GIT Module, Pathology
COMPLICATION OF CIRRHOSIS

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OBJECTIVES

- Recognize the major complications of cirrhosis
- Understand the pathogenetic mechanisms underlying the occurrence of the complications
- Recognize the clinical features inherent to the above-mentioned complications
- Describe the pathological findings of the different complications

Clinical manifestation

- About 40% of patients are asymptomatic until most advanced stages of disease
- Non-specific symptoms such as anorexia, weight loss, weakness & eventually signs & symptoms of liver failure discussed earlier (jaundice, encephalopathy & coagulopathy) , much as the same as in acute liver hepatitis
- Additional significant manifestations and Complications

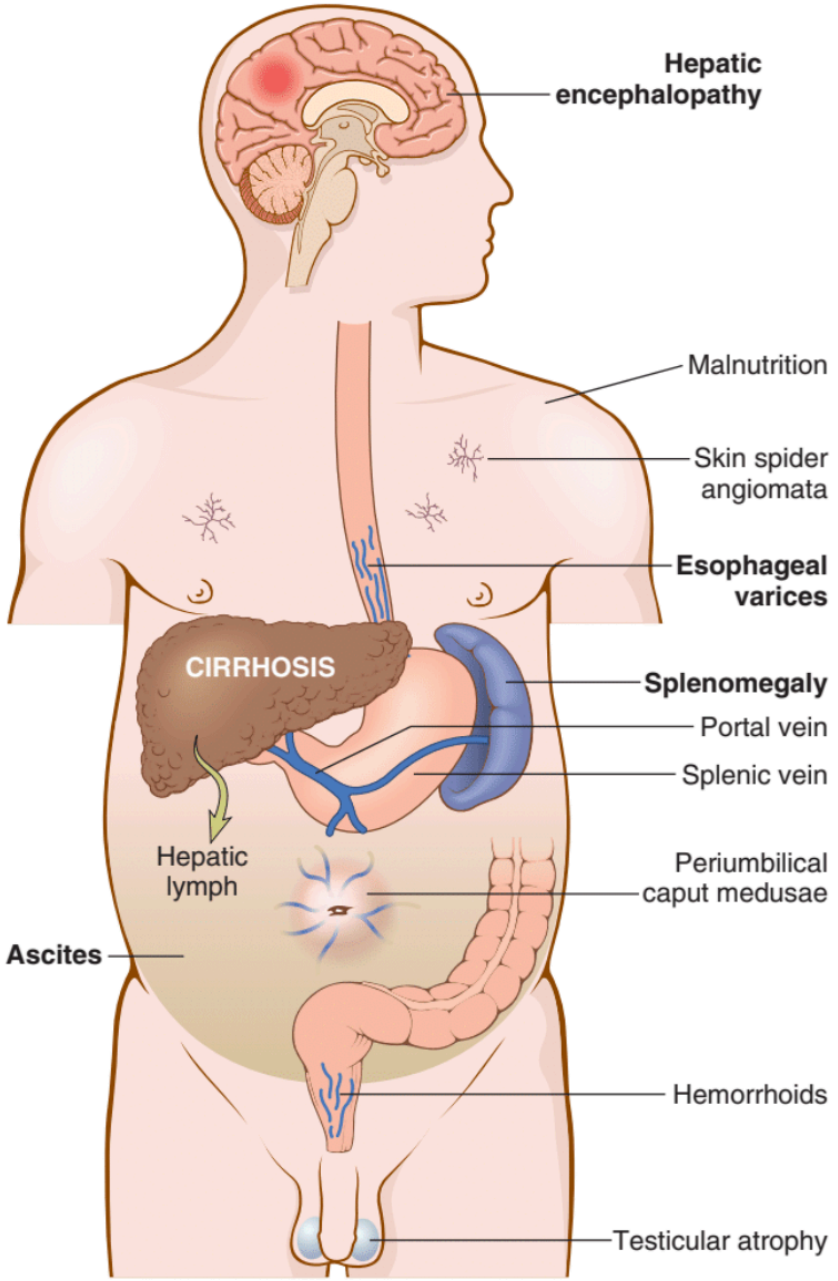


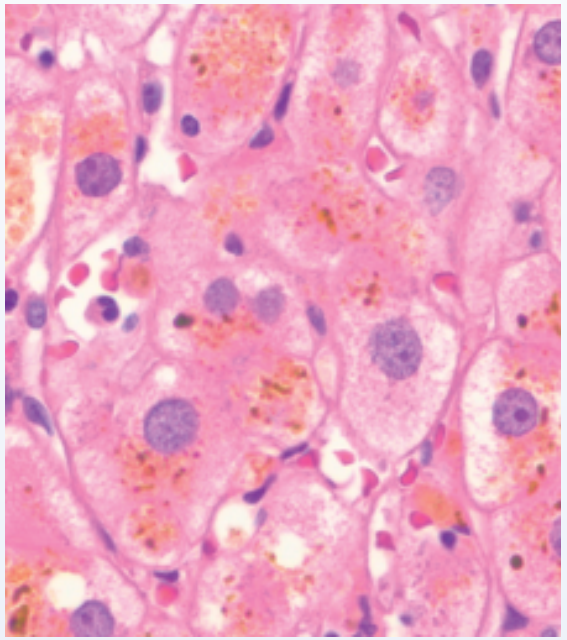
Fig. 16.7 Major clinical consequences of portal hypertension in the setting of cirrhosis, shown for the male. In females, oligomenorrhea, amenorrhea, and sterility are frequent as a result of hypogonadism.

1. Jaundice and cholestasis can lead to pruritus (itching)
2. Portal hypertension and Portosystemic Shunts
    1. Splenomegaly
    2. Variceal bleeding
    3. Hemorrhoids
    4. Periumbilical venous collaterals (caput medusa)
3. Hepatic failure
    1. Coagulopathy
    2. Hypoalbuminemia
    3. Hepatic encephalopathy
    4. Hyperestrogenemia in males
    5. Hypogonadism
4. Ascites
5. Spontaneous bacterial peritonitis
6. Hepatorenal syndrome
7. Hepatocellular carcinoma

1. Cholestasis, Jaundice and Pruritis

Cholestasis

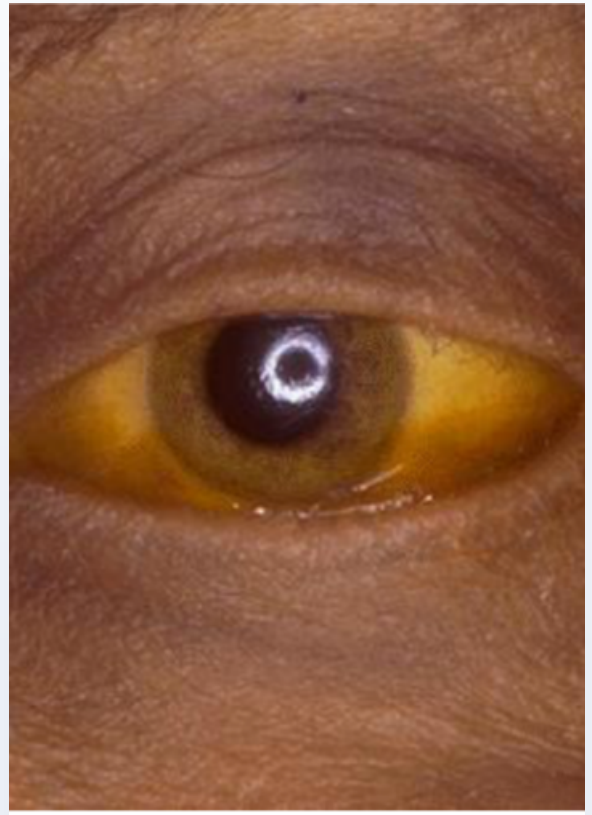
- Condition of impaired bile formation and bile flow, leading to accumulation of bile pigment in the hepatic parenchyma
- It can be caused by extrahepatic or intrahepatic obstruction of bile channels, or by defects in hepatocyte bile secretion
- Patients may have jaundice, pruritus, skin xanthomas (focal accumulation of cholesterol), or symptoms related to intestinal malabsorption, including nutritional deficiencies of the fat-soluble vitamins A, D, or K

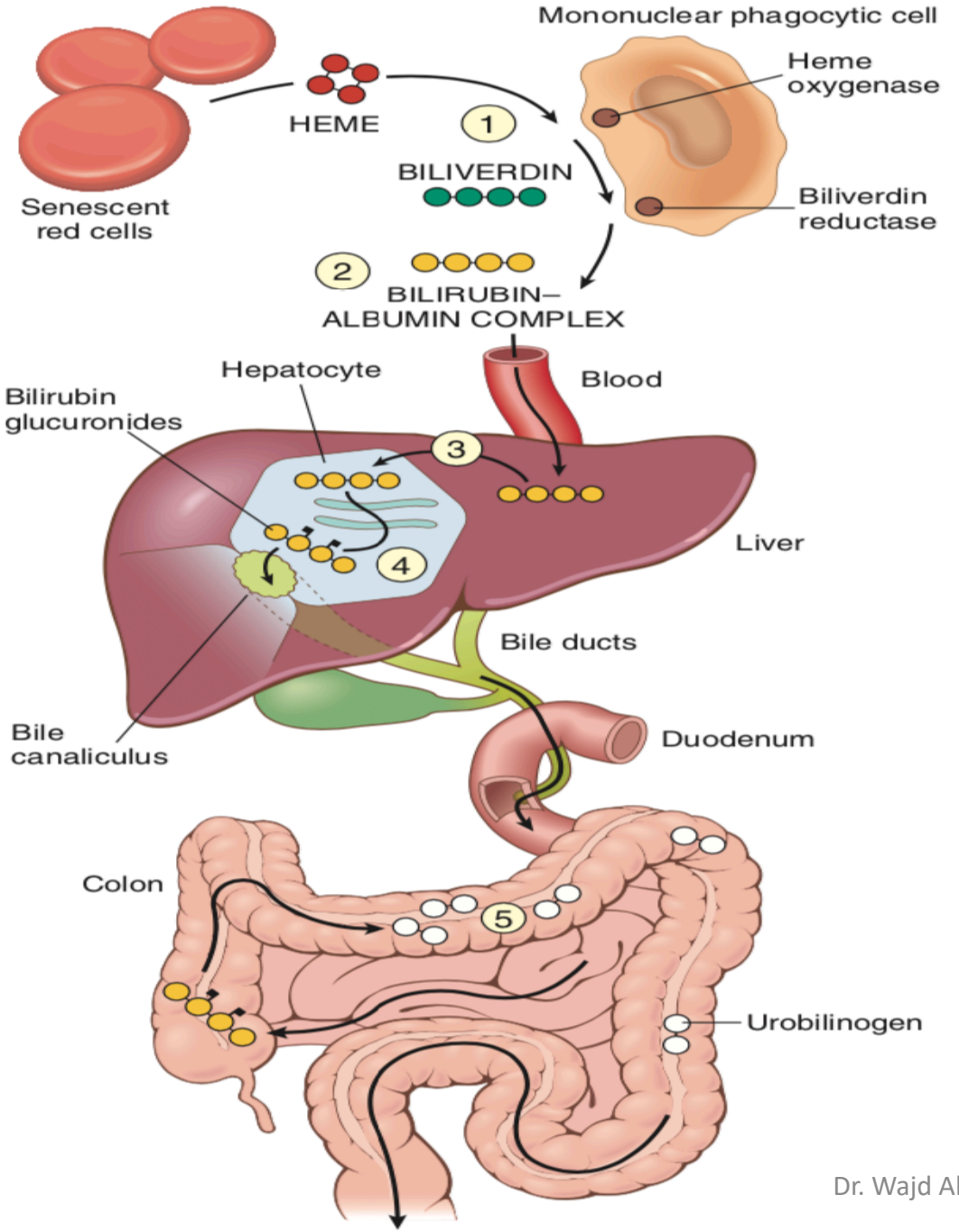


1. Jaundice, Cholestasis and Pruritis

Jaundice and icterus

- Yellowish or greenish pigmentation of the skin and sclera of the eyes respectively due to high bilirubin levels
- Jaundice occurs when the equilibrium between bilirubin production and clearance is disturbed
- To understand the pathophysiology of jaundice it is important first to become familiar with the major aspects of bile formation and metabolism





Bilirubin metabolism and elimination

Metabolism of bilirubin by the liver consists of four separate but interrelated events:

1. Uptake from the circulation
2. Intracellular storage
3. Conjugation with glucoronic acid
4. Biliary excretion

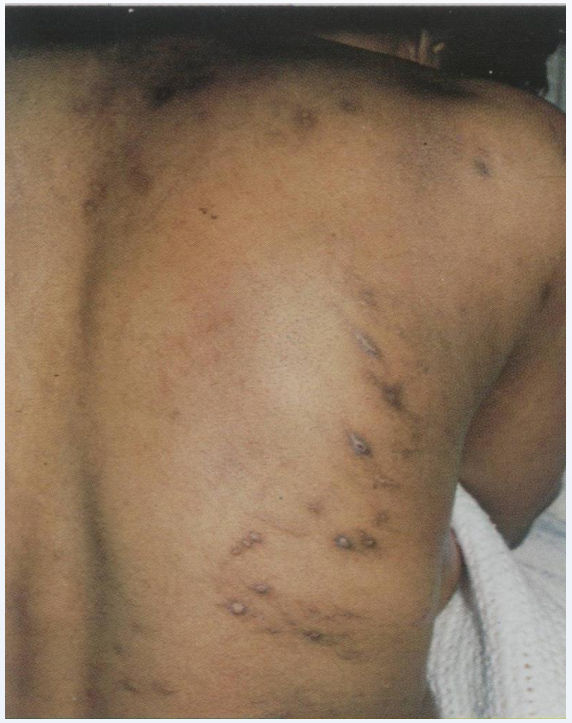
Cause of Jaundice

Predominantly Unconjugated Hyperbilirubinemia
Excess Production of Bilirubin
Hemolytic anemias
Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas)
Ineffective erythropoiesis (e.g., pernicious anemia, thalassemia)
Reduced Hepatic Uptake
Drug interference with membrane carrier systems
Impaired Bilirubin Conjugation
Physiologic jaundice of the newborn
Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis)
Predominantly Conjugated Hyperbilirubinemia
Decreased Hepatocellular Excretion
Drug-induced canalicular membrane dysfunction (e.g., oral contraceptives, cyclosporine)
Hepatocellular damage or toxicity (e.g., viral or drug-induced hepatitis, total parenteral nutrition, systemic infection)
Impaired Intrahepatic or Extrahepatic Bile Flow
Inflammatory destruction of intrahepatic bile ducts (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, graft-versus-host disease, liver transplantation)
Gallstones
External compression (e.g., carcinoma of the pancreas)

1. Jaundice, Cholestasis and Pruritis

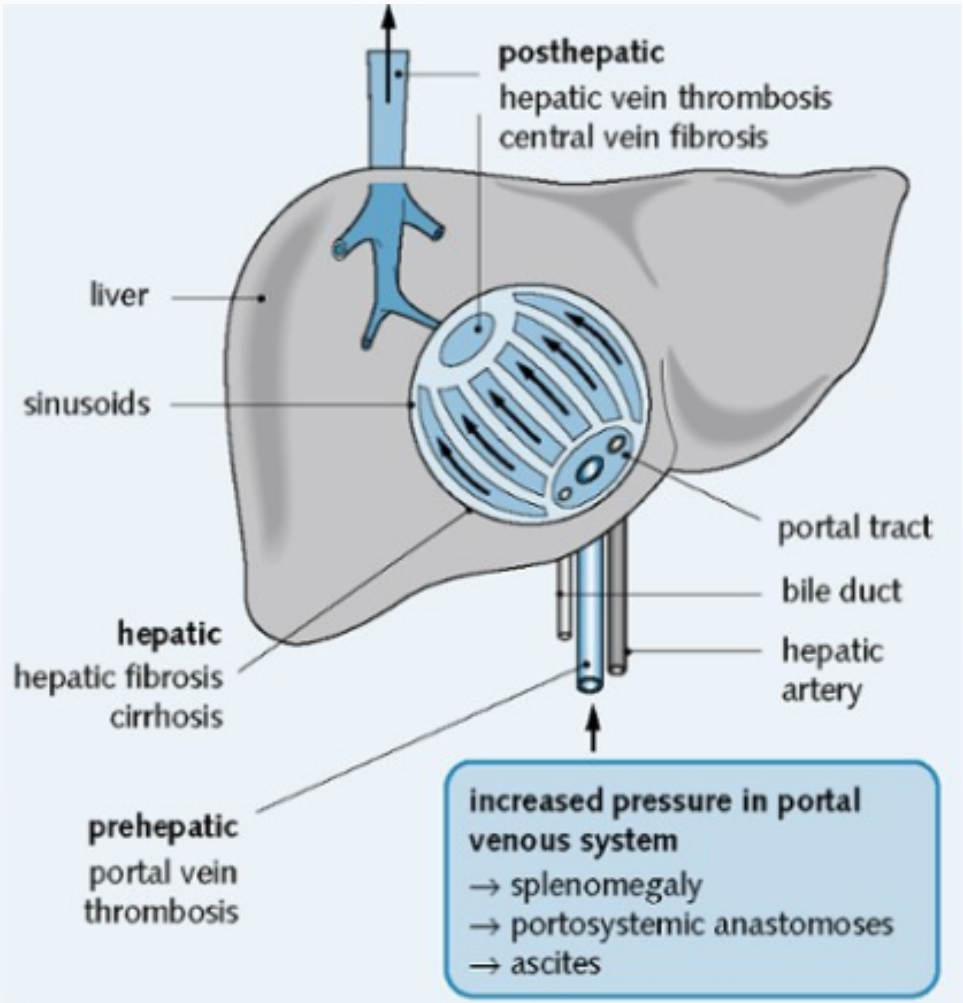
Pruritis

- Chronic severe jaundice ➔ itching
- May be so profound ➔ risk of repeated bouts of potentially life-threatening infection
- Severe pruritis in some patients is 1ry indication for liver transplantation
- Is also frequently seen in other disorders associated with cholestasis
- Precise pathogenesis is unknown



2. Portal Hypertension

- More frequent and more complex than in acute liver failure
- Due to Resistance to blood flow and. by diminished flow through the portal venous system,
- Causes could be because obstruction at the prehepatic, intrahepatic, or posthepatic level

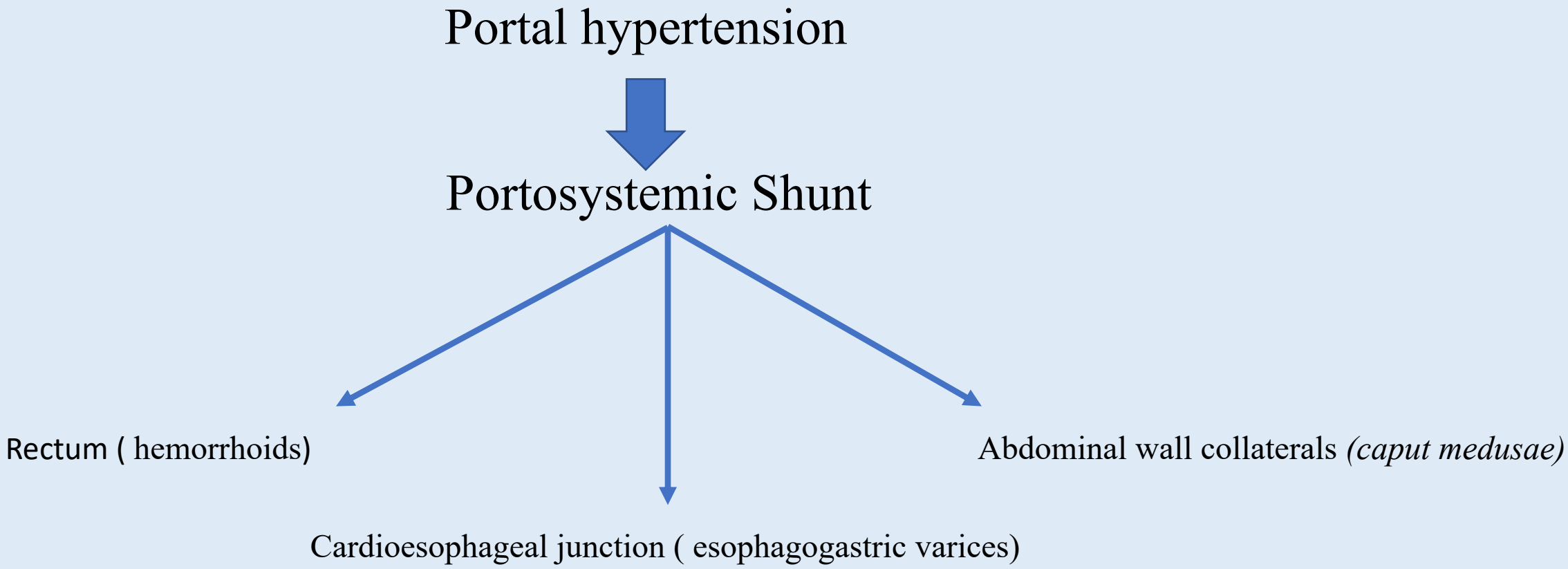


2. Portal Hypertension

Portosystemic shunt:

- ✓Develop when blood flow is reversed from portal to systemic circulation
- ✓Produced by dilation of collateral vessels
- ✓Most clinically important is *oesophageal varices* which appear in ~ 40% of patients with advanced-stage liver disease
- ✓Often cause massive, frequently fatal hematemesis, particularly with compounding coagulopathy

In summery


Portal hypertension
Portosystemic Shunt
Rectum (hemorrhoids)
Cardioesophageal junction (esophagogastric varices)
Abdominal wall collaterals *(caput medusae)*

2. Portal Hypertension

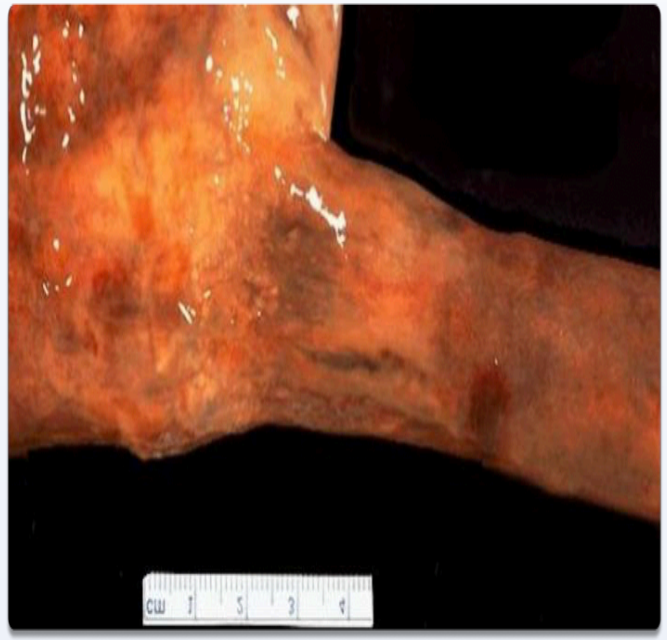
Splenomegaly

- Long-standing congestion may cause congestive splenomegaly
- The degree of splenic enlargement varies widely and may reach as much as 1000 gm
- Massive splenomegaly may secondarily induce hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia or even pancytopenia

2. Portal Hypertension

Oesophageal varices

- Venous blood from the GI tract is delivered to the liver via the portal vein before reaching the inferior vena cava.
- This circulatory pattern is responsible for the first-pass effect in which drugs and other materials absorbed in the intestines are processed by the liver before entering the systemic circulation.
- Diseases that impede this flow cause portal hypertension and can lead to the development of esophageal varices, an important cause of esophageal bleeding



2. Portal Hypertension

Oesophageal varices

Pathogenesis

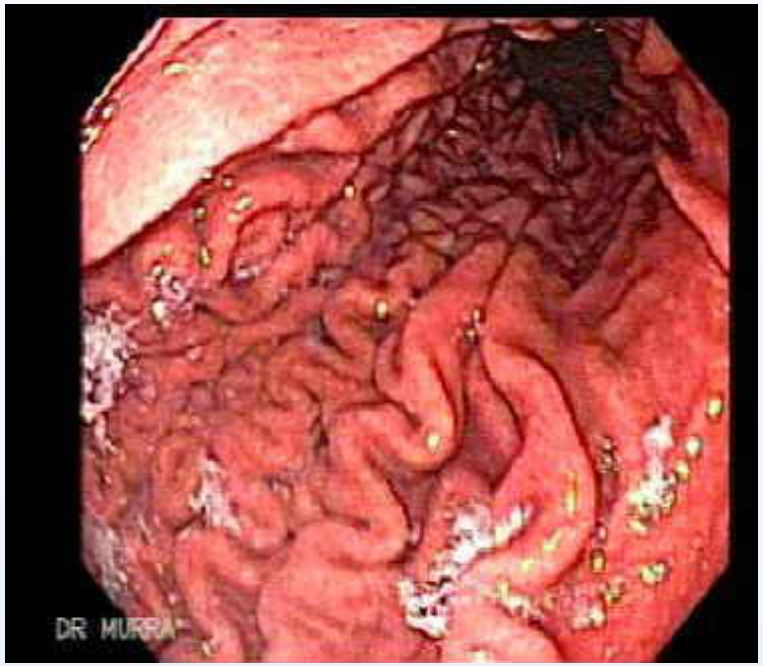
- Portal hypertension results in the development of collateral channels at sites where the portal and caval systems communicate
- Although these collateral veins allow some drainage to occur, they lead to development of a congested subepithelial and submucosal venous plexus within the distal esophagus (*varices)*
- Most commonly in association with alcoholic liver disease and hepatic schistosomiasis

2. Portal Hypertension

Oesophageal varices

Morphology

- Varices can be detected by venogram: tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach. Venous channels directly beneath the esophageal epithelium may also become massively dilated
- Varices may not be grossly obvious in surgical or postmortem specimens, because they collapse in the absence of blood flow



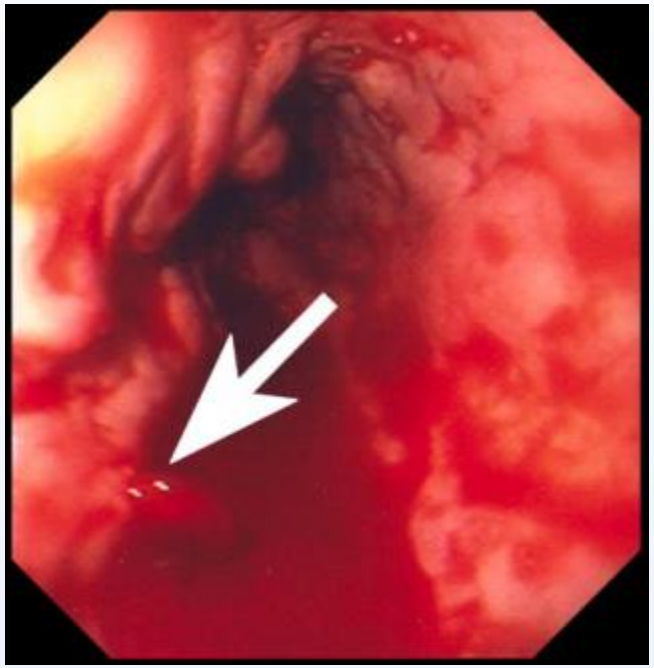
massively dilated venous channels

2. Portal Hypertension

Oesophageal varices

Morphology:

- Variceal rupture results in hemorrhage into the lumen or esophageal wall, in which case the overlying mucosa appears ulcerated and necrotic
- If rupture has occurred in the past, venous thrombosis, inflammation, and evidence of prior therapy may also be present



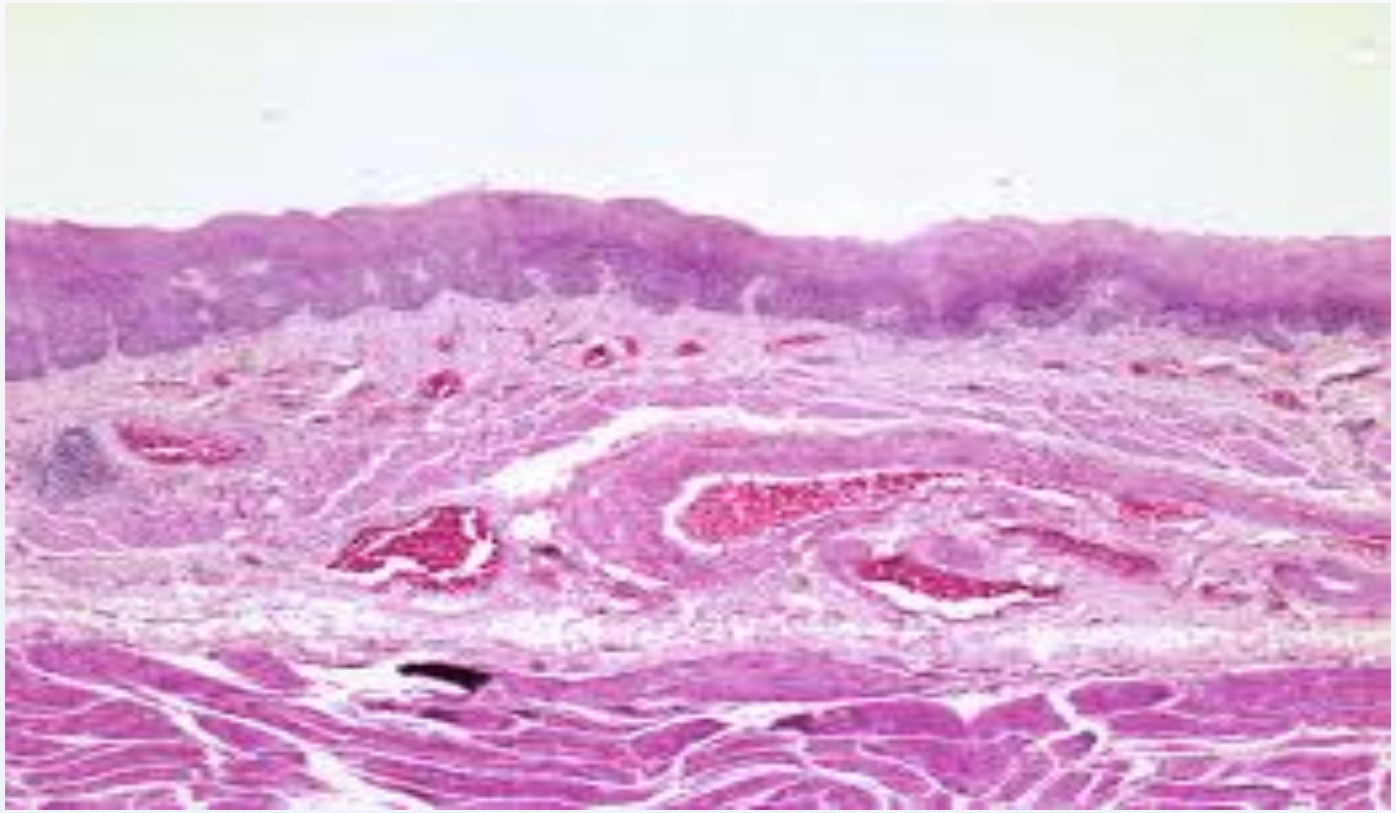
Variceal rupture with hemorrhage

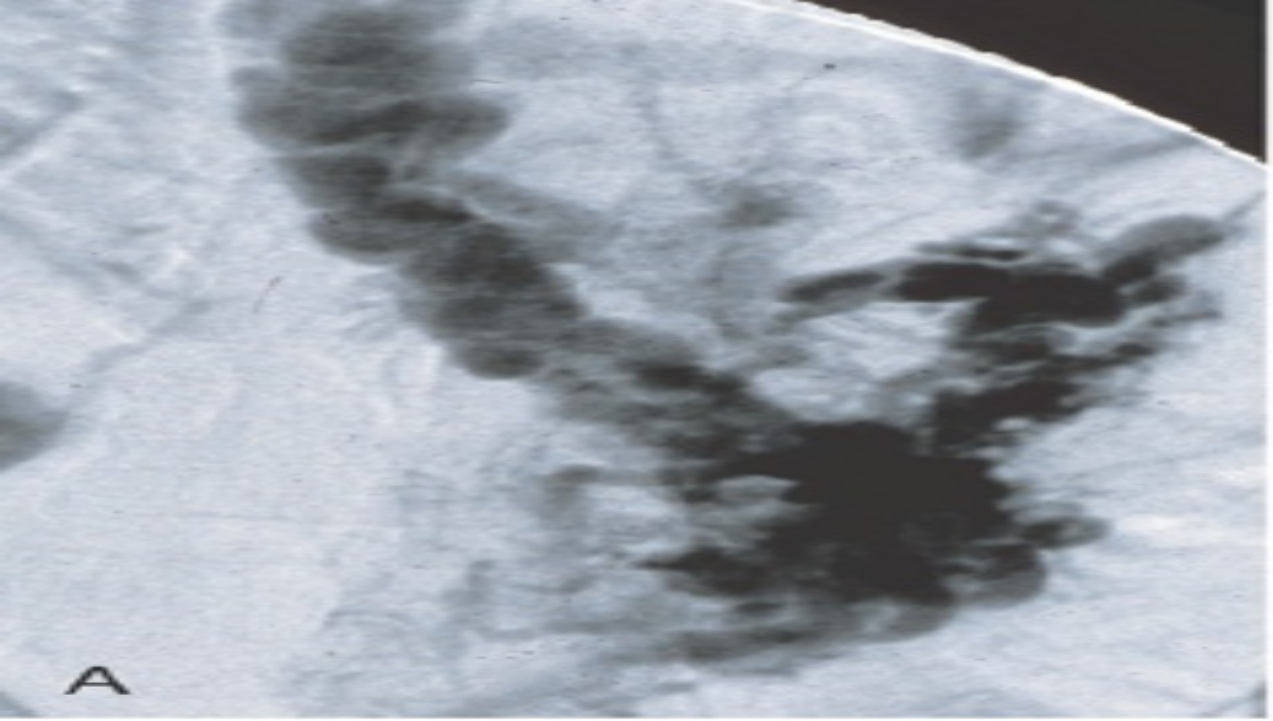
2. Portal Hypertension

Oesophageal varices

Morphology

- Dilated, thin-walled vessels are seen, mostly in the submucosa

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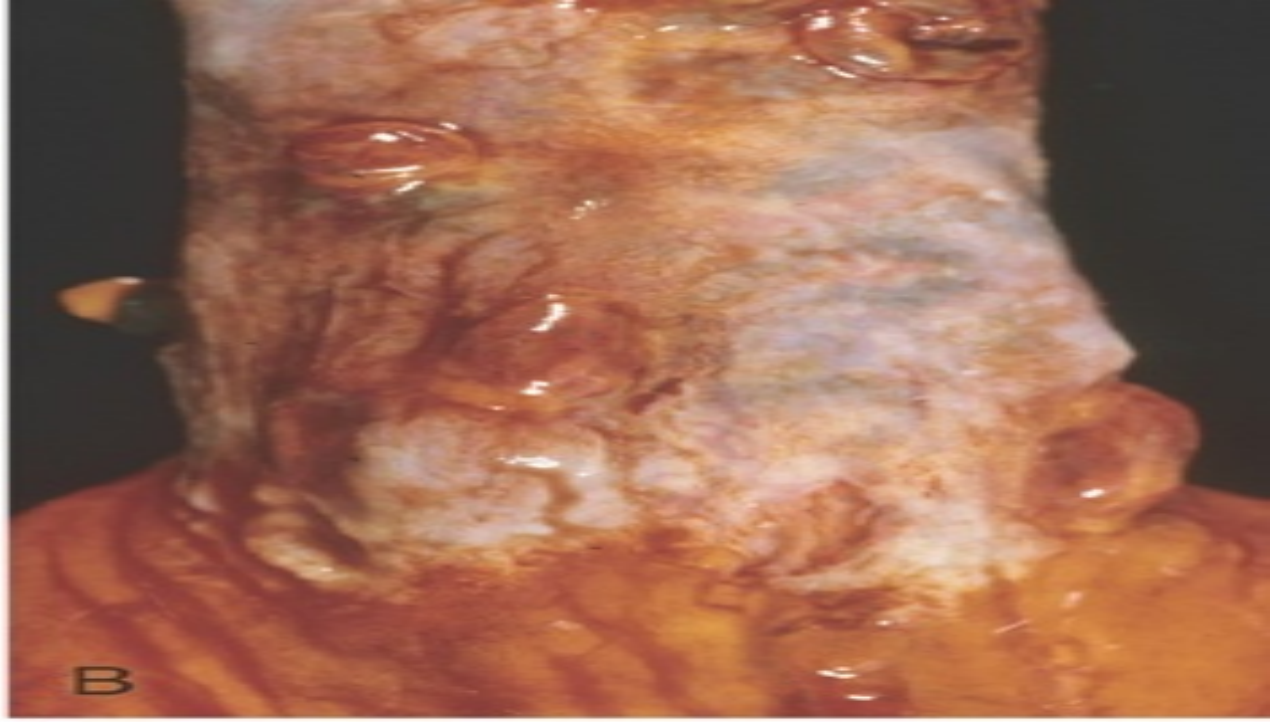
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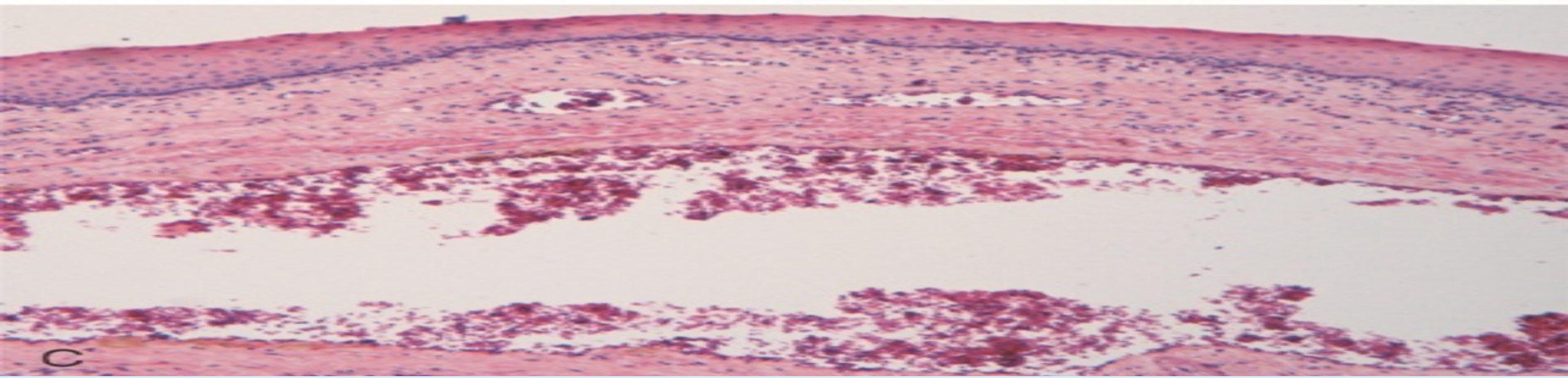
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2. Portal Hypertension

Oesophageal varices

Clinical features

- Asymptomatic or rupture → massive hematemesis
- Inflammatory erosion of thinned overlying mucosa
- Increased tension in progressively dilated veins
- Increased vascular hydrostatic pressure associated with vomiting are likely to contribute to medical emergency that is treated by any of several methods:
  1. Sclerotherapy
  2. Endoscopic balloon tamponade
  3. Endoscopic rubber band ligation

2. Portal Hypertension

Oesophageal varices

Clinical features

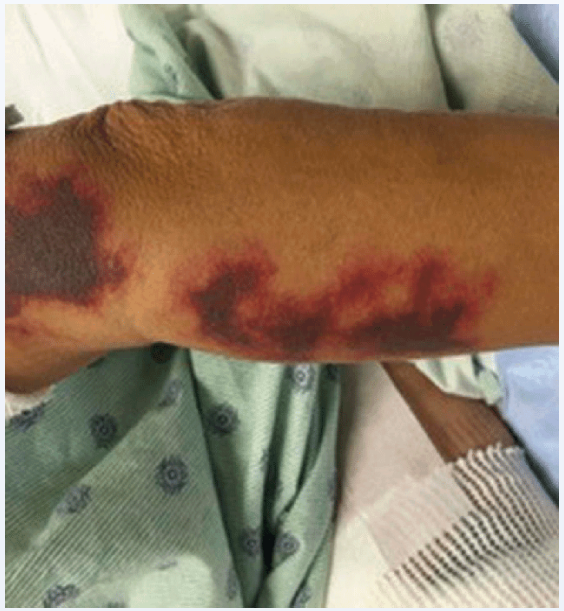
- Half of patients die from the first bleeding episode either as a direct consequence of hemorrhage or following hepatic coma triggered by hypovolemic shock
- Additional 50% within 1 year
- Each episode has a similar rate of mortality
- Over half of deaths among individuals with advanced cirrhosis result from variceal rupture

3. Hepatic failure

Coagulopathy

- Coagulation factors that decline in the face of liver failure, leading to easy bruising and bleeding. Paradoxically, disseminated intravascular coagulation

- Hypercoagulation state also may occur due to failure of the damaged liver to remove activated coagulation factors



3. Hepatic failure

Hypoalbuminemia

- Hypoalbuminemia from decreased synthesis of albumin

- Produces dependent pitting edema and ascites due to a decrease in plasma oncotic pressure

3. Hepatic failure

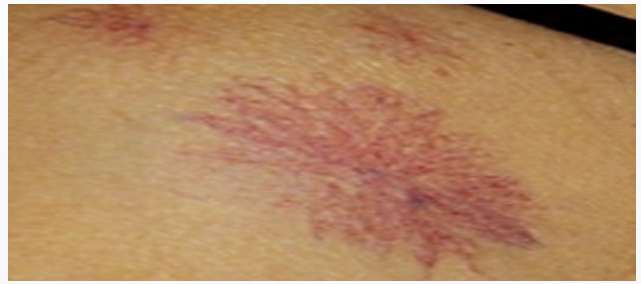
Hyperestrogenemia

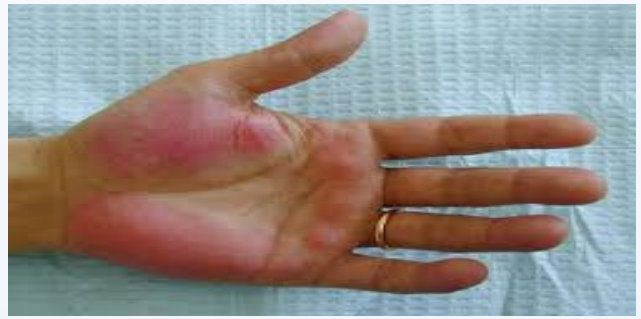
- Due to impaired estrogen metabolism
  - Liver cannot degrade estrogen and 17-ketosteroids (Androstenedione)
  - Androstenedione is aromatized into estrogen in the adipose cells

3. Hepatic failure

- ♀:
  - ✓ hypogonadism ➔ oligomenorrhea, amenorrhea & sterility

- ♂:
  - ✓Palmar erythema “due to local vasodilatation
  - ✓Spider angiomas of skin
  - ✓Hypogonadism
  - ✓Female distribution of hair
  - ✓Gynecomastia



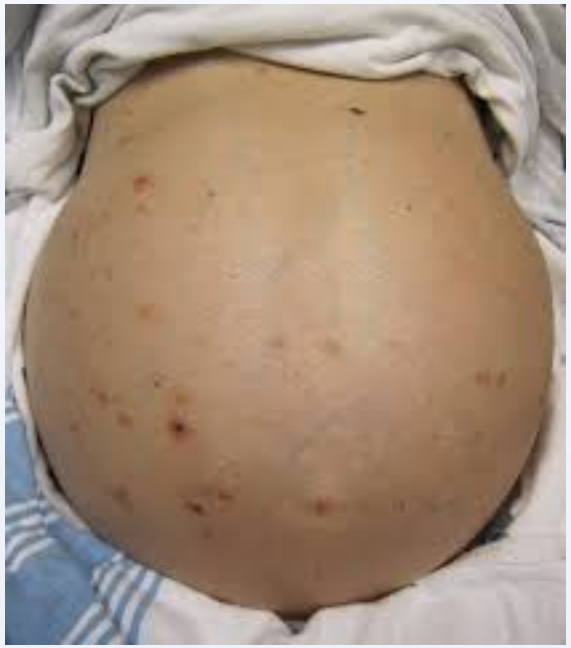


3. Hepatic failure

- Hepatic encephalopathy:
  - A spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to confusion & stupor, to coma & death
  - **Course:** develop over days, weeks, or a few months after acute injury
  - **Features:** fluctuating neurologic signs, including rigidity, hyperreflexia, and asterixis
  - **Mechanism:** elevated ammonia levels in blood and the central nervous system correlate with impaired neuronal function and brain edema

4. Ascites

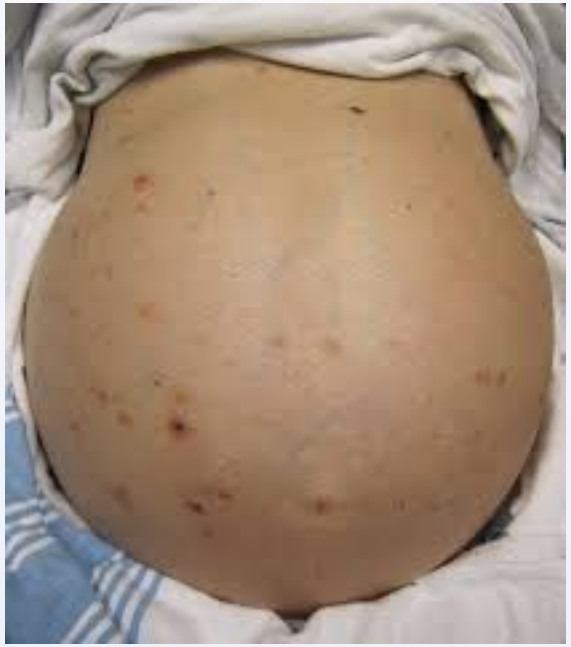
- Is the accumulation of excess fluid in the peritoneal cavity
- 85% of cases are caused by cirrhosis
- Clinically detectable when at least 500 mL have accumulated
- The fluid is generally serous, having less than 3 gm/dL of protein (largely albumin), and a serum to ascites albumin gradient of ≥1.1 gm/dL



4. Ascites

The pathogenesis of ascites is complex, involving the following mechanisms:

- Increase in portal vein hydrostatic pressure
- Decreases oncotic pressure
- Liver is unable to metabolize aldosterone



5. Spontaneous bacterial peritonitis

Increased risk for spontaneous bacterial infection on top of ascites

6. Hepatorenal syndrome

- Is a form of renal failure occurring in individuals with liver failure in whom there are no intrinsic morphologic or functional causes for kidney dysfunction
- The incidence of this syndrome is about 8% per year among patients who have cirrhosis and ascites
- Main functional abnormalities:
  - Sodium retention, impaired free-water excretion, ↓ renal perfusion & ↓ glomerular filtration rate
- Features: ↓ Urine output, ↑ blood urea nitrogen & creatinine levels

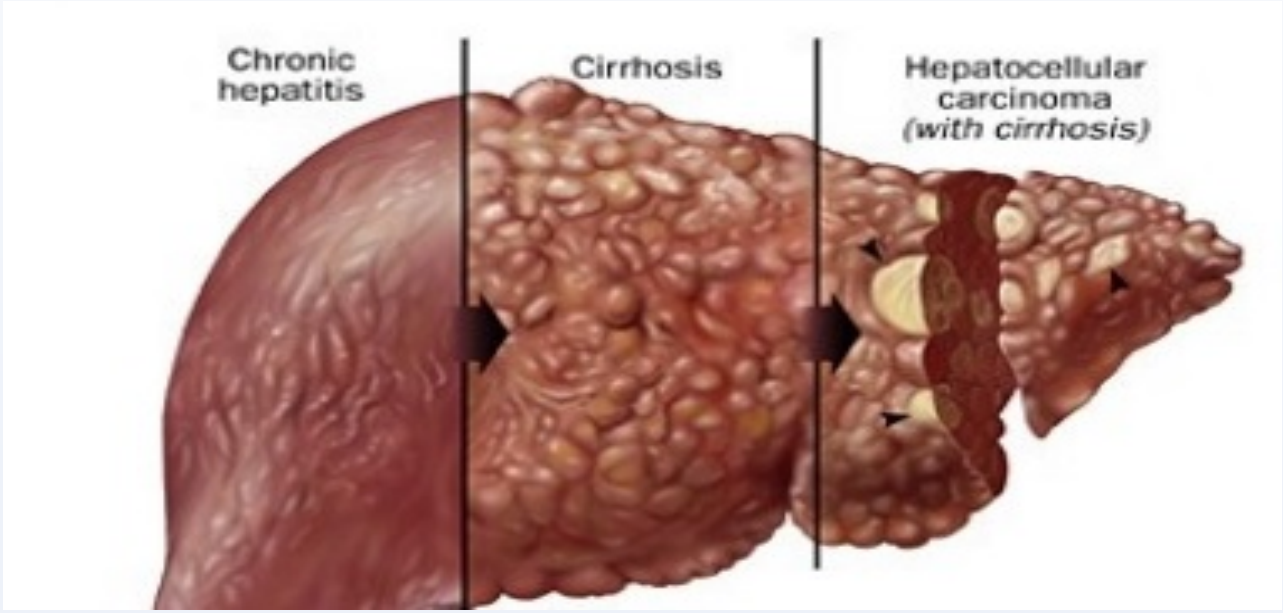
6. Hepatorenal syndrome

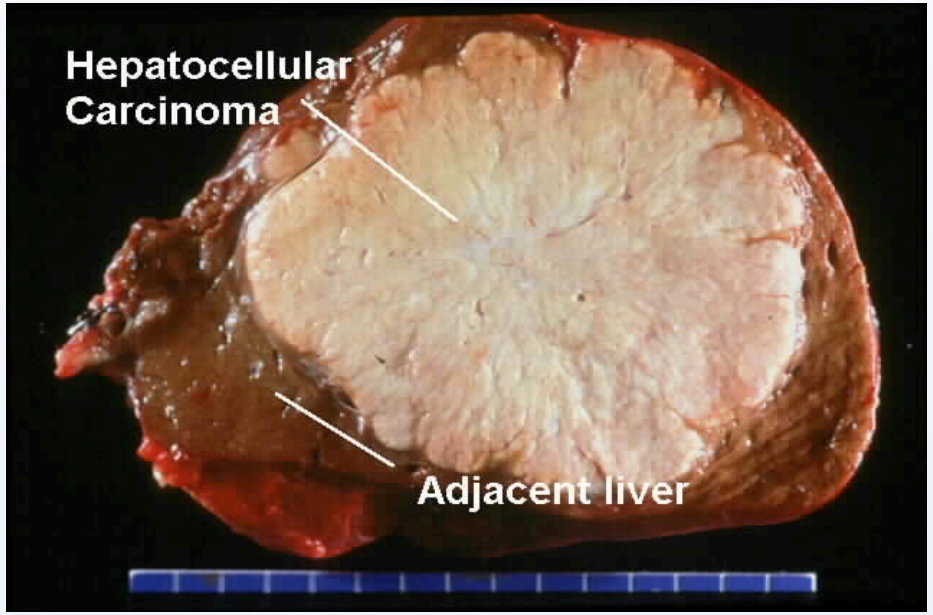
Causes

- Decreased renal perfusion pressure due to systemic vasodilation
- Activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles
- Increased synthesis of renal vasoactive mediators (activation of the renin/angiotensin axis), that decrease glomerular filtration

7. Hepatocellular Carcinoma

Most chronic liver disease predispose to development of hepatocellular carcinoma





Thank you for your attention

References:

- **ROBBINS BASIC PATHOLOGY, TENTH EDITION**