Liver cirrhosis

Definition:

Diffuse liver disease characterized by degeneration (hepatocellular necrosis), regeneration nodules, fibrosis and loss of lobular architecture.

Causes:

- Chronic viral hepatitis (B,C,D).
- Autoimmune hepatitis.
- Alcoholic cirrhosis
- Metabolic :NAFLD; Wilson's disease, hemochromatosis and alpha 1 anti-trypsin deficiency.
- Cholestasis (chronic): If prolonged, it may be end by biliary cirrhosis as PBC
- Heart failure and constrictive pericarditis may lead to hepatic fibrosis ("cardiac cirrhosis")

Pathogenesis

Although the liver has a remarkable capacity to adapt to injury through tissue repair, chronic injury results in inflammation, matrix deposition, necrosis and angiogenesis, all of which lead to fibrosis

Liver injury causes necrosis and apoptosis, releasing cell contents and reactive oxygen species (ROS).

This activates hepatic stellate cells and tissue macrophages

These cells phagocytose necrotic and apoptotic cells and secrete pro-inflammatory mediators, including transforming growth factor-beta (TGF-ß); this leads to trans differentiation of stellate cells to myofibroblasts and platelet-derived growth factor (PDGF), which stimulates myofibroblast proliferation.

Macrophages degrade scar matrix by secretion of matrix metalloproteinases (MMPs), but this is inhibited by concurrent myofibroblast and macrophage production of tissue inhibitors of metalloproteinases (TIMPs). This results in progressive matrix deposition and scar accumulation.

Increased gut permeability and hepatic lipopolysaccharide–Toll-like receptor 4 (LPS–TLR4) signalling also promotes fibrogenesis.

Repetitive or chronic injury and inflammation perpetuate this process.

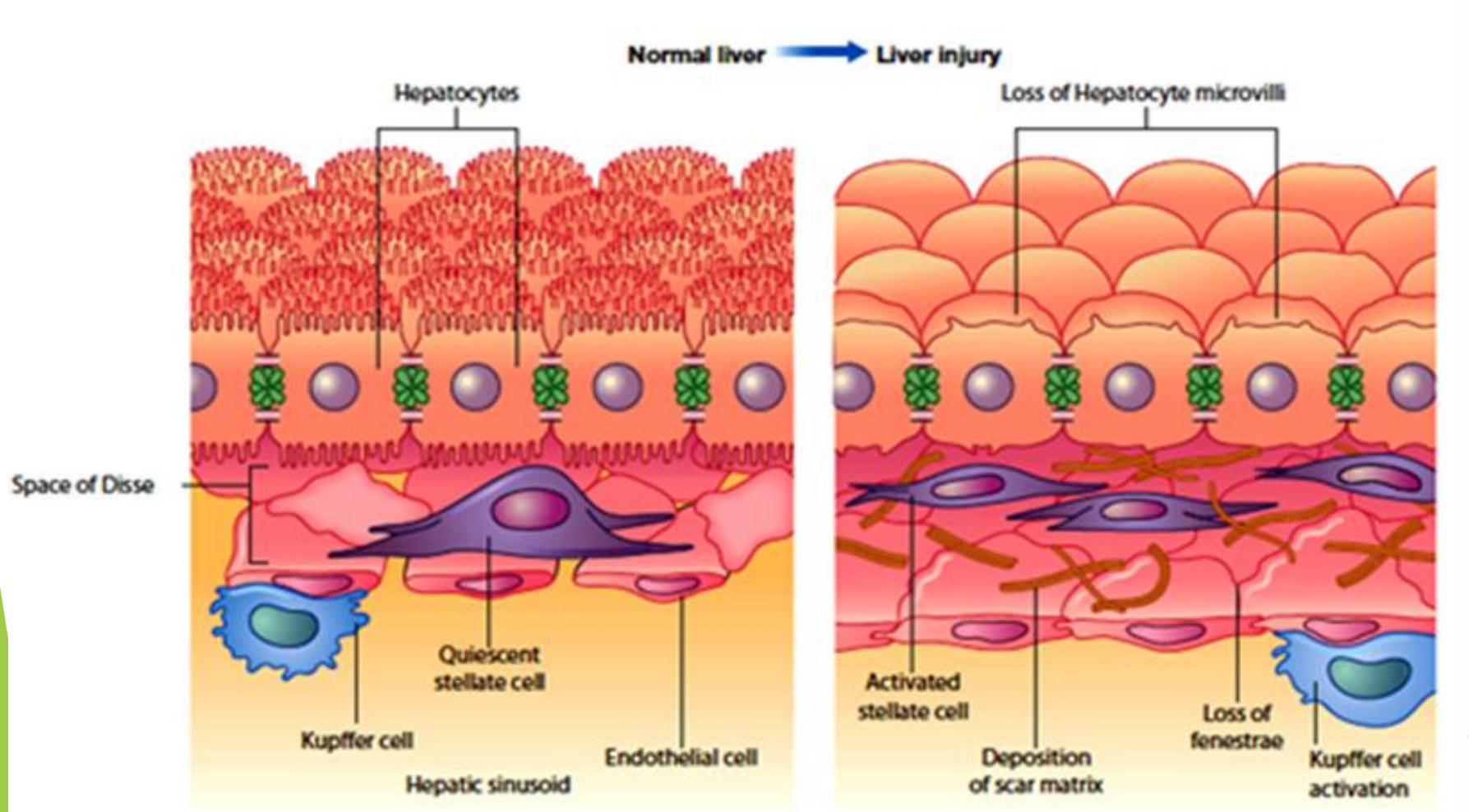
Pathology

The characteristic features of cirrhosis are regenerating nodules separated by fibrous septa, and loss of lobular architecture within the nodules

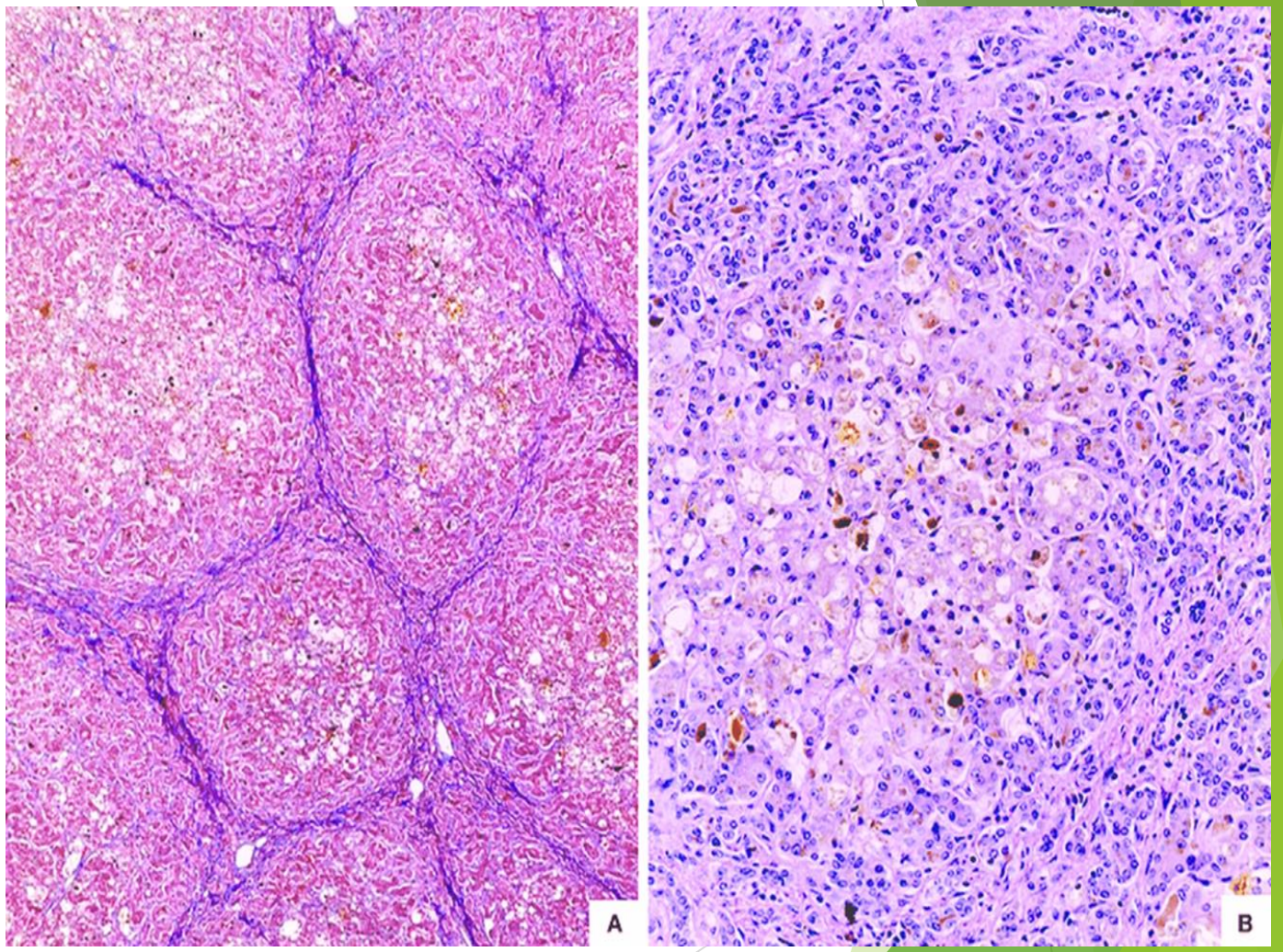
Two types are described:

- **Micronodular cirrhosis.** Regenerating nodules are usually less than 3 mm in size and the liver is involved uniformly.
- This type is often caused by ongoing alcohol damage or biliary tract disease
- **Macronodular cirrhosis.** The nodules are of variable size and normal acini may be seen within the larger nodules
- This type is often seen following chronic viral hepatitis
- **A mixed picture with small and large nodules is sometimes seen**

Hepatic liver cells and the hepatic sinusoid in normal and injured liver.



Regeneration nodules



Clinical picture

A- (Compensated cirrhosis): Discovered accidentally

B- (Decompensated cirrhosis):(ascites, variceal bleeding, encephalopathy, or jaundice).

1- Manifestation of liver cell failure (parenchymal):

The onset of symptoms is usually insidious with development of fatigue, muscle cramps, and weight loss.

- **Anorexia** is usually present and may be extreme, with associated reduced muscle strength and exercise capacity.

- Abdominal pain may be present and is related either to hepatic enlargement and stretching of Glisson capsule or to the presence of ascites

- Hormonal disturbances including menstrual abnormalities (usually amenorrhea), erectile dysfunction, loss of libido, sterility, and gynecomastia.

- -Weight loss occurs in advanced cirrhosis (Spider man appearance).

- **Skin manifestations:** consist of spider telangiectasias (invariably on the upper half of the body), palmar erythema and Dupuytren contractures specially in alcoholic cirrhosis. Evidence of vitamin deficiencies (glossitis and cheilosis) is common. Itchy skin due to increased bilirubin and bile salts, Ecchymotic patches due to thrombocytopenia
- **Jaundice**
- **Ascites**, pleural effusions, peripheral edema.
- **Encephalopathy**: day-night reversal, asterixis, tremor, dysarthria, delirium, drowsiness, and ultimately coma
- **Fever** is present in up to 35% of patients and usually reflects associated alcohol-associated hepatitis, spontaneous bacterial peritonitis, or another infection.

2-Manifestation of portal hypertension :

- **Hematemesis** is the presenting symptom in 15–25% due to development of esophageal varices as a result of portal hypertension .
- **Splenomegaly** usually present.

C- Specific features related to the cause of cirrhosis.

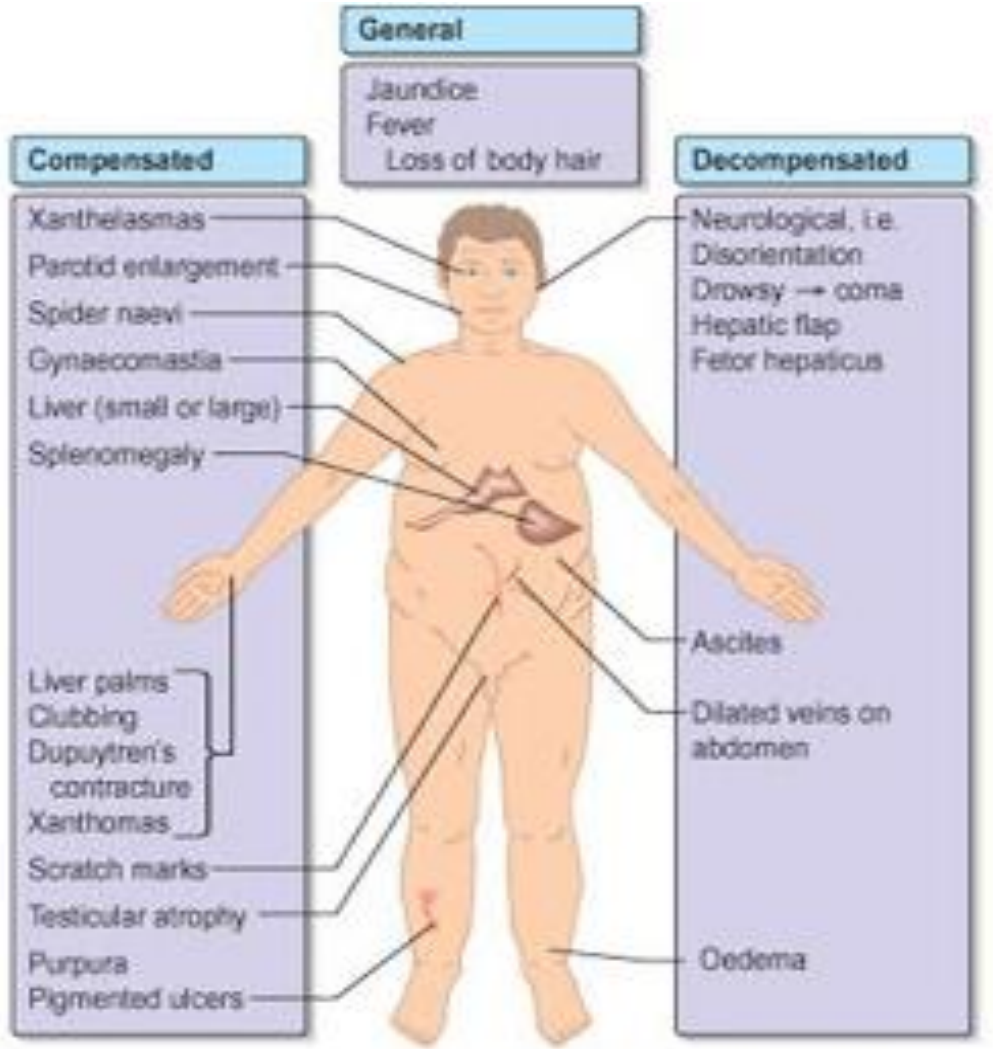
D- Complications:

- Hepatocellular carcinoma,
- Hepatorenal and
- Hepatopulmonary syndrome

Complications

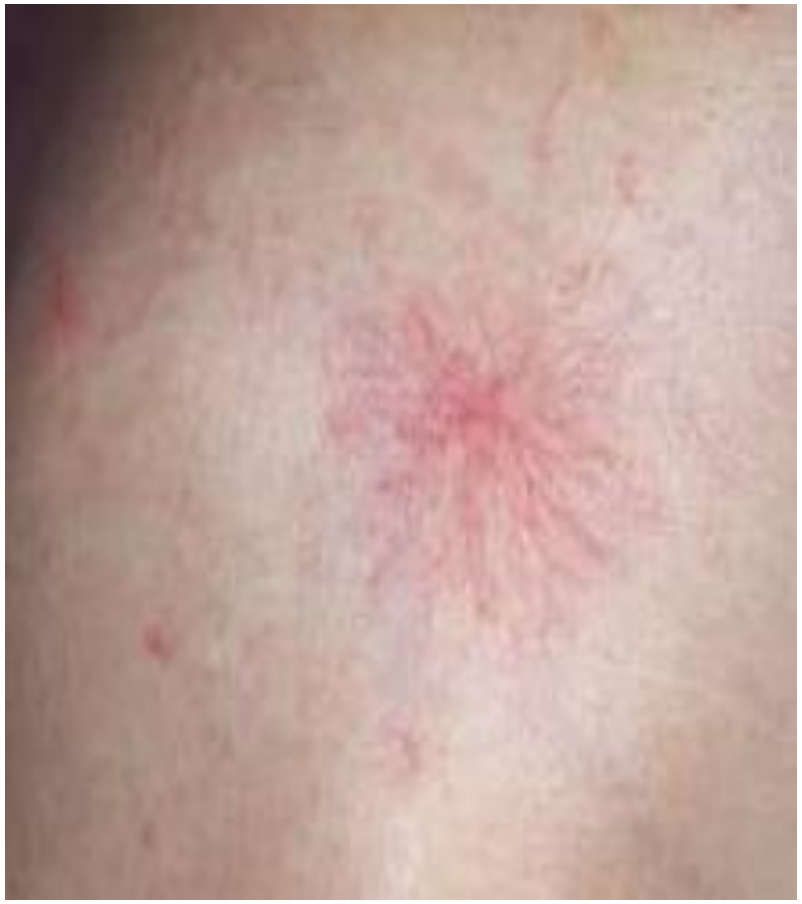
- Portal hypertension
- Variceal bleeding
- Ascites
- Portosystemic encephalopathy
- Spontaneous bacterial peritonitis
- Renal failure (hepatorenal syndrome)
- Hepatopulmonary syndrome
- Primary hepatocellular carcinoma

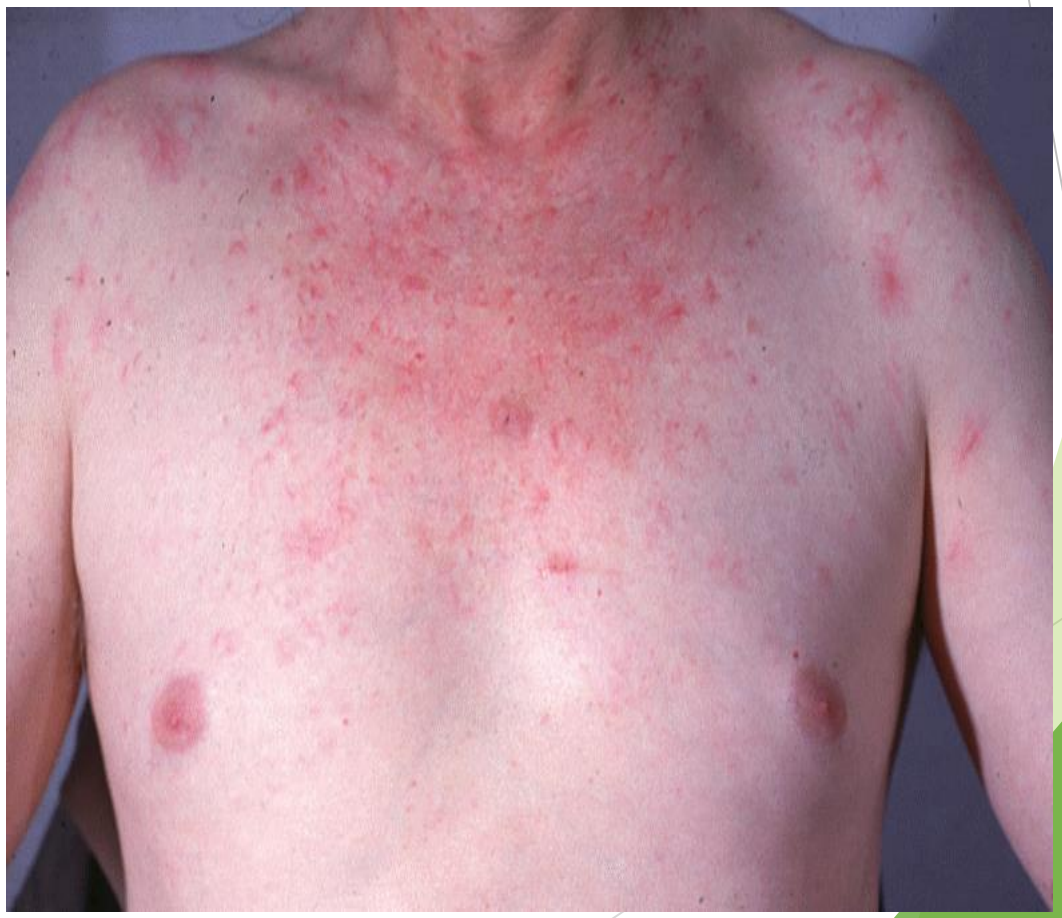
Signs of chronic liver disease



SPIDER NEVI

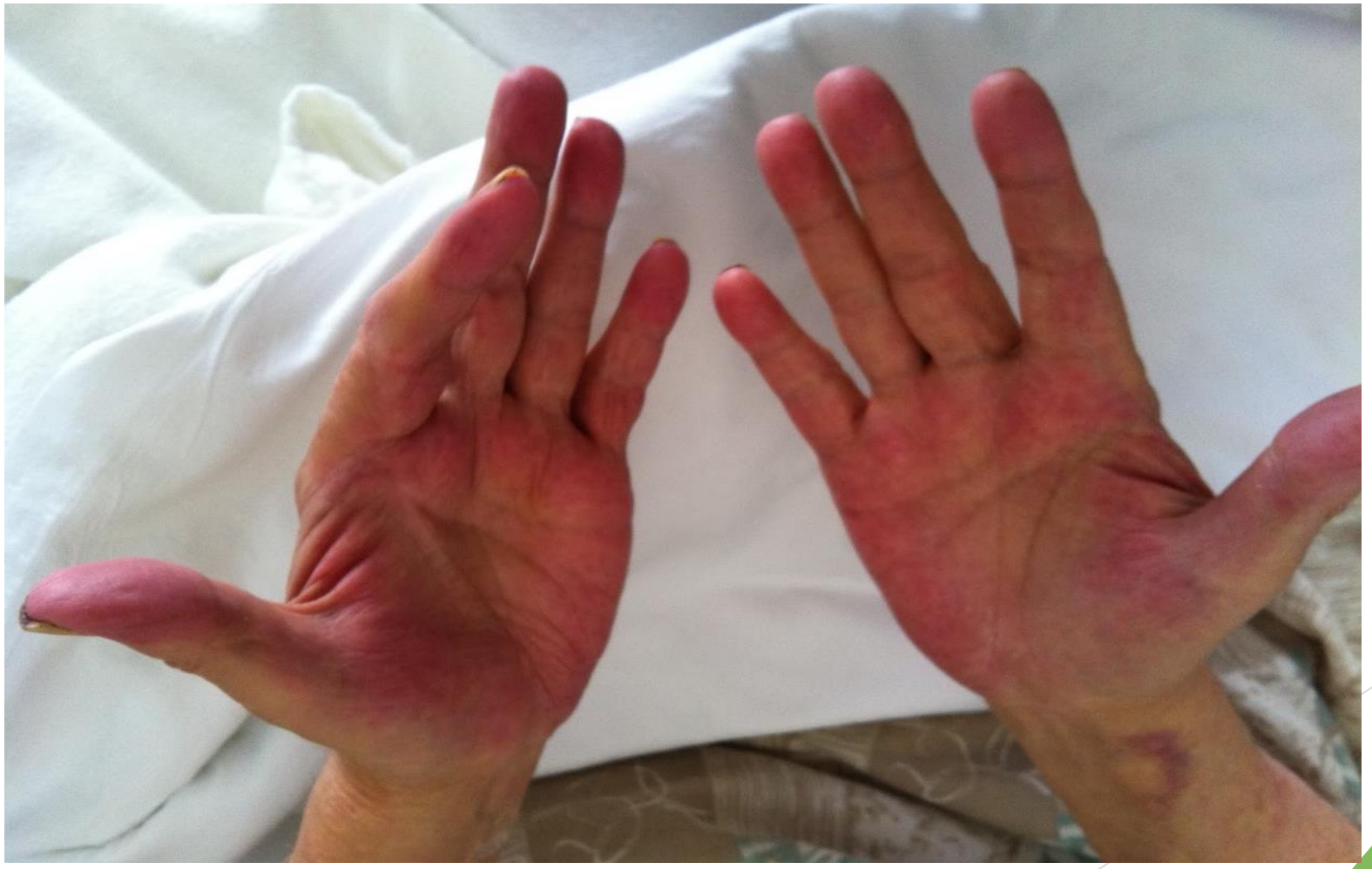
- Telangiectasias that consist of a central arteriole with radiating small vessels. They are found in the distribution of the superior vena cava (above the nipple line)





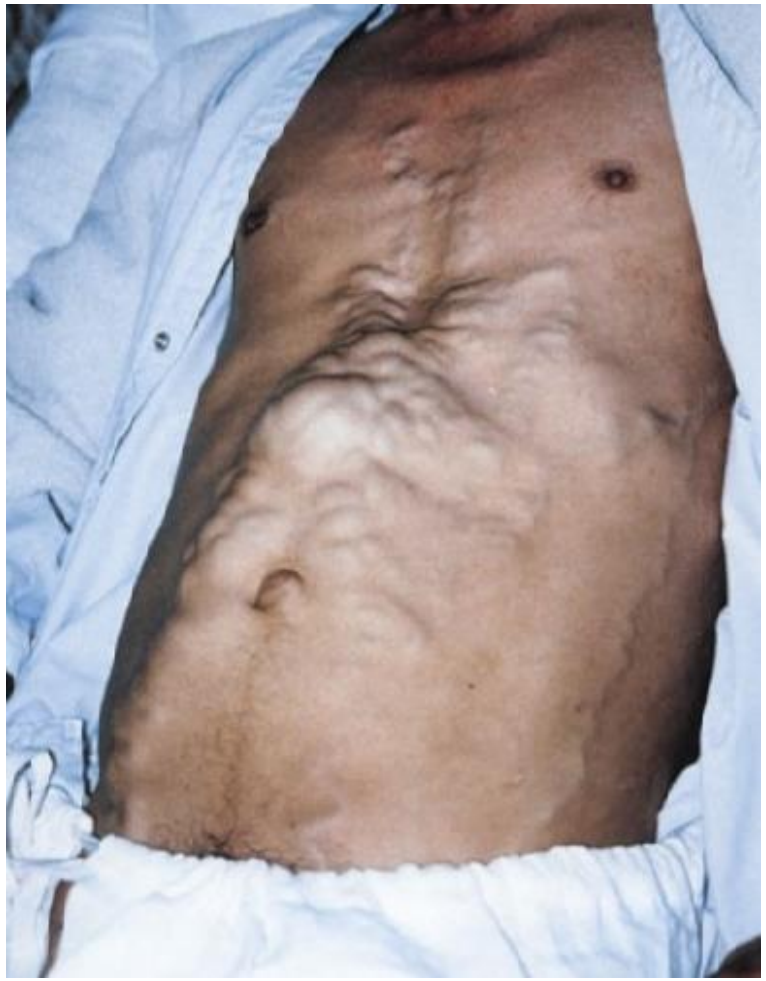
PALMAR ERYTHEMA

- A non-specific change, indicative of a hyperdynamic circulation



DUPUYTREN’S CONTRACTURE

CAPUT MEDUSA



Diagnosis

A- Diagnosis of liver cirrhosis

1- Suggestive:

- Sonar (echogenicity, irregular borders & prominent caudate lobe).
- C.T. scan. .

B-To assess function & complications:

- Laboratory Findings : CBC, L.F.T, PT, PTT, INR ,KFT.

-Upper G.I.T endoscopy

Triphasic CT and dynamic MRI for detecting HCC

N.B: once cirrhosis developed, screening for HCC must be done every 6 months using ultrasound and AFP.

a serum α-fetoprotein of >200ng/mL is strongly suggestive of HCC.

- Anemia: is present in up to 75% of patients. It may be normocytic anemia of chronic disease or due to acute variceal hemorrhage or hypersplenism; microcytic in chronic blood loss due to portal gastropathy; macrocytic due to Vit B12 or folate deficiency.

- - Leukocytic count may be low, reflecting hypersplenism, or high, suggesting infection

- - Thrombocytopenia, the most common cytopenia in cirrhotic patients, is secondary to alcohol-induced marrow suppression, sepsis, folate deficiency, or splenic sequestration

- **C- To find cause**
- -Viral markers (HBsAg, HCV Ab.), auto antibodies & Fe, Cu level

Liver Biopsy

- Widely replaced by the use of ultrasound and fibroelastography along with serologic testing
- Performed to confirm the severity and type of liver disease
- Special stains are required for iron and copper, and various immunocytochemical stains can identify viruses, bile ducts and angiogenic structures
- Chemical measurement of iron and copper is necessary to confirm diagnosis of iron overload or Wilson’s disease

Transient elastography

is increasingly used to avoid liver biopsy .Technical limitations preclude its use in patients with ascites or morbid obesity but it is suitable for most. If the reading is high (>25), portal hypertension is likely, and some experts recommend that endoscopy to identify varices should be restricted to patients with high fibroscan

Score

TABLE 11.1 ■ Etiology and Diagnostic Evaluation of the Common Causes of Cirrhosis

Etiology	Diagnostic Evaluation
Infection	
Hepatitis B	HBsAg, anti-HBs, anti-HBc, HBV DNA
Hepatitis C	Anti-HCV, HCV RNA
Hepatitis D	Anti-HDV
Toxins	
Alcohol	History, AST/ALT ratio, IgA level, liver biopsy
Cholestasis	
Primary biliary cholangitis	AMA, IgM level, liver biopsy
Secondary biliary cirrhosis	MRCP, ERCP, liver biopsy
Primary sclerosing cholangitis	MRCP, ERCP, liver biopsy
Autoimmune	
Autoimmune hepatitis	ANA, IgG level, smooth muscle antibodies, liver-kidney microsomal antibodies, liver biopsy
Vascular	
Cardiac cirrhosis	Echocardiogram, liver biopsy
Budd-Chiari syndrome	CT, US, MRI/MRA
Sinusoidal obstruction syndrome	History of offending drug use, liver biopsy
Metabolic	
Hemochromatosis	Iron studies, *HFE* gene mutation, liver biopsy
Wilson disease	Serum and urinary copper, ceruloplasmin, slit-lamp eye examination, liver biopsy
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin level, protease inhibitor type, liver biopsy
NASH	History, risk factors (obesity, diabetes mellitus, hyperlipidemia), liver biopsy
Cryptogenic	Exclude NASH, celiac disease, drugs

AMA, Antimitochodrial antibodies; *anti-HBc,* antibody to hepatitis B core antigen; *anti-HBs,* antibody to hepatitis B surface antigen; *anti-HCV,* antibody to hepatitis C virus; *anti-HDV,* antibody to hepatitis D virus; *AST,* aspartate aminotransferase; *ALT,* alanine aminotransferase; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *HBsAg,* hepatitis B surface antigen; *IgA,* immunoglobulin A; *IgM,* immunoglobulin M; *MRCP,* magnetic resonance cholangiopancreatography; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *NASH,* nonalcoholic steatohepatitis; *US,* ultrasonography.

treatment

A- Treatment of liver cell failure and portal hypertension.

-Liver transplantation in appropriate candidates is curable

B-Treatment of the cause if curable: Ex. hemochromatosis & Wilson.

C-Treatment of decompensation consequence or complications

1. Ascites and edema 2- Bleeding varices.

3-. Spontaneous bacterial peritonitis 4-. Hepatorenal syndrome

5. Hepatic encephalopathy

6-Hepatopulmonary syndrome Long-term oxygen therapy is recommended for severely hypoxemic patients.

7- Hepatocellular carcinoma

Course and Prognosis

- This is extremely variable, depending on many factors, including the aetiology and the presence of complications
- Development of any complication usually worsens the prognosis
- In general, the 5-year survival rate is approximately 50%, but this also varies depending on the aetiology and the stage at which the diagnosis is made
- There are a number of prognostic classifications based on modifications of Child's grading (A, B and C) and the model for end-stage disease (MELD), based on serum bilirubin, creatinine and INR, which is widely used as a predictor of mortality in patients awaiting liver transplantation.

Child-Pugh classification of cirrhosis[2]

Factor	Units	1	2	3
Serum bilirubin	µmol/L mg/dL	<34 <2.0	34-51 2.0-3.0	>51 >3.0
Serum albumin	g/L g/dL	>35 >3.5	30-35 3.0-3.5	<30 <3.0
Prothrombin time	Second prolonged INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

Child-Pugh class assignment[2]

Total Points	Class	Liver Status
5-6	A	Compensated
7-9	B	Decompensated
10-15	C	Decompensated

Poor Prognostic Indicators in Cirrhosis

Blood tests

- Low albumin (< 28 g/L)
- Low serum sodium (< 125 mmol/L)
- Prolonged prothrombin time > 6 seconds above normal value
- Raised creatinine > 130 µmol/L

Clinical

- Persistent jaundice
- Poor response to therapy
- Ascites
- Variceal hemorrhage
- Neuropsychiatric complications developing with progressive liver failure
- Small liver
- Persistent hypotension

Ascites

Ascites, fluid within the peritoneal cavity, is a common complication of cirrhosis. Several factors underlie its pathogenesis:

- Sodium and water retention results from peripheral arterial vasodilation (secondary to nitric oxide, atrial natriuretic peptide and prostaglandins), which causes a reduction in the effective blood volume. This reduction activates the sympathetic nervous system and the renin–angiotensin system, promoting salt and water retention
- Portal hypertension exerts a local hydrostatic pressure, leading to increased hepatic and splanchnic production of lymph, and transudation of fluid into the peritoneal cavity.
- Low serum albumin (due to poor liver function) may further contribute by reducing plasma oncotic pressure.

Investigations

A diagnostic aspiration of 10–20mL of fluid should be obtained for:

• Cell count. A neutrophil count >250cells/mm3 is indicative of an underlying (usually spontaneous) bacterial peritonitis.

• Gram stain and culture.

• Protein measurement. A high serum–ascites albumin gradient of >11g/L suggests portal hypertension, while a low gradient of is associated with non-liver disease-related abnormalities of the peritoneum, such as neoplasia

Cytology. A search should be made for malignant cells.

• Amylase. Pancreatic ascites should be excluded.

ASCITES

Serum-Ascites Albumin Gradient

$[Albumin]_{Serum} - [Albumin]_{Ascites}$

High (≥1.1 g/dL)	Low (<1.1 g/dL)
Cirrhosis; alcoholic hepatitis	Peritoneal carcinomatosis
Cardiac disease	Tuberculous peritonitis
Massive liver metastases	Pancreatic duct leak
Fulminant hepatic failure	Biliary leak
Hepatic outflow block	Nephrotic syndrome
Portal vein thrombosis	Serositis

Management

The aim is both to reduce sodium intake and to increase renal sodium excretion, producing a net reabsorption of fluid from the ascites into the circulating volume. The maximum rate at which ascites can be mobilized is 500–700mL in 24 hours (see later).

• Serum electrolytes, creatinine and estimated glomerular filtration rate (eGFR). Check on alternate days; weigh the patient and measure urinary output daily.

• Bed rest. This will cause a diuresis by improving renal perfusion but is rarely helpful.

• Dietary sodium restriction. It is possible to reduce sodium intake to 40mmol in 24 hours and still maintain an adequate protein and calorie intake with a palatable diet.

- Drugs. Many contain significant amounts of sodium (up to 50mmol daily). Examples include antacids and antibiotics (particularly penicillins and cephalosporins). Sodium-retaining drugs (NSAIDs, corticosteroids) should be avoided.

Fluid restriction. This is unnecessary unless the serum sodium is below 125 mmol/L

Diuretics

Diuretics Most patients require diuretics in addition to sodium restriction

Spironolactone (100-400 mg/day): is the first-line drug because it is a powerful aldosterone antagonist

side effect :painful gynaecomastia and hyperkalaemia

amiloride (5-10 mg/day) can be substitution for spironolactone

loop diuretics, such as furosemide: but these can lead to fluid and electrolyte imbalance and renal dysfunction

Patients who do not respond to doses of 400 mg spironolactone and 160 mg furosemide, or who are unable to tolerate these doses due to hyponatraemia or renal impairment, are considered to have refractory or diuretic-resistant ascites and should be treated by other measures

Paracentesis

First-line treatment of refractory ascites is large-volume paracentesis.

Paracentesis to dryness is safe, provided the circulation is supported with an intravenous colloid such as human albumin (6–8 g albumin for each one liter of aspirated fluid if 5 L removed at once) .

Paracentesis can be used as an initial therapy or when other treatments fail

Spontaneous bacterial peritonitis (SBP)

SBP is the most common type of ascitic fluid infection which occurs in about 10% of cirrhotic patients with ascites.

Pathogenesis:

Causative bacterial flora: - E.coli, pneumococci and klebsiella

Routes of transmission (Bacterial seeding of ascitic fluid):

- Translocation of bacteria through the intestinal wall → >70%

- Hematogenous spread → 50% of cases are accompanied with bacteremia (sometimes the organism cultured from urine or sputum)

Risks for ascitic fluid infection:

A prior episode of SBP: the most important risk factor (2/3 of patients will develop a recurrence within the following year.

- GIT bleeding (esp. variceal hemorrhage).

- Ascitic fluid total protein < 1 g/dl -Proton pump inhibitors usage.

Treatment of SBP:

- Third generation cephalosporins: Is the recommended treatment for 5- 7 days. - Alternative drugs → amoxicillin-clavulanic acid & fluroquinolones.

Prophylaxis of ascitic fluid infection indicated in:

- High risk for development of SBP [Previous episode of SBP, GIT bleeding, Ascitic fluid total protein < 1g/dl during hospitalization]

- I.V. ceftriaxone, Norfloxacin, Trimethoprim-sulfamethoxazole, are used in Prophylaxis of SBP.

Hepatorenal syndrome (HRS)

Cirrhosis and ascites are present.

No improvement in the serum creatinine level after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg/day)

Absence of shock, no recent use of nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs, iodinated contrast)

Exclusion of structural renal disease : No hematuria (≤50 RBC per high-power field) No proteinuria (≤500 mg/24 hours) No obstructive nephropathy and/or abnormal renal U/S

Clinical features

Type 1 HRS:

- Severe and rapidly progressive renal failure defined as doubling of serum creatinine, reaching > 2.5 mg/dL in < 2 weeks

Usually severe liver failure (jaundice, encephalopathy, and coagulopathy). -

- It may occur following a precipitating factor (severe bacterial infection, - gastrointestinal hemorrhage, or therapeutic paracentesis without plasma expansion).

- It is the complication with the poorest prognosis in cirrhosis - Median survival - time is only 2 weeks

Type 2 HRS

Moderate and stable renal failure

The main clinical consequence is refractory ascites

- Median survival is approximately 6 months

Treatment principles

- The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin

The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion

- In settings where terlipressin is not available, norepinephrine should be given.

If neither can be administered, a trial of oral midodrine (5 to 15 mg every 8 hours) in combination with octreotide (100 to 200 µg every 8 hours or 50 µg/hour IV) may be considered, yet the efficacy is low.

- Patients should be closely monitored for the possible development of side effects of vasoconstrictors and albumin, including ischemic complications and pulmonary edema.

All patients with cirrhosis and AKI should be considered for urgent liver transplantation (LT) evaluation given the high short-term mortality even in responders to vasoconstrictors

Portosystemic encephalopathy

Portosystemic encephalopathy (PSE) is a chronic neuropsychiatric syndrome that is secondary to cirrhosis. Acute encephalopathy can occur in acute hepatic failure . PSE can arise in portal hypertensive patients due to spontaneous ‘shunting’, or in those with surgical or TIPS shunts

Pathogenesis

In cirrhosis, the portal blood bypasses the liver via collaterals, and ‘toxic’ metabolites pass directly to the brain to produce encephalopathy.

Ammonia-induced alteration of brain neurotransmitter balance, especially at the astrocyte–neurone interface, is considered to be the leading pathophysiological mechanism.

Ammonia is produced by the breakdown of protein by intestinal bacteria.

Other implicated substances are free fatty acids and mercaptans; accumulation of false neurotransmitters (octopamine) or activation of the γ-aminobutyric acid (GABA) inhibitory neurotransmitter system may also be responsible.

Increased blood levels of aromatic amino acids (tyrosine and phenylalanine) and reduced branched-chain amino acids (valine, leucine and isoleucine) also occur.

-Hypokalaemia: Enhancing ammonia entry into brain cell.

An acute onset often has a precipitating factor .

The patient becomes increasingly drowsy and comatose.

Chronically, there is a disorder of personality, mood and intellect, with a reversal of normal sleep rhythm.

There is hyper-reflexia and increased tone. Coma occurs as the encephalopathy becomes more marked.

Convulsions are very rare, and if they do occur, other causes must be considered.

Precipitating factors:

1- Excess production of nitrogenous compounds as Excess protein in diet, bleeding O.V. (heavy protein load into intestine), stored blood transfusion (NH_3).

2-Excess nitrogenous toxins absorption: Excess tapping (lowering intra-abdominal pressure).

3- Deterioration of liver function.

4-Factors causing hypokalemia due to diuretics, diarrhea, paracentesis.

Signs include:

fetor hepaticus (a sweet smell to the breath)

a coarse flapping tremor seen when the hands are outstretched and wrists hyperextended (asterixis)

constructional apraxia, with the patient being unable to write or draw a five-pointed star, for example

Management

Identify and remove the possible precipitating cause, such as cerebral depressant drugs, constipation or electrolyte imbalance due to over-diuresis.

Give purgation and enemas to empty the bowels of nitrogenous substances.

Lactulose (10–30mL three times daily) is an osmotic purgative that reduces the colonic pH and limits ammonia absorption.

Protein restriction (50 g /day) in stage I, II → to cover the body catabolism of protein → then ↑ gradually 10g every 3rd day if there is no worsening of the condition (the amount is supplied by milk products and vegetable proteins).

Give antibiotics. Rifaximin is a poorly absorbed semisynthetic antibiotic based on rifamycin that has a beneficial effect on secondary prevention of PSE. Metronidazole (200mg four times daily) may be effective acutely. Neomycin should be avoided.

Treatments to Increase Ammonia Clearance:

- L-ornithine L-aspartate (LOLA).
- Zinc

Options for intractable or recurrent HE:

- Liver transplantation
- Modification of existing portosystemic shunts.

Hepatopulmonary syndrome

This is hypoxaemia in patients with advanced liver disease due to intrapulmonary vascular dilation with no evidence of primary pulmonary disease.

The patients have features of cirrhosis with spider naevi and clubbing, as well as cyanosis.

Most are asymptomatic, but with more severe disease become breathless on standing.

Transthoracic echocardiography shows intrapulmonary shunting and arterial blood gases confirm hypoxaemia. These changes are improved with liver transplantation.


Thank You!