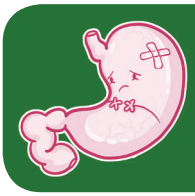

NOTES
LIVER DISEASES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Diseases affecting hepatic parenchymal tissue or vasculature
- Variable insults
  - Impairment in function of/destruction of liver parenchyma → inflammation → scarring (cirrhosis) → liver failure
  - Obstruction or restriction of blood flow through liver → hypertension in portal circuit producing secondary systemic effects
  - Diseases caused by anomalies in absorbing, storing, converting or detoxification → accumulation of substances in the liver and other tissues causing damage

SIGNS & SYMPTOMS

- Early stages generally asymptomatic
- Non-specific symptoms
  - Weakness, weight loss, fatigue

Portal hypertension

- Abdominal distension (ascites)
- Splenomegaly
- Esophageal varices → trouble swallowing, hematemesis, dark stools
- Caput medusae
  - Dilated periumbilical collateral veins
- Cruveilhier–Baumgarten murmur
  - Venous hum heard in epigastric region with stethoscope

Liver cellular dysfunction

- Decreased hepatic albumin production
  - Decreased osmotic pressure → edema
  - Increase in levels of free circulating compounds normally bound to albumin (e.g. increase in free calcium)
- Decreased hepatic metabolism of circulating estrogens → hyperestrogenism
  - *Spider nevi:* vascular lesions, central arteriole surrounded by smaller vessels
  - Palmar erythema
  - Gynecomastia
- Fetor hepaticus (breath odor due to increased dimethyl sulfide levels)
- Jaundice (cellular necrosis → reduced hepatic ability to metabolize, excrete bilirubin → buildup of unconjugated bilirubin in the blood)
- Decreased production of coagulation factors → easy bruising, bleeding
- Hepatic encephalopathy
  - Ammonia, related nitrogenous substances not cleared from blood → accumulate in brain → impaired cerebral function

MNEMONIC: ABCDEFGHIJ

Common signs of liver disease

Asterixis, **A**scites, **A**nkle edema, **A**trophy of testicles
Bruising
Clubbing/ **C**olor change of nails (leukonychia)
Dupuytren's contracture
Encephalopathy / palmar **E**rythema
Fetor hepaticus
Gynecomastia
Hepatomegaly
Increase size of parotids
Jaundice

- Neglect of personal appearance
- Unresponsive, forgetful, trouble concentrating
- Changes in sleeping habits
- Psychosis
- Asterixis (bilateral asynchronous flapping of outstretches, dorsiflexed hands)

- Decreased metabolism of active compounds → increased sensitivity to certain medications
- Pruritus

MNEMONIC: 3Cs & 3Cs

Hepatomegaly common causes

Cirrhosis
Carcinoma
Cardiac failure

Hepatomegaly rare causes

Cholestasis
Cysts
Cellular infiltration

DIAGNOSIS

DIAGNOSTIC IMAGING

- CT scan with contrast, MRI, ultrasound, radionuclide imaging

LAB RESULTS

- Complete blood count (CBC)
- Liver function tests
  - *Tests of synthetic function:* serum albumin level, international normalized ratio (INR)
  - *Hepatocellular enzymes:* aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, direct bilirubin
  - *Ductal enzymes:* alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT)
- Hepatitis virus serology
  - *Hepatitis A:* anti-hepatitis A IgM, anti-hepatitis A IgG
  - *Hepatitis B:* hepatitis B surface antigen, anti-hepatitis B core/surface antibodies, anti-hepatitis B core IgM
  - *Hepatitis C:* hepatitis C antibody, hepatitis C RNA
  - *Hepatitis D & E:* IgM, IgG antibodies
- Autoimmune panel
  - Rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (CCP), anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), anti-extractable nuclear antigen (anti-ENA), antineutrophil cytoplasmic antibody (ANCA)
- Liver biopsy

TREATMENT

- Initially disease-specific; see individual disorders

SURGERY

- Advanced disease → liver transplant

ALCOHOLIC LIVER DISEASE

osms.it/alcoholic-liver-disease

PATHOLOGY & CAUSES

- Abnormal lipid retention in hepatocytes (steatosis) → large triglyceride fat vacuoles accumulate in liver cells → fatty liver
- Fat content of liver exceeds 5–10% by weight
- Can be accompanied by progressive inflammation (hepatitis) → steatohepatitis

RISK FACTORS

- Glycogen storage diseases, acute fatty liver during pregnancy, malnutrition, obesity, HIV, hepatitis C

Alcohol

- Most common cause
- Chronic alcohol use → production of toxic metabolites (e.g. aldehydes)
  - Damages mitochondria, cellular structures → impaired cellular energy mechanisms
  - Alcohol metabolised to aldehyde hepatic enzymes (reaction facilitates conversion of NAD+ → NADH; lower NAD+ concentration → less fatty acid oxidation → fatty acids accumulate → steatosis)

STAGING

- Stages of intracytoplasmic accumulation of triglycerides → fatty change

Initial stage

- Hepatocytes contain small fat vacuoles (liposomes) around nucleus (microvesicular fatty change)

Late stage

- Vacuoles enlarge → nucleus pushed to cell periphery → signet ring appearance (macrovesicular fatty change)
- Vesicles well-delineated, optically empty
  - Fats dissolve during tissue processing
- Large vacuoles coalesce → fatty cysts → irreversible lesions
- Macrovesicular steatosis most commonly associated with alcohol, diabetes, obesity, corticosteroids
- Severe fatty liver may be accompanied by inflammation, steatosis → steatohepatitis
  - Steatohepatitis → hepatocyte ballooning, necrosis → liver cell death, inflammatory response → hepatic stellate cell activation → fibrosis → cirrhosis

COMPLICATIONS

- Hepatocellular carcinoma

SIGNS & SYMPTOMS

- Fatigue, malaise, dull right-upper-quadrant pain, mild jaundice (rare), significant damage → hepatomegaly, ascites

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Steatosis → bright liver with increased echogenicity
- Fibrosis → coarse echo pattern
- Cirrhosis → nodules → irregular outline of liver surface

CT scan

- Lower density than spleen on CT scan

MRI

- Fat → bright on T1 and T2-weighted images

LAB RESULTS

Liver function tests

- Serum aminotransferases normal/

moderately elevated
    - AST usually more elevated than ALT in alcoholic fatty liver disease
    - GGT often elevated in alcoholic fatty liver disease

Secondary causes of steatosis

- Hepatitis C virus antibodies
- Hepatitis A IgG
- Hepatitis B surface antigen, surface antibody, core antibody
- Plasma iron, ferritin, total iron-binding capacity

Biopsy

- Early changes
    - Accumulation of membrane bound large droplet steatosis (Large macrovesicular drops → alcoholic steatosis; small microvesicular droplets → acute fatty liver of pregnancy, tetracycline toxicity, Reye's syndrome)
    - Proliferation of smooth endoplasmic reticulum
    - Gradual distortion of mitochondria
- Steatohepatitis
    - Presence of neutrophils → alcoholic steatohepatitis, unusual in chronic viral hepatitis
    - Mallory-Denk bodies (clusters of intracellular cytoskeletal protein aggregates)
- Advanced changes
    - *Fibrosis:* accumulation of scar tissue or extracellular matrix, potentially reversible if individual stops drinking alcohol, not true cirrhosis characterized by presence of regenerative nodules (irreversible)

TREATMENT

- Hepatic steatosis reversible, non-progressive if underlying cause controlled (e.g. cease alcohol use)

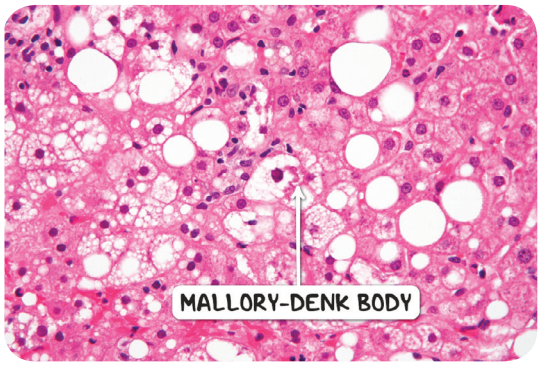

Figure 36.1 A Mallory–Denk body is a feature of many liver pathologies including alcoholic hepatitis and alcoholic cirrhosis.

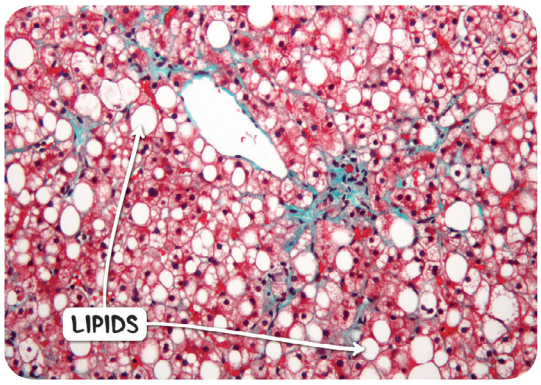

Figure 36.2 Histological appearance of fatty liver. The numerous white spaces represent the accumulation of lipid.

AUTOIMMUNE HEPATITIS

osms.it/autoimmune-hepatitis

PATHOLOGY & CAUSES

- Inflammation of the liver tissue caused by autoimmunity

TYPES

- *Type 1:* 80% of cases
- *Type 2:* most common in young biologically-female individuals
- *Type 3:* different antibodies but presents as Type 1
- *Type 4:* no detectable antibodies

CAUSES

- Combination of environmental triggers and genetic predisposition

RISK FACTORS

- Young biologically-female individuals; presence of HLA-DR3.DR4

COMPLICATIONS

- Acute liver failure, chronic liver failure, hepatocellular carcinoma, long term immunosuppression can lead to malignancies

SIGNS & SYMPTOMS

- Wide spectrum of presentation, from asymptomatic to cirrhosis and liver failure
- Common moderate symptoms
  - Fever, jaundice, and hepatosplenomegaly
- Chronic disease symptoms
  - Coagulation disturbance, impaired immunity
- Type 2 is associated with other diseases (Hashimoto's thyroiditis, Grave's disease)

DIAGNOSIS

LAB RESULTS

- ↑↑ALT, ↑ AST, ↓ albumin, ↑ prothrombin time
- Type 1
  - Antinuclear antibodies (ANAs), antibodies against smooth muscle proteins, or (ASMAs)
- Type 2
  - Antibodies to the microsomes of the liver or kidney (ALKM-1), liver cytosol antigen (ALC-1)
- Type 3
  - Soluble liver antigen positive

TREATMENT

MEDICATIONS

Immunosuppressants

- Corticosteroids, azathioprine

SURGERY

Liver transplantation

- If resistant to drug therapies

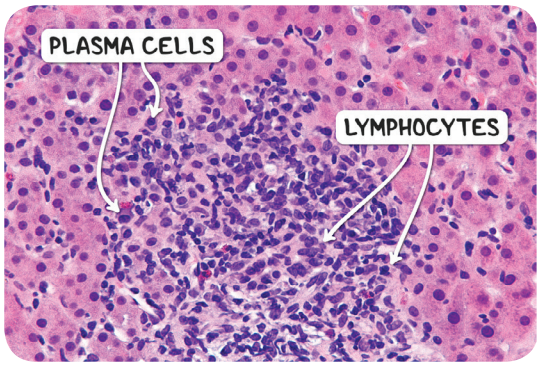

Figure 36.3 The histological appearance of autoimmune hepatitis. There is an infiltration of lymphocytes and plasma cells at the interface between the hepatic lobule and the portal tract i.e. lymphoplasmacytic interface hepatitis.

BUDD–CHIARI SYNDROME

osms.it/budd-chiari-syndrome

PATHOLOGY & CAUSES

- Congestive hepatic disease caused by obstruction of hepatic venous outflow
- Usually > one hepatic vein or hepatic section of vena cava
- Venous congestion leads to
  - Ischemia and centrilobular necrosis
  - Increased pressure in portal system → portal hypertension

CAUSES

- Occlusion (primary)
  - Thrombosis (most common)
- Compression (secondary)
  - Tumor mass, granuloma

RISK FACTORS

- Myeloproliferative and hematologic disorders (e.g. polycythemia vera)
- Hypocoagulative disorders
- Tumors
- Infections (e.g. tuberculosis)
- Inflammatory diseases
- Trauma
- Pregnancy
- Contraceptive therapy

COMPLICATIONS

- Cirrhosis and liver failure
- Esophageal, gastric and rectal varices
- Kidney dysfunction (hepatorenal syndrome)

SIGNS & SYMPTOMS

- Can present acutely or chronically
- Classic triad
  - Hepatomegaly
  - Abdominal pain
  - Ascites
- Jaundice
- Fever
- Other signs and symptoms of portal hypertension (e.g. splenomegaly, encephalopathy)

DIAGNOSIS

DIAGNOSTIC IMAGING

Doppler ultrasound

- Thrombus
- Alteration of hepatic venous outflow
- 'Spider web' formation around the obstruction duto collateral vessels proliferation

Venography

CT scan, MRI

LAB RESULTS

- Elevated aminotransferases
- Liver biopsy

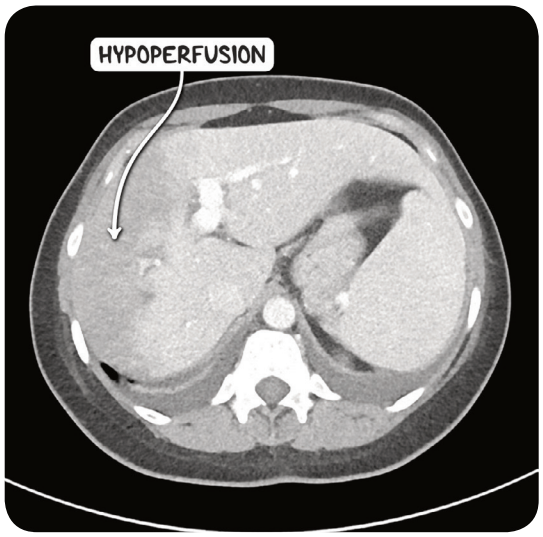

Figure 36.4 An abdominal CT scan in the axial plane demonstrating hypoperfusion of the right lobe of the liver secondary to Budd-Chiari syndrome.

TREATMENT

- Treat the underlying cause

MEDICATIONS

- Usually insufficient
- Anticoagulants
- Diuretics

SURGERY

Liver transplantation

- In case of fulminant liver failure

Portosystemic shunt

- Divert the flow away from the obstruction
- Transjugular intrahepatic portosystemic shunt (TIPS)
- Surgical shunt

OTHER INTERVENTIONS

Thrombolytic therapy

- Dissolve clots
- Balloon angioplasty

CHOLESTATIC LIVER DISEASE

osms.it/cholestatic-liver-disease

PATHOLOGY & CAUSES

- *Cholestasis:* decrease in bile flow through bile ducts into duodenum
- Hepatic retention, spillage into systemic circulation of cholesterol, bile salts → incorporation into biological membranes → altered membrane fluidity → injury to biological membranes, impaired function of membrane channels → bile secretion impaired in liver
- No bile reaches small intestine → intestinal malabsorption → nutritional deficiencies of fat soluble vitamins (A, D, E, K)

CAUSES

Hepatocellular cholestasis

- Impaired secretion of bile by hepatocytes
  - Intracellular accumulation of bile acids → ↓ regulation of bile synthesis → ↓ total bile production/secretion → accumulation of bile components (e.g. conjugated bilirubin) → diffuse/exocytose into interstitium → diffuse into blood

Elevated levels of estrogen

- Breakdown of cholesterol → cholic acid (bile acid)
- ↑ estrogen → inhibition of export pump → estrogen-induced cholestasis
- Risk factors
  - Oral contraceptives (increase estrogen exposure), pregnancy (pregnancy-induced cholestasis), anabolic steroids (similar in structure to estrogen)
- Extrahepatic cholestasis
  - Physical obstruction blocks bile flow
  - Ductal obstruction → bile accumulates in liver → ↑ pressure in bile ducts → bile leaks through tight junctions between hepatocytes → enters serum, interstitial space
  - *Causes:* cholelithiasis (gallstones), malignancy (biliary tree/head of pancreas), strictures, cystic fibrosis (impaired secretory function of biliary epithelium), primary sclerosing cholangitis (immune system attacks bile ducts → inflammation, scar tissue), biliary atresia (≥ one newborn infant's bile ducts narrow/blocked/absent)
  - *Complications:* prolonged obstruction → biliary cirrhosis; subtotal/intermittent obstruction → ascending cholangitis (secondary bacterial infection of biliary tree) → sepsis, if untreated

SIGNS & SYMPTOMS

- Jaundice
  - Individual components of bile enter serum (e.g. conjugated bilirubin)
- Pain
  - Right upper quadrant (RUQ) pain, radiates to right shoulder, minutes to hours in duration (often after fatty meal)
- Pruritus
  - Systemic accumulation of bile salts/endogenous opioids/lysophosphatidic acid
- Skin xanthomas
  - Focal accumulations of cholesterol (common in obstructive jaundice)
- Pale stools/dark urine
  - Absence of bile in gut → conjugated bilirubin (water soluble) not excreted with bile, excreted via kidneys

DIAGNOSIS

LAB RESULTS

Liver function tests (LFTs)

- Elevated membrane-bound enzymes (sensitive to hepatocyte damage) → ↑ serum alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT)

Histology

- Individual hepatocytes take on brownish-green stippled appearance (due to trapped bile), canalicular bile plugs form between individual hepatocytes/bile ducts (excreted bile cannot travel further due to obstruction)
  - Under sufficient pressure, canalicular plugs may rupture → spillage of bile into surrounding tissue → hepatic necrosis

TREATMENT

MEDICATIONS

- Associated vitamin deficiency
  - Fat-soluble vitamin supplementation
- Children
  - Ursodeoxycholic acid → increased bile formation

SURGERY

- Extrahepatic obstruction
  - Surgical correction of obstruction (e.g. cholecystectomy; if gallstone obstructing common bile duct, removal of gallbladder)

OTHER INTERVENTIONS

- Pregnancy-induced cholestasis
  - Early delivery (around week 36 of gestation)

CIRRHOSIS

osms.it/cirrhosis

PATHOLOGY & CAUSES

- Hepatic parenchyma replaced by scar tissue → scar tissue blocks portal flow of blood through liver → raised blood pressure and disturbance of function
- Reversible phase → hepatitis/fatty liver (steatosis) often precedes cirrhosis
- Long term accumulation of liver damage → disruption of liver architecture → functional impairment
- Develops over months to years
- Damage to parenchyma → activation of stellate cells (sit between sinusoids and hepatocytes in perisinusoidal space) → secretion of
  - TGF-β1 → production of myofibroblasts → increased fibrosis, proliferation of connective tissue
  - TIMP 1 & 2 (matrix metalloproteinase inhibitors) → prevents breakdown of fibrotic material in extracellular matrix
- Fibrotic cascade → formation of fibrous septa → separation of hepatocyte nodules → distortion of liver architecture → decrease blood flow throughout → splenic congestion → hypersplenism, splenic sequestration of platelets
- Injured liver cells group together → regenerative nodules (clumps of cells between fibrotic tissue, collagen) → bumpy cirrhotic liver

RISK FACTORS

- Chronic alcohol use, chronic hepatitis C infection, chronic hepatitis B (+/- hepatitis D) infection, autoimmune hepatitis, hereditary hemochromatosis, Wilson disease, alpha 1-antitrypsin deficiency, medications

COMPLICATIONS

- Portal hypertension, hepatic encephalopathy, increased blood levels of estrogens, hepatocellular carcinoma

MNEMONIC: HEPATIC

Causes of Cirrhosis

Hemochromatosis (primary)

Enzyme deficiency (alpha-1-anti-trypsin)

Post hepatic (infection + drug induced)

Alcoholic

Tyrosinosis

Indigenous people in America (galactosemia)

Cardiac/ **C**holestatic (biliary)/ **C**ancer/ **C**opper (Wilson's)

SIGNS & SYMPTOMS

- Early stages generally asymptomatic
  - Liver may be enlarged, shrinks as cirrhosis progresses
  - Non-specific symptoms: weakness, weight loss, fatigue
- Portal hypertension
- Liver cellular dysfunction
- Nail changes (Muehrcke's lines, Terry's nails, clubbing)
- Hypertrophic osteoarthropathy
- Dupuytren's contracture

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Small nodular liver (advanced cirrhosis), increased echogenicity, irregular- looking areas, widening fissures, splenomegaly, imaging of blood flow in portal vein

Endoscopy

- Esophagogastroduodenoscopy (EGD)
  - Exclude esophageal varices
- Imaging of bile ducts (endoscopic retrograde cholangiopancreatography (ERCP) /magnetic resonance cholangiopancreatography (MRCP))

Diagnostic paracentesis

- Determine ascitic fluid origin
- Portal hypertension
- Suspected spontaneous bacterial peritonitis
  - Cell count, gram stain, culture
  - *Serum:* ascites albumin gradient (SAAG) > 1.1 g/dL → portal HTN

LAB RESULTS

- AST, ALT moderately elevated, AST > ALT
- ALP 2–3x normal
- GGT very high in chronic alcoholic liver disease
- Bilirubin increases as cirrhosis worsens
- Albumin decreases as synthetic function declines
- Prothrombin time increases as synthetic function declines
- Hyponatremia from inability to excrete free water (high levels of antidiuretic hormone, aldosterone)
- Serum biomarkers correlate with degree of liver damage in variety of liver diseases
- A2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, age, biological sex

Histology

- Macroscopic appearance
  - Surface irregular, consistency firm
  - Yellow color (in steatosis)
  - Nodular
- Liver biopsy
  - Microscopic appearance of hepatocytes (regenerating nodules) and fibrosis/ connective tissue deposits between nodules
- Cause specific abnormalities
  - *Chronic hepatitis B:* infiltration of liver parenchyma with lymphocytes
  - *Cardiac cirrhosis:* erythrocytes, greater amount of fibrosis in tissue surrounding hepatic vein
  - *Primary biliary cholangitis:* fibrosis around bile duct, presence of granulomas, pooling of bile
  - *Alcoholic cirrhosis:* neutrophilic infiltration

OTHER DIAGNOSTICS

Child-Pugh score

- Grading of cirrhosis
  - *Class A (5–6 points):* one year survival 100%, two year survival 85%
  - *Class B (7–9 points):* one year survival 81%, two year survival 57%
  - *Class C (10–15 points):* one year survival 45%, two year survival 35%

TREATMENT

MEDICATIONS

- Antiviral medication (e.g. interferon)
  - For hepatitis B, C
- Corticosteroids
  - For autoimmune hepatitis
- Diuretics, antibiotics, laxatives, enemas, thiamine, steroids, acetylcysteine, pentoxifylline
  - For decompensation (compensated cirrhosis—no jaundice, ascites, variceal bleeding, hepatic encephalopathy; development of any of above → decompensated)

OTHER INTERVENTIONS

- Abstain from alcohol
  - For alcoholic hepatitis
- Chelation therapy (e.g. penicillamine)
  - For Wilson disease
- Dissolve gallstones
  - Blockage of bile ducts

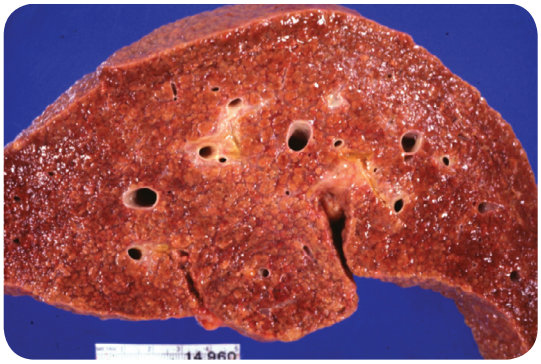

Figure 36.5 Gross pathology of micronodular liver cirrhosis.

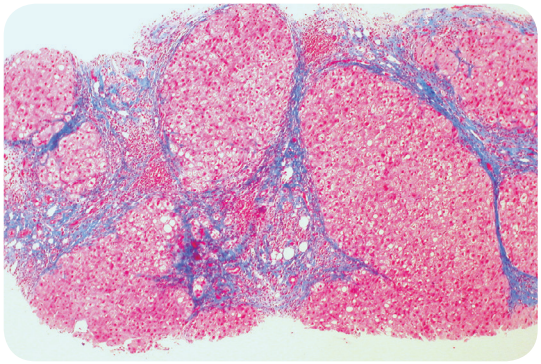

Figure 36.6 Histological appearance of liver cirrhosis (trichrome stain). The blue highlights the bands of fibrosis between islands of hepatocytes.

CHILD-PUGH GRADING OF CIRRHOSIS

	1 POINT	2 POINTS	3 POINTS
TOTAL BILIRUBIN, μmol/L (mg/dL)	< 34 (< 2)	34–50 (2–3)	> 50 (> 3)
SERUM ALBUMIN, g/dL	> 3.5	2.8–3.5	<2.8
PROTHROMBIN TIME, PROLONGATION(S) OR INR	< 4.0 < 1.7	4.0–6.0 1.7-2.3	> 6.0 > 2.3
ASCITES	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
HEPATIC ENCEPHALOPATHY	None	Grade I–II	Grade III–IV

FITZ-HUGH-CURTIS SYNDROME

osms.it/fitz-hugh-curtis-syndrome

PATHOLOGY & CAUSES

- Pelvic inflammatory disease (PID) → inflammation of local structures → anterior liver capsule inflammation (perihepatitis) → patchy purulent, fibrinous exudate → adhesions form

CAUSES

- Etiology of inflammation poorly understood
- Thinning of cervical mucus → bacteria colonizing vagina enters uterus, fallopian tubes → infection, inflammation → possibly spreads via
  - Direct intraperitoneal spread from initial pelvic inflammation and infection
  - Bacterial seeding via lymphatic bloodstream
  - Autoimmune response to PID
- Causative organisms
  - **Commonly:** *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycobacterium tuberculosis* (endemic areas)
  - **Reported:** *Trichomonas vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Bacteroides spp.*, *Gardnerella vaginalis*, *E. coli* and *Streptococcus spp.*

RISK FACTORS

- Biological females of reproductive age

SIGNS & SYMPTOMS

- Vomiting, nausea, hiccupping, headaches
- Acute onset right upper quadrant abdominal pain; aggravated by breathing, coughing, laughing (pleuritic pain), may refer to right shoulder, tenderness to

palpation, tenderness to percussion of overlying ribs
- Fever, chills, night sweats, malaise, vaginal discharge, lower abdominal pain, cervical motion tenderness

DIAGNOSIS

- History of pelvic inflammatory disease

DIAGNOSTIC IMAGING

Abdominal ultrasound
- Typically normal

Abdominal CT scan with contrast
- Perihepatic
  - Subtle enhancement of liver capsule, inflammatory stranding and fluid along right paracolic gutter and perihepatic region, gallbladder wall thickening, pericholecystic inflammatory change
- Pelvic
  - Possible tubo-ovarian abscess

LAB RESULTS
- Liver function tests
  - Typically normal
- D-dimer
  - Markedly raised
  - Often ordered due to pleuritic chest pain
- Endocervical/low vaginal swab
  - Culture causative organism

OTHER DIAGNOSTICS

Laparoscopy
- "Violin string" adhesions of parietal peritoneum to liver/diaphragm

TREATMENT

MEDICATIONS
- Organism-specific antibiotics
- Pain management
  - Appropriate analgesia
  - Laparoscopy for lysis of adhesions for refractory pain

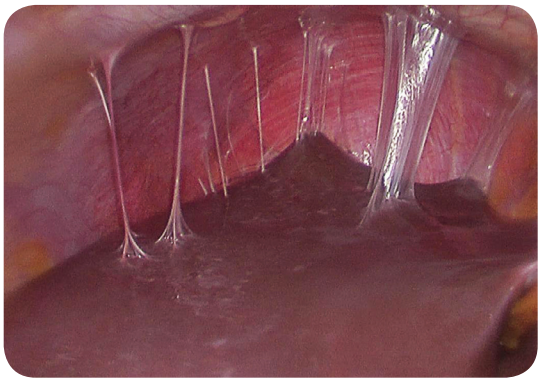

Figure 36.7 A laparoscopic view of intra abdominal adhesions caused by Fitz-Hugh-Curtis syndrome.

HEMOCHROMATOSIS

osms.it/hemochromatosis

PATHOLOGY & CAUSES

- Excessive iron absorption in the intestine → iron deposited in organs and tissues → free radical generation → cellular damage → cell death → tissue fibrosis

TYPES

Primary (hereditary: autosomal recessive)

- Variety of possible mutations (C282Y being the most common) in *HFE* gene on chromosome 6 regulating iron absorption from food → most of the iron in the food is absorbed by enterocytes in the gut and pass into the bloodstream → iron overload

Secondary (not genetic)

- Multiple blood transfusions → erythrocytes contain iron bound to the hemoglobin → heme is released in bloodstream when erythrocytes die after 120 days
- Chronic hemolytic anemias
- Excessive iron intake (very rare)

COMPLICATIONS

- Caused by deposition of iron in tissues
  - *Liver:* cirrhosis, cancer
  - *Pancreas:* altered endocrine and exocrine function
  - *Skin:* bronze pigmentation
  - *Heart:* cardiomyopathy, arrhythmias
  - *Gonads (related to impaired pituitary function):* amenorrhea in biologically-female individuals, testicular atrophy in biologically-male individuals
  - *Adrenal gland:* gland insufficiency
  - *Joints:* degenerative joint disease

SIGNS & SYMPTOMS

- Initially asymptomatic
  - *Biogically male:* symptoms appear around age 50
  - *Biologically female:* eliminate iron through menstrual bleeding → symptoms appear 10-20 years after menopause
- Signs and symptoms of liver disease
- Altered glucose homeostasis (hyper/hypoglycemia)
- Fatigue
- Arthralgia
- Sexual dysfunction
- Abdominal pain
- Cardiac arrhythmias

DIAGNOSIS

LAB RESULTS

- High levels of serum iron
- Elevated ferritin
- High transferrin saturation
- Decreased total iron binding capacity

Liver biopsy

- Iron can be seen as brown spots inside hepatocytes → it becomes blue with a Prussian blue stain

OTHER DIAGNOSTICS

- Genetic analysis and screening of family members

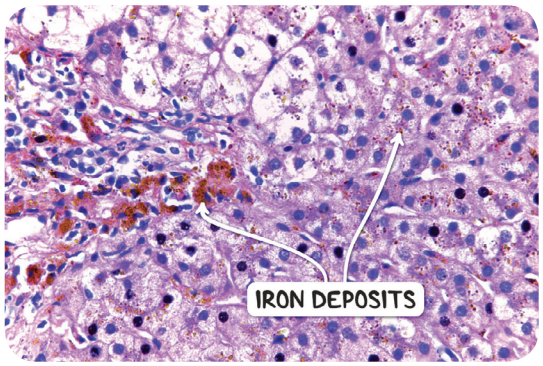

Figure 36.8 Iron deposition (hemosiderosis) in the liver parenchyma in a case hemochromatosis. There is associated hepatocyte damage.

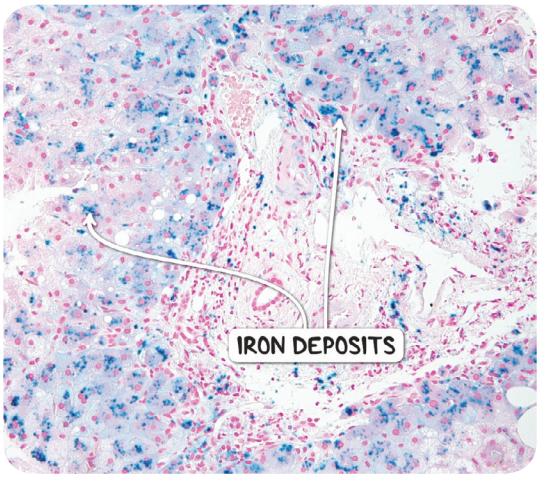

Figure 36.9 Prussian blue stain on a liver biopsy highlights iron deposits in a case of hemochromatosis.

TREATMENT

MEDICATIONS

Deferoxamine

- Chelating agent binds iron molecules → deferoxamine excreted by kidneys → urine excretion → decreases iron load

SURGERY

- Advanced liver damage → transplantation

OTHER INTERVENTIONS

- Phlebotomy
- Dietary changes to reduce iron absorption

HEPATITIS B

osms.it/hepatitis

PATHOLOGY & CAUSES

- Infection of the liver caused by hepatitis B virus (HBV)
- DNA virus from the hepadna group
- Incubation is 1–6 months, long term carrier state established after, transmitted through blood or semen
- Immune system attacks infected hepatocytes

RISK FACTORS

- Intravenous drug users, unprotected sexual intercourse, blood transfusions; hemodialysis

COMPLICATIONS

- Liver cirrhosis, hepatocellular carcinoma

SIGNS & SYMPTOMS

- General infection
  - Low grade fever, malaise, lethargy, anorexia
- Liver related
  - Fatty stool, dark urine, jaundice, hepatomegaly, scleral icterus, pruritus, right upper quadrant tenderness

DIAGNOSIS

LAB RESULTS

- HBV virions found in blood serum, proves viral replication
- ↑ ALT, ↑ AST
- ↑ CRP, ↑ ESR, ↑ WBC
- HBsAg (surface antigen); present in acute infection then cleared in recovery; if present over six months → chronic infection; used to create vaccine
- Anti-HBc IgM (core antigen); present in active infection for six months; if present longer individual is carrier; used for screening because present most of the time
- Anti-HBc IgG develop after IgM, lifelong secretion indicates individual is immune
- Anti-HBe secreted core antigen, appears during viral replication, indicates active infection
- Bilirubin normal to increased

OTHER DIAGNOSTICS

- Physical exams shows hepatomegaly

TREATMENT

MEDICATIONS

- Interferon alpha, nucleoside reverse transcriptase inhibitors (NRTI)
- Post exposure prophylaxis available with HBV immunoglobulins
- Vaccine available

HEPATITIS C

osms.it/hepatitis

PATHOLOGY & CAUSES

- Viral hepatitis caused by hepatitis C virus (HCV)
- RNA virus from the class of flaviviridae
- Incubation is 6–7 weeks, lifelong infectious carrier state
- Virus mutates often to bypass the host immune system
- Minority of individuals develop acute hepatitis symptoms, due to this majority progress to chronic infection

RISK FACTORS

- Intravenous drug use, sexual contact, from mother to child in neonatal period (vertical transmission); chronic hemodialysis

COMPLICATIONS

- Cirrhosis, hepatocellular carcinoma, renal dysfunction (HCV immune complexes involved in pathogenesis)

SIGNS & SYMPTOMS

- General infection
  - Low grade fever, malaise, lethargy, anorexia
- Liver related
  - Fatty stool, dark urine (iron), jaundice, hepatomegaly, icterus, pruritus

DIAGNOSIS

LAB RESULTS

- Enzyme-linked immunosorbent assay (ELISA) used to detect antibodies in chronic cases, may be false negative in immunosuppressed
- Specific hepatitis C antigens immunoassay
- HCV RNA test with PCR
- ↑ ALT
- ↑ CRP, ↑ ESR, ↑ WBC

OTHER DIAGNOSTICS

- Physical exam shows enlarged liver

TREATMENT

MEDICATIONS

- Interferon alfa, ribavirin
- Screen for HBV, HIV and HAV; vaccinate against HBV and HAV if tests are negative
- No HCV vaccine available

SURGERY

- Liver transplant in case of liver failure

HEPATITIS E

osms.it/hepatitis

PATHOLOGY & CAUSES

- Viral hepatitis caused by hepatitis E virus (HEV)
- RNA virus from the class hepeviridae
- Transmitted via fecal-oral route

RISK FACTORS

- Consuming contaminated food and water in endemic areas, blood transfusions, from mother to child in neonatal period

COMPLICATIONS

- Rare but if present then cholestatic hepatitis, chronic infection in immunosuppressed individuals, liver failure, high mortality rate in pregnant individuals

SIGNS & SYMPTOMS

- General infection
  - Low grade fever, malaise, lethargy, anorexia
- Liver related
  - Fatty stool, dark urine (iron), jaundice, hepatomegaly, icterus, pruritus
- Other
  - Diarrhea, arthralgia, urticarial rash

DIAGNOSIS

LAB RESULTS

- Anti - HEV IgM assay in acute infection, PCR in chronic cases
- ↑ ALT
- ↑ CRP, ↑ ESR, ↑ WBC

OTHER DIAGNOSTICS

- Physical exam shows enlarged liver

TREATMENT

MEDICATIONS

- Ribavirin used in immunosuppressed individuals

SURGERY

- Liver transplant in case of liver failure

HEPATOCELLULAR ADENOMA

osms.it/hepatocellular-adenoma

PATHOLOGY & CAUSES

- Rare, benign liver tumor
- Formed from hepatic epithelial cells, often in healthy liver
  - Enlarged, nonfunctional epithelial cells
  - More glycogen, lipids than expected
  - Surrounding tissue highly vascularized
  - Bile ducts, portal triads absent

CAUSES

- Exact mechanisms unknown; associated with estrogen-based drugs: oral contraceptives, anabolic steroids
- Genetic diseases
  - *Glycogen storage disease type I (von Gierke's disease):* glucose cannot be generated from glycogen via gluconeogenesis

RISK FACTORS

- Diabetes, metabolic syndrome, obesity

COMPLICATIONS

- Rupture, bleeding; malignant transformation (rare)

SIGNS & SYMPTOMS

- Usually asymptomatic
- Abdominal pain (esp. epigastric/RUQ), palpable mass
- If adenoma ruptures, bleeds
  - Hypotension, tachycardia, diaphoresis

DIAGNOSIS

DIAGNOSTIC IMAGING

- Often incidental finding on abdominal imaging

Ultrasound

- Solitary well-demarcated heterogeneous mass with variable echogenicity

CT scan

- Well-marginated isoattenuating hepatic lesions; fat content → hypoattenuation

LAB RESULTS

Histology (definitive)

- Well-circumscribed nodules
  - Sheets of hepatocytes with bubbly vacuolated cytoplasm
- Lack portal tracts/central veins

TREATMENT

SURGERY

- Surgical resection

OTHER INTERVENTIONS

- Estrogen-associated
  - Cessation of estrogen-based medication → adenoma regression
- Von Gierke's disease
  - Strict dietary management → adenoma regression

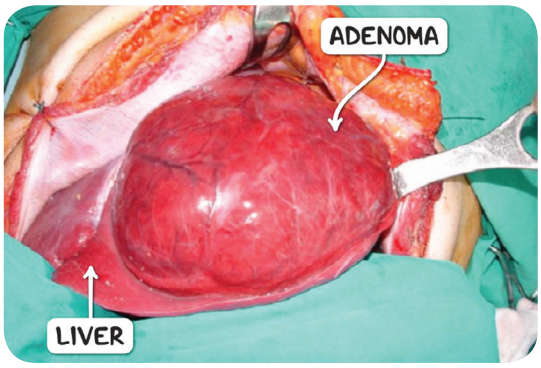

Figure 36.10 Intraoperative photograph of a large, well-circumscribed hepatocellular adenoma of the left lobe of the liver. There is a rim of normal liver surrounding the adenoma. The right lobe of the liver is just visible to the left of the image.

NEONATAL HEPATITIS

osms.it/neonatal-hepatitis

PATHOLOGY & CAUSES

- Inflammation of liver in newborns (usually 1–2 months after birth)

CAUSES

- Viruses (20%)
  - Infect mother during pregnancy/baby shortly after birth
  - Rubella; *Cytomegalovirus* (CMV); hepatitis A,B,C
- Idiopathic (80%)
  - Unknown origin
  - Viral
  - Neonatal cholestasis
  - Newborn bile production immature → ↓ bile production
  - Developing liver more sensitive to injury → ↓ bile synthesis, flow
- Genetic
  - *Alpha 1-antitrypsin deficiency:* malformation → cannot be transported out of hepatocytes → accumulation within cells → cell death → hepatitis

COMPLICATIONS

- If untreated > six months
  - Chronic liver disease → hepatic cirrhosis → liver failure

SIGNS & SYMPTOMS

- Jaundice, pruritus, rashes, dark urine, pale stools, hepatomegaly (due to liver inflammation)
- Decreased intestinal bile flow → impaired fat digestion, vitamin absorption → failure to grow

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Check bile ducts for obstruction, correct development

LAB RESULTS

Liver biopsy

- Multinucleated giant cells
  - Arise from combination of neighboring cells (hepatocytes)
  - Signs of cholestatic liver disease

Blood tests

- ↑ serum bilirubin

TREATMENT

MEDICATIONS

- Ursodeoxycholic acid
  - Increase bile formation

SURGERY

- Cirrhotic liver disease/liver failure requires liver transplant

OTHER INTERVENTIONS

- Optimize nutrition/vitamin supplementation

NON-ALCOHOLIC FATTY LIVER DISEASE

osms.it/non-alcoholic-fatty-liver

PATHOLOGY & CAUSES

- Disease due to fat accumulation in liver, associated inflammation

TYPES

Non-alcoholic fatty liver (NAFL)

- Steatosis without inflammation

Non-alcoholic steatohepatitis (NASH)

- Steatosis with hepatic inflammation, indistinguishable from alcoholic steatohepatitis

Subtype

- Liver steatosis without evident secondary cause (e.g. chronic alcohol use/persistent viral infection)
  - Liver large, soft, yellow greasy
  - Bloating, hepatocyte necrosis
  - Mallory–Denk bodies
  - Damage attracts neutrophils → more inflammation
  - Inflammation → hepatic stellate cells activate → fibrosis → cirrhosis

NAFL → NASH

- Second hit hypothesis
  - Initial fatty change benign → oxidative stress, hormonal imbalances, mitochondrial abnormalities → progression
- Hepatocytic fat vulnerable to degradation
  - *Unsaturated fatty acids:* ≥ one double bond, hydrogen atoms vulnerable to initiators (e.g. reactive oxygen species)
  - Process damages cell lipid membranes → mitochondrial dysfunction → cell death → inflammation → steatohepatitis (NASH)

RISK FACTORS

- NAFL → NASH
  - Age > 50
  - BMI ≥ 28kg/m^2 (5.7lbs/ft^2)
  - Diabetes mellitus
  - Elevated serum aminotransferases
  - Ballooning degeneration, Mallory–Denk bodies or fibrosis on biopsy
- NAFL (general)
  - Insulin resistance, metabolic syndrome,
  - ≥ *Three of:* obesity, hypertension,

diabetes, hypertriglyceridemia, hyperlipidemia, excessive soft drink consumption (high concentration of fructose), diet rich in saturated fats, medications (corticosteroids)

COMPLICATIONS

- Liver cirrhosis, hepatocellular carcinoma

SIGNS & SYMPTOMS

- Usually asymptomatic
- Fatigue, malaise, dull right upper quadrant pain, mild jaundice (rare), significant liver damage → hepatomegaly, ascites

DIAGNOSIS

- Typically diagnosed as incidental finding on liver function panel

DIAGNOSTIC IMAGING

- Identify fatty infiltrates

Ultrasound

- Increased echogenicity → bright appearing liver → diffuse fatty infiltration

CT scan

- Decreased hepatic attenuation

MRI

- Increased fat signal

LAB RESULTS

- Destruction of hepatocytes → increase in liver enzymes AST/ALT
- Serum ALT > AST level = NAFL

Liver biopsy

- > 5% fat content → NAFL
- Iron deposits
- NAFL
  - Steatosis alone
  - Steatosis with lobular/portal inflammation without hepatocyte ballooning
  - Steatosis with hepatocyte ballooning but without inflammation
- NASH
  - Hepatocyte ballooning degeneration, hepatic lobular inflammation, apoptotic bodies, mild chronic portal inflammation, perisinusoidal collagen deposition → zone 3 accentuation (chicken wire pattern), portal fibrosis without perisinusoidal or pericellular fibrosis, cirrhosis (macronodular or mixed), Mallory–Denk bodies, megamitochondria, vacuolated nuclei in periportal hepatocytes

OTHER DIAGNOSTICS

- Alcohol consumption > 25 ml/day pure ethanol excludes diagnosis

TREATMENT

OTHER INTERVENTIONS

Dietary changes

- Avoid high fructose-corn syrup, trans-fats
- Omega 3 fatty acid supplementation → improvement in liver fat deposition
- Coffee and olive oil consumption may be protective

Treat insulin resistance

- Weight-loss
- Insulin sensitizers

Treat hyperlipidemia

- Statins

PORTAL HYPERTENSION

osms.it/portal-hypertension

PATHOLOGY & CAUSES

- Elevation of blood pressure in the portal venous system above 5mmHg

CAUSES

Prehepatic causes

- Portal vein obstruction (e.g. thrombosis)

Intrahepatic causes

- Cirrhosis (most common of all causes)
- Schistosomiasis
- Sarcoidosis

Posthepatic causes

- Right-sided heart failure
- Constrictive pericarditis
- Budd–Chiari syndrome

COMPLICATIONS

- Portosystemic shunts and development of collateral channels
  - Esophageal varices
  - Hemorrhoids
  - Caput medusae (distension of abdominal wall veins)
- Increased hydrostatic pressure and hypoalbuminemia → ascites
- Splenomegaly (blood drainage backs up to spleen due to high pressure portal system) → sequestration of blood elements → anemia, thrombocytopenia, leukopenia
- Liver disease and blood shunting away from liver → decreased blood detoxification → increased ammonia in the blood → encephalopathy
- Spontaneous bacterial peritonitis

SIGNS & SYMPTOMS

- GI bleeding (secondary to esophagogastric varices) → most life-threatening complication
  - Hematemesis
  - Melena
- Jaundice
- Ascites
- Periumbilical caput medusae
- Signs and symptoms of encephalopathy
  - Altered level of consciousness
  - Lethargy
  - Hand tremor when the wrist is extended (aka asterixis)
  - Seizure, coma and death

DIAGNOSIS

DIAGNOSITC IMAGING

Liver ultrasound

- Nodules in case of cirrhosis

CT scan, MRI

- Ascites
- Cirrhosis
- Splenomegaly
- Vascular alteration such as inferior vena cava dilatation

LAB RESULTS

- Full blood count
- Liver enzymes and serology
- Perform emergent upper GI endoscopy, to diagnose/treat varices

OTHER DIAGNOSTICS

Diagnostic paracentesis

- Will determine if ascites is due to portal HTN or other etiology
- Serum ascites albumin gradient (SAAG) > 1.1 mg/dL
  - Portal HTN is likely

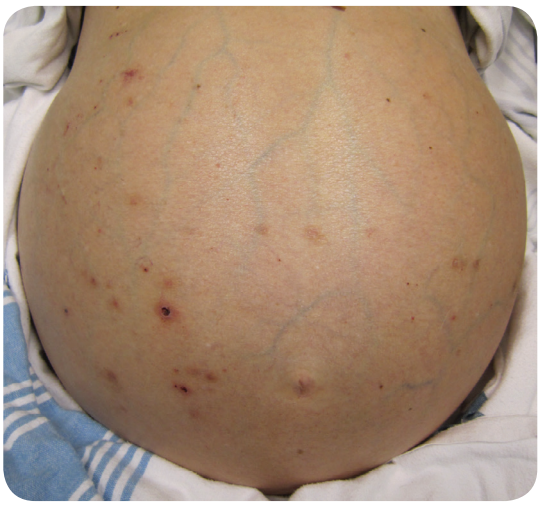

Figure 36.11 Ascites as a consequence of portal hypertension caused by cirrhosis of the liver.

MNEMONIC: ABCDE

Features of Portal hypertension

Ascites
Bleeding (haematemesis, piles)
Caput medusae
Diminished liver
Enlarged spleen

TREATMENT

- Prevent and treat the complications

MEDICATIONS

- Beta-blockers
  - → decrease portal venous pressure
- IV octreotide
  - If bleeding, non-selective beta blockers (prophylaxis), antibiotics (prophylaxis for spontaneous bacterial peritonitis)
  - For esophageal varices
- Diuretics and sodium restriction
  - For ascites

SURGERY

- Transjugular intrahepatic portosystemic shunt
  - Communication between portal vein and hepatic vein → blood bypasses the liver circulation → reduced intrahepatic pressure
- Balloon tamponade, sclerotherapy, variceal ligation/banding
  - For esophageal varices

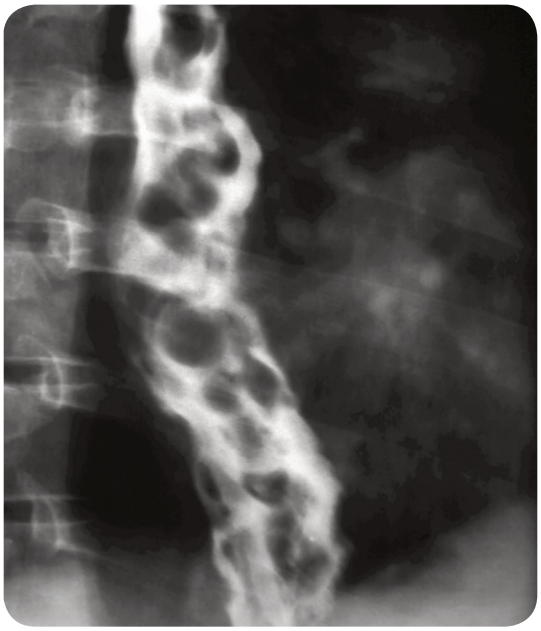

Figure 36.12 Barium swallow demonstrating esophageal varices.

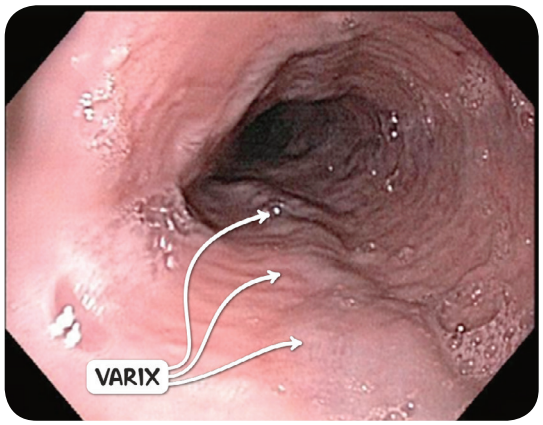

Figure 36.13 Endoscopic appearance of esophageal varices.

PRIMARY BILIARY CIRRHOSIS

osms.it/primary-biliary-cirrhosis

PATHOLOGY & CAUSES

- Autoimmune disease of liver → progressive destruction of cells lining small intrahepatic bile ducts → leakage of bile, toxins into liver parenchyma, blood → inflammation, fibrosis → cirrhosis
- AKA primary biliary cholangitis

CAUSES

- Failure of immune tolerance against mitochondrial pyruvate dehydrogenase complex (PDC-E2), other hepatic proteins → destruction of cells lining bile ducts → autoimmunity

RISK FACTORS

- Biological female, family history of disease, extrahepatic autoimmune disease
  - Previous infection with environmental gram-negative Novosphingobium aromaticivorans → cross-reaction between bacterial antigens, hepatic mitochondrial proteins

COMPLICATIONS

- Osteoporosis, hyperlipidemia, fat soluble vitamin deficiencies

SIGNS & SYMPTOMS

- Fatigue, pruritus, jaundice, right upper quadrant pain
- Loss of bone density → fractures
- Hypercholesterolemia → xanthelasma, xanthoma
- Liver cirrhosis → ascites, splenomegaly, esophageal varices, hepatic encephalopathy

DIAGNOSIS

DIAGNOSTIC IMAGING

Abdominal ultrasound/MRCP/CT scan

- Rule out bile duct obstruction

LAB RESULTS

- Antimitochondrial antibodies (most individuals)

- Other autoantibodies may be present
  - Antinuclear antibody, anti-glycoprotein-210 antibodies, anti-p62 antibodies (suggests more severe disease → liver failure), anticentromere antibodies (correlates with developing portal hypertension), anti-np62 and anti-sp100
- Elevated IgM, total cholesterol, HDL, GGT, ALP (released from damaged bile ducts), bilirubin = advanced disease

Liver biopsy (percutaneous/laparoscopic)

- Interlobular bile duct destruction, bile duct inflammation (intraepithelial lymphocytes), periductal epithelioid granulomas

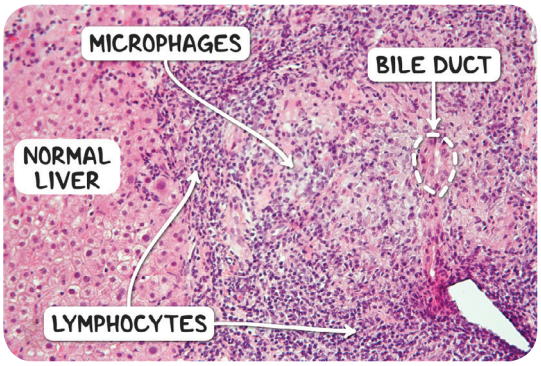

Figure 36.14 The histological appearance of primary biliary cirrhosis. The bile duct is surrounded by epithelioid macrophages which in turn are surrounded by a rim of lymphocytes, indicative of granulomatous inflammation.

TREATMENT

MEDICATIONS

- Ursodeoxycholic acid
  - Reduces intestinal absorption of cholesterol → reduces cholestasis, improves liver function tests
- Cholestyramine
  - Bile acid sequestrant → reduces bile acid absorption in gut → relieves itching due to bile acids in circulation
- Modafinil
  - For fatigue

OTHER INTERVENTIONS

- Cease all alcohol intake

WILSON'S DISEASE

osms.it/wilsons-disease

PATHOLOGY & CAUSES

- Autosomal recessive mutation in *ATP7B* gene → defect in ATP7B transport protein action in the hepatocyte
- AKA hepatolenticular degeneration
- Reduced copper incorporation into apoceruloplasmin and reduction of its copper-bound form (ceruloplasmin)
- Reduced copper elimination in the bile
- Copper accumulation in hepatocytes → free radical generation → hepatocyte damage → spilling of free copper into the blood → copper accumulation in organs and tissues → free radical generation → tissues damage

COMPLICATIONS

- *Liver:* cirrhosis, liver failure
- *Brain:* movement disorders, dementia, and psychiatric issues
- *Kidney:* renal disease
- *Eye:* Kayser–Fleischer's ring, sunflower cataract
- *Blood:* hemolytic anemia

SIGNS & SYMPTOMS

- Presents at a young age (< 30 years old)
- Signs and symptoms of cirrhosis and portal hypertension (e.g. hepatosplenomegaly, jaundice, ascites, esophageal varices)
- Signs of renal dysfunction
- Parkinsonian-like movement disorders
  - Tremors
  - Rigidity
- Psychiatric illness
  - Depression
  - Personality changes
  - Psychosis
  - Cognitive dysfunctions
- Kayser–Fleischer ring
  - Ring of copper deposition in the cornea (Descemet's membrane)
  - Appears to encircle the iris

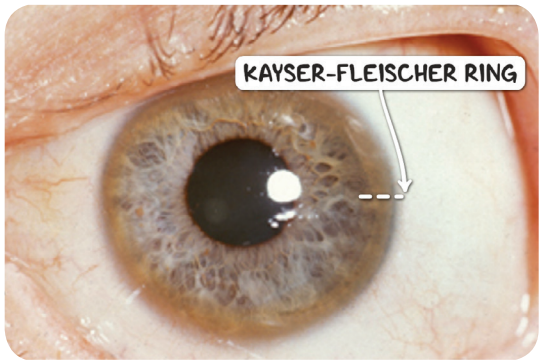

Figure 36.15 Copper deposition in Descemet's membrane of the sclera results in a Kayser–Fleischer ring.

DIAGNOSIS

LAB RESULTS

- Signs of liver dysfunction (e.g. high liver enzymes)
- Low serum ceruloplasmin
- High 24-hour copper excretion

TREATMENT

MEDICATIONS

- Chelating agents → make it easier to excrete copper
  - Penicillamine (penicillin metabolite without antibiotic properties)
  - Trientine hydrochloride
- Agents that block intestinal absorption of copper
  - Ammonium tetrathiomolybdate
  - Zinc

SURGERY

- Advanced liver damage → transplantation

OTHER INTERVENTIONS

- Eliminate copper-rich food (e.g. mushrooms, nuts, shellfish)