal HAV within 1-2 weeks of infection, lasting 2-12 weeks

How does the community prevalence of hepatitis A differ between resource rich and resource poor countries?
In developed nations - 50% at age 50 years have serological evidence of HAV infection
In developing or low resource countries almost 100% of people have serological evidence of infection by their late teens

4. **Hepatitis B**
What are the serological markers for hepatitis B and what do they mean?
Note: You will probably be shown someones serological markers and asked to interpret them
    - HB surface Antigen positive - indicates current infection
    - Total Anti-HB core antibody - indicates exposure to previous HBV
    - IgM anti HB core - indicates acute or recent exposure
    - Anti- HB surface antigen - reflects immunity to HBV (negative in chronic hepatitis)

How may hepatitis B lead to upper GI bleeding?
Cirrhosis and portal HTN contribute to the development of oesophageal varices
Coagulopathy due to loss of liver synthetic function also contributes

In general, how may a patient acquire hepatitis B?
- Congenital or vertical from a mother to baby during childbirth- the most common form of transmission worldwide
- Contaminated blood products - IVDU, transfusions (from many years ago), needlestick injury
- Anything involving bodily fluids i.e. sexual contact, splash of fluid into the eyes
- One third of cases are unknown transmission

What are the possible outcomes of hepatitis B exposure?
- Asymptomatic or subclinical disease with complete recovery
- Acute hepatitis - where the majority of people recover fully but some can progress to fulminant hepatitis
- Healthy carrier state
- Non-progressive chronic hepatitis
- Progressive chronic hepatitis - where 10% progress to hepatocellular carcinoma

5. **Hepatitis C**
What type of virus causes hepatitis C?
RNA virus from the flaviviridae family

What are the risk factors for acquiring hepatitis C?
- IVDU
- Multiple sexual partners
- Recent surgery
- Needlestick injury

- Multiple contacts with a HCV infected person
- Being a healthcare worker
- Perinatal transmission
- Dialysis
- Many cases also unknown source

What is the natural expected course of hepatitis C?

- Incubation period is variable - 2 to 26 weeks
- 85% are asymptomatic
- HCV RNA is detectable in 1-3 weeks
- Anti HCV antibody detectable in 50-70% of people while symptomatic
- Usually a mild disease in the acute phase
- 15% of people will recover
- Persistent infection is common - occurs in 85% of people
- Cirrhosis occurs in 20-30% within 5-20 years
- Fulminant hepatitis is rare

6. **Hepatitis D**

What is hepatitis D and why is it different from the others?

RNA virus
Must always be in conjunction with Hep B
Replication defective, meaning it can only cause infection when it is encapsulated by hep B surface antigen

Describe how hepatitis D virus infects the human body

Option 1: An acute co-infection is indistinguishable from classic acute Hep B infection
Occurs following exposure to serum containing both HBV and HDV. The HBV must establish first in order to support the development of complete hep D viridons

Option 2: Superinfection. Someone with chronic HBV is exposed to HDV. The disease manifests around 30-40 days later

Option 3: Latent infection which occurs in liver transplant patients

How does a superinfection with Hepatitis D manifest?

- Severe acute hepatitis in a previously unrecognised HBV carrier
- Exacerbation of pre-existing chronic Hep B
- 80-90% of cases involve chronic progressive disease and cirrhosis

7. **Jaundice**

Please outline the normal metabolism and elimination of bilirubin

- Bilirubin is produced from haeme, which is a byproduct of erythrocyte breakdown
- Binds to serum albumin and is delivered to the liver
- Taken up by hepatocytes
- Undergoes glucuronidation - then bilirubin glucuronides are excreted in bile
- Gut deconjugation converts these glucuronides into colourless urobilinogens
- These and their associated pigment residues are excreted in the faeces
- Around 20% of urobilinogen is reabsorbed and returned to the liver via enterohepatic circulation

What are the common causes of jaundice?

Unconjugated

- Increased production of bilirubin i.e. haemolysis, resorption of haemorrhage, thalassaemia
- Decreased hepatic uptake i.e. drugs, gilbert syndrome
- Impaired conjugation i.e. newborn physiological jaundice, hepatitis

Conjugated

- Impaired bile flow i.e. cholangiopathy, biliary stricture, malignancy, choledocholithiasis
- Deficiency of membrane transporters i.e. various genetic syndromes

Apart from jaundice, what are some other clinical features of liver failure?

- Icterus
- Pruritus
- Fetor hepaticus
- Palmar erythema
- Spider naevi
- Hypogonadism
- Coagulopathy
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Portal HTN

8. **Cholecystitis**

Describe the pathogenesis of acute calculous cholecystitis

Cholecystitis is the chemical irritation of an obstructed gallbladder

Steps:

- Mucosal phospholipases hydrolyse luminal lecithins to toxic lysolecithin
- Protective glycoprotein mucous layer is disrupted
- Allows bile salts to have a detergent like action on the exposed mucosal epithelium
- Prostaglandins contribute to inflammation
- Gallbladder develops dysmotility

- Distension and increased intraluminal pressure decreases the mucosal blood flow

What are the complications of cholecystitis

- Bacterial infection causing cholangitis and/or sepsis
- Perforation or a localised abscess
- Rupture and peritonitis
- Biliary fistula
- Porcelain gallbladder

How is the pathogenesis of acalculous cholecystitis different?

- Acalculous is more rare (10% of cases)
- Usually occurs in predisposed individuals
- Onset is slower
- Secondary to ischaemia from the cystic end arteries
- Other promoting factors including inflammation, sludging, local inflammation
- Occurs in patients with other significant illness i.e. sepsis with hypotension, immunosuppression, major trauma and burns

How does it differ clinically?

- Calculus cholecystitis usually acute onset, RUQ pain and vomiting, tender, anorexia, mild vomiting, sweating, nausea.
- Acalculous more insidious onset, patients may have no typical gallbladder symptoms, usually occurs in those patients already unwell with serious illness, more risk of serious complications i.e, perforation

9. Cholelithiasis

What are the risk factors for the development of cholesterol stones?

- Age and gender are the main ones - theres a 25% increase in cases over the age of 80. Women are more at risk than men.
- Environmental factors: OCP use, pregnancy more common due to hormonal related increase in the expression of lipid receptors and stimulation of cholesterol uptake and synthesis pathways. Obesity and rapid weight loss are also factors.
- Acquired disorders: gallbladder stasis
- Hereditary factors: e.g. genetic factors that encode lipid transport proteins

Describe the pathogenesis of cholesterol stone formation

Requires the following simultaneous conditions:

- Bile supersaturated with cholesterol
- Hypomotility of gallbladder
- Cholesterol crystal nucleation
- Hypersecretion of mucus in the gallbladder which traps the crystals - causing aggregation into stones

10. Pancreatitis

What are the causes of pancreatitis?

- Gallstones
- Alcohol
- Iatrogenic
- Viral
- Hyperlipoproteinaemia
- Hypercalcaemia
- Trauma or shock
- Duct

What is the pathogenesis of acute pancreatitis?

- Autodigestion of the pancreatic substance by inappropriately activated pancreatic enzymes e.g. trypsinogen
- Typically precipitated by duct obstruction, primary acinar cell injury or defective intracellular transport of proenzymes
- This causes interstitial inflammation, oedema, proteolysis, fat necrosis and haemorrhage

What are the acute complications of pancreatitis

- Haemolysis
- DIC
- Fluid sequestration
- ARDS
- Diffuse fat necrosis
- Peripheral vascular collapse
- Shock

What are the lab findings of acute pancreatitis?

- Marked elevation of serum amylase
- Rising lipase within 72 hours
- Glycosuria
- Hypocalcaemia - a poor prognostic sign
- Leukocytosis
- Acute kidney injury

What is the cellular morphology of acute pancreatitis?

- Inflammation and oedema
- Can involve haemorrhage and extensive necrosis in severe cases
- Microvascular leakage causes oedema
- Lipolysis via enzymes = fat necrosis
- Fatty acids react with calcium to precipitate as salts
- There may also be extra pancreatic fat necrosis such as in the omentum
- There may be a presence of peritoneal fluid with fat globules

What are the morphological changes in chronic pancreatitis?

- Parenchymal fibrosis
- Reduced number and size of acini with relative sparing of islet cells
- Variable dilation and blockage of pancreatic ducts
- Destruction of exocrine parenchyma
- Calcification

What are some of the clinical consequences of chronic pancreatitis?

- Irreversible impairment of pancreatic function including diabetes, steatorrhoea, malabsorption
- Amylase and lipase may not be raised in chronic
- Pseudocyst formation
- Not immediately life threatening but long term outlook is poor

GI Pathology

11. Bowel Obstruction

Describe the common causes of bowel obstruction

- Adhesions
- Hernia
- Malignancy
- Volvulus
- Intussusception
- Mesenteric infarct
- Strictures

How does a hernia form and cause a bowel obstruction?

- Initially, a weakness or defect in the abdominal wall, results in a protrusion of serosa-lined pouch of the peritoneum
- Then there is visceral protrusion (which can be the small or large bowel, but the omentum is most often involved)
- Entrapment of the hernia sac in a narrow neck causes pain
- Ongoing obstruction leads to venous stasis, oedema, incarceration and strangulation
- Common locations include inguinal, femoral, umbilical and previous scars

What are the important clinical sequelae of an ongoing bowel obstruction?

- Intestinal perforation
- Intestinal ischaemia
- Peritonitis
- Sepsis
- Abscess
- Electrolyte disturbance
- Vomiting and aspiration
- Death

12. Gastritis

What are the common causes of chronic gastritis?

- Helicobacter pylori
- Chronic bile reflux
- NSAIDs
- Autoimmune
- Allergic
- Other infections
- Irritants i.e. coffee, alcohol
- Systemic disease

Describe the features of h. Pylori induced gastritis

- Most common cause
- Predominantly antral
- High acid production
- Hypergastrinaemia
- Generates ammonia
- Disrupts the normal mucosal defence mechanism

What are the complications of a gastric ulcer?

- Bleeding
- Perforation
- Obstruction
- Gastric adenocarcinoma

13. Crohn's disease

What are the pathological features of crohn's disease?

- Transmural inflammation of bowel with skip lesions
- Can affect anywhere along the GI tract
- Noncaseating granulomas
- Fissures and fistulae
- Chronic, relapsing condition

What are the extraintestinal manifestations of Crohn's disease?

- Polyarthritis
- Finger clubbing
- Sclerosing cholangitis
- Uveitis
- Renal disorders

What are some of the complications of Crohn's disease?

- Strictures
- Fistulae

- Malabsorption syndromes
- GI cancers are less common than people with UC

14. Ulcerative Colitis

What are the pathological features of ulcerative colitis?

- Severe ulcerating inflammatory bowel disease
- Limited to the colon and rectum
- No skip lesions
- Not transmural, extends only to the mucosa and submucosa
- Superficial, broad based ulcers
- Has malignant potential
- Can cause toxic megacolon

What extraintestinal manifestations occur?

- Skin lesions
- Uveitis
- Polyarthritis
- Cholangitis
- Ankylosing spondylitis

15. Ischaemic Bowel Disease

What conditions can lead to infarction of the bowel?

- Acute arterial obstruction - from atherosclerosis, aortic aneurysm, hypercoagulable state, hormonal therapies, embolism
- Intestinal hypoperfusion - from cardiac failure, shock, dehydration, vasoactive drugs
- Systemic vasculitis
- Mesenteric venous thrombosis - from neoplasm, cirrhosis, trauma, abdominal masses
- Miscellaneous - volvulus, stricture, amyloid

What are the clinical features of ischaemic bowel?

- Severe pain
- Tenderness - peritonism
- Nausea & vomiting
- Bloody diarrhoea or melena
- May have absent bowel sounds
- Shock

What parts of the bowel are most susceptible to ischaemic injury and why?

- Watershed zones at the splenic flexure, sigmoid colon and rectum
- Located at the end of the arterial supply so most sensitive to hypoperfusion

- Surface epithelium is also at more risk on the villi than in the crypts because the capillaries run to the crypts first then out to the villi

Describe the intestinal response to an acute ischaemic insult - what is the mechanism by which the ischaemic bowel injury occurs?

- Initial hypoxic injury
- Secondary reperfusion injury - major injury is caused by reperfusion
- Free radical production, neutrophil infiltrates, inflammatory mediator release
- Oedema and haemorrhage in the bowel wall
- Mucosal necrosis, gangrene
- Metabolic and cardiovascular derangements e.g. acidosis and fluid shifts
- Perforation can lead to death
- The magnitude of the response is determined by the vessels affected and the timeframe over which the ischaemia develops