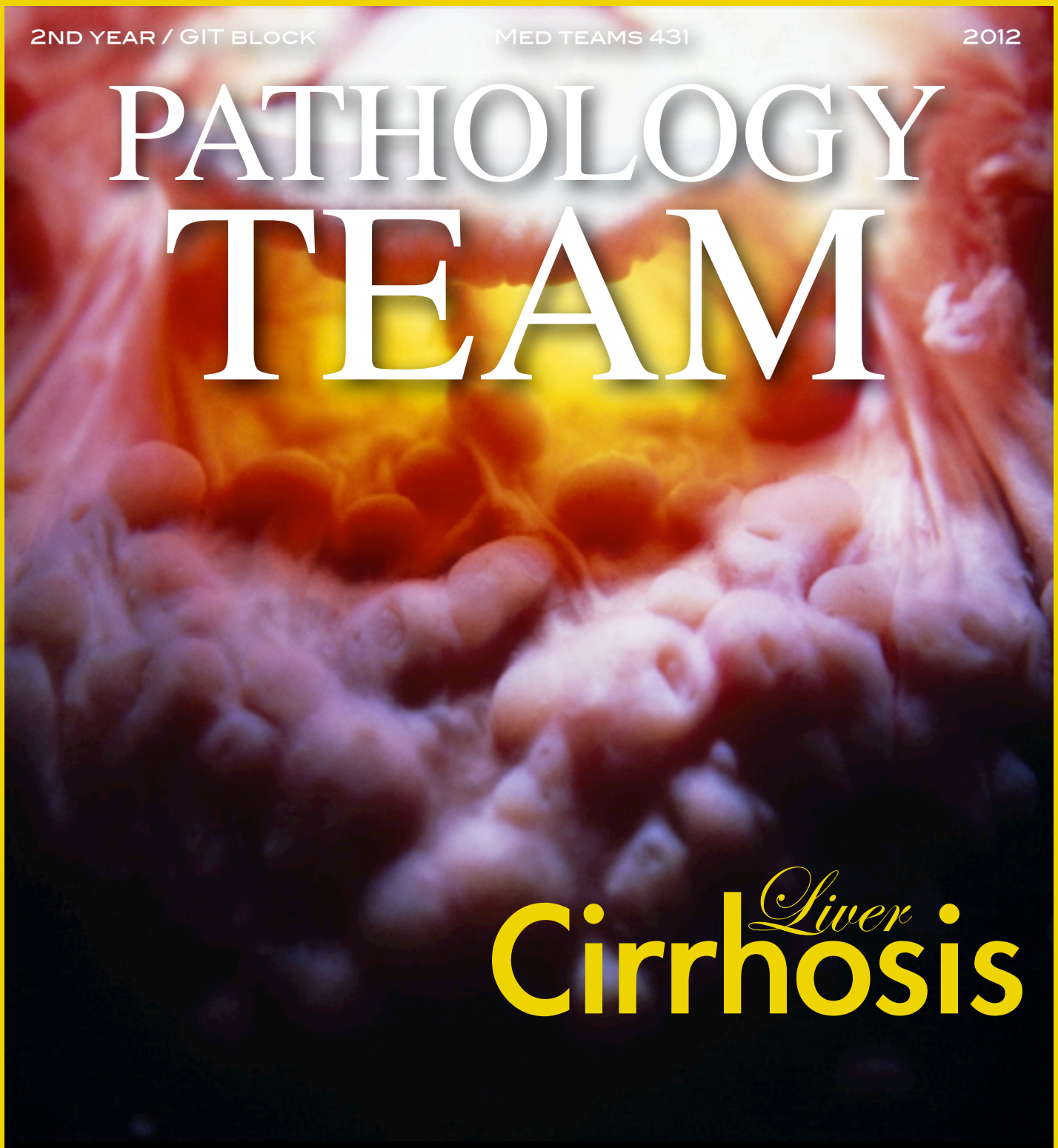
PATHOLOGY TEAM



Liver Cirrhosis

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Pathology

Liver Cirrhosis

Objectives:

Definition, types/causes, pathophysiology and mechanisms leading to cirrhosis, pathological findings, clinical manifestations

Cirrhosis is among the top 10 causes of death in the Western world.

The chief worldwide contributors are alcohol abuse (in the west) and viral hepatitis (in KSA). Other causes include biliary disease, and iron overload.

Cirrhosis is the end-stage of chronic liver disease

Classification:

The classification is based on the underlying etiology.

In the western population mainly:

Alcoholic liver disease	60% to 70%
Viral hepatitis	10%
Biliary diseases	5% to 10%
Primary hemochromatosis →abnormal accumulation of iron	5%
Wilson disease → abnormal accumulation of copper	Rare
α1-Antitrypsin deficiency	Rare
Cryptogenic cirrhosis → unknown cause	10% to 15%

Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular, but there is a tendency for nodules to increase in size with the progression of the disease forming macronodules.

In KSA, the most common cause of liver cirrhosis is:

- Viral hepatitis due to the wide spread of this infection.
- Infrequent types of cirrhosis also include:
- Cirrhosis in infants and children with galactosemia and tyrosinosis
- Drug-induced cirrhosis (ex; NSAIDs and Asprin)
- Severe fibrosis can occur in the setting of cardiac disease (sometimes called "cardiac cirrhosis")
- In some cases there is no cause and these are referred to as cryptogenic cirrhosis.

Once cirrhosis (end-stage) is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone. Earlier that however, some histopathological hints indicated a certain cause rather than others.

Cirrhosis is defined by three characteristics:

1)Fibrosis; in the form of delicate bands or broad scars/septa forming bridges between portal tracts

2)Nodules; containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm, micronodules) to large (several centimeters, macronodules)

3)Disruption of the architecture of the entire liver

Other features include:

Vascular architecture is reorganized by the parenchymal damage and scarring, with the formation of abnormal interconnections between vascular inflow and hepatic vein outflow channels.

Fibrosis is the key feature of progressive damage to the liver. Once cirrhosis has developed, reversal is thought to be rare. → Cirrhosis is an end stage liver disease, which is irreversible!

Clinical features:

*note that hepatocytes are very metabolically active → have various functions

All forms of cirrhosis may be clinically silent.

When symptomatic they lead to nonspecific clinical manifestations:

anorexia, weight loss, weakness, osteoporosis, and, in advanced disease, frank debilitation.

Incipient or overt hepatic failure may develop.

The ultimate mechanism of most cirrhotic deaths is

(1) progressive liver failure.
(2) a complication related to portal hypertension (highest causing mortality).
(3) the development of hepatocellular carcinoma.

→ The cirrhotic patient may develop jaundice and even hepatic failure

→ Case told by Dr. Hala:

Presentation: very skinny patient with a large abdomen (ascitis) presents with jaundice, palmer erythema, cachexia, telangeictasias
prognosis: very poor, 1-2 months left until he/she decompensates and develops hepatic encephalopathy (esp since patient has many comlications)

Pathogenesis:

→ In the normal liver, interstitial collagens (types I and III) are concentrated in the capsule, portal tracts and around central veins. The type IV collagen _____ is in the space of Disse (between sinusoids and hepatocytes)

The pathogenic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the ENTIRE liver.

In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts.

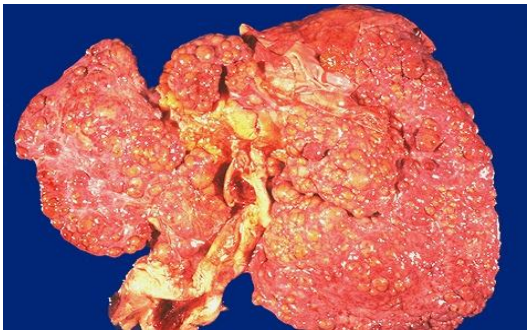
There is loss of fenestrations in the sinusoidal endothelial cells (capillarization of sinusoids, that is the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma). This leads to decreased blood reaching the hepatocytes → ischemia → cell death + inability to regenerate due to lack of O_2

The major source of excess collagen in cirrhosis is the perisinusoidal stellate cells (Ito/fat-storing cells), which lie in the space of Disse. Although normally functioning as Vit A fat-storing cells, during the development of cirrhosis they become activated and transform into myofibroblast-like cells.

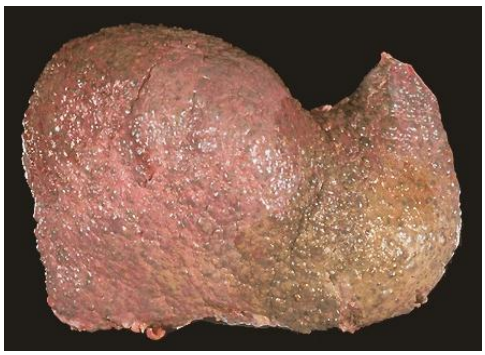
Collagen synthesis is stimulated by:

- Chronic inflammation, with production of inflammatory cytokines that attract fibroblasts
- Cytokine production by activated endogenous cells (Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells)
- Disruption of the normal extracellular matrix
- Direct stimulation of stellate cells by toxins

Macronodular cirrhosis
(nodules >3mm large)



Micronodular cirrhosis
(< 3 mm small) → most commonly chonic alcoholism



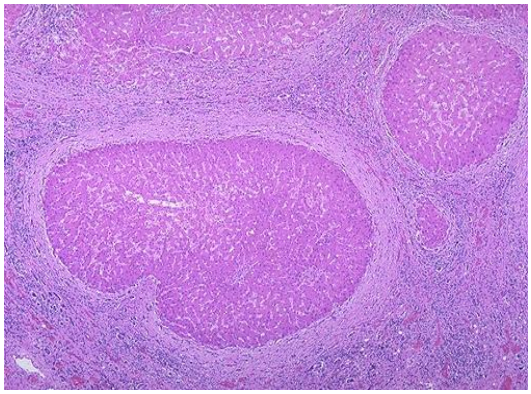
Histopathology:

Loss of normal histological tissue architecture.

Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts. Within this collagenous tissue are scattered lymphocytes as well as a proliferation of bile ducts.

Grading depends on degree of inflammation

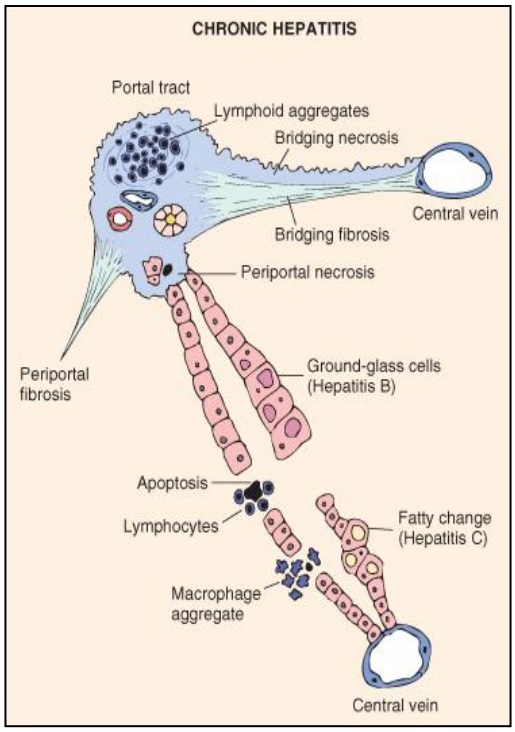
Staging depends on degree of fibrosis



Biopsy from an obese patient may show the same nodules surrounded by fibrosis if taken from the subcapsular area of the liver → does not ultimately direct to cirrhosis? because they have high tendency from non-acoholic fatty liver disease which shows similar morphology in SOME areas only. → must confirm with deeper wedge-shaped biopsy tissue

Morphology based on cause:

Chronic Hepatitis:



Some changes are shared with acute hepatitis.

Hepatocyte injury, necrosis, and regeneration

Sinusoidal cell reactive changes

Portal tract Inflammation:

-Confined to portal tracts, *or*

-Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis")

-Bridging inflammation and necrosis

Fibrosis:

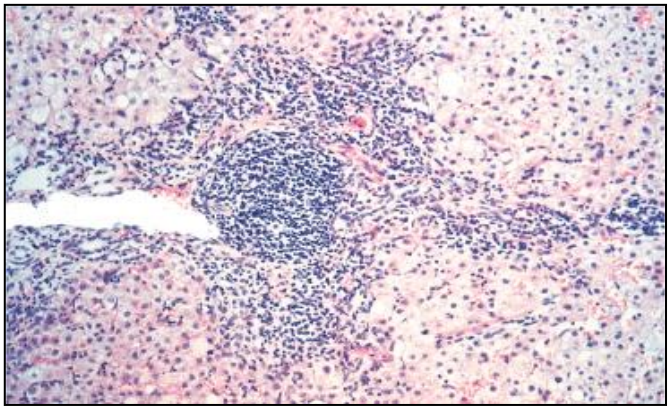
-continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis

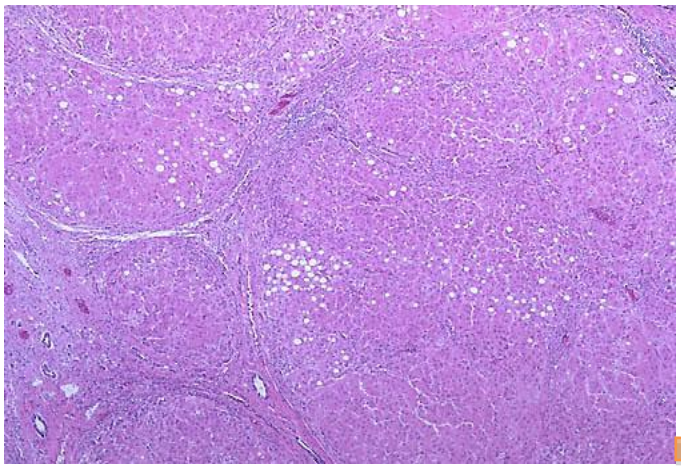
- bridging fibrosis connecting 3 portal tarcts into a circle

HBV: "ground-glass" hepatocytes → looks like opaque windows, "sanded" nuclei

HCV: bile duct damage, lymphoid aggregate formation

Cirrhosis: The end-stage outcome





Viral hepatitis C which is at a high stage with extensive fibrosis and progression to macronodular cirrhosis, as evidenced by the large regenerative nodule at the center right.

Autoimmune hepatitis:

Ideal diagnonsis:

Clinicopathological in addition to serology for autoantibodies

Is a chronic hepatitis with histologic features like that of chronic viral hepatitis. This disease may run an indolent or severe course; salient features include the following:

Female predominance, particularly in young and perimenopausal women. Especially immunocomrpomised (eg; on immunosuppressant's) or those on macrobiotic diets (no animal orgin foods)

The absence of viral serologic markers

Elevated serum IgG and γ-globulin levels (>1.5 times normal) as well as serum plasma cells

High serum titers of autoantibodies in 80% of cases, including antinuclear (ANA), antismooth muscle (SMA) etc.

Negative anti-mitochondrial antibodies

In untreated severe disease, as many as 40% of patients die within 6 months of diagnosis, and cirrhosis develops in at least 40% of survivors.

Treatment include immunosuppressive therapy, and liver transplantation.

Associated with other autoimmune diseases eg. Rheumatoid arthritis, Sjogren's syndrome etc. → mixed diseases

Intrahepatic Biliary Tract Disease

In general; obstruction → stagnant bile → toxic towards hepatocytes

three disorders of intrahepatic bile ducts

- Secondary biliary cirrhosis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Secondary biliary cirrhosis:

Prolonged obstruction of the extrahepatic biliary tree results in profound alteration of the liver itself.

The most common cause of obstruction in adults is extrahepatic cholelithiasis (gallstones), followed by malignancies of the biliary tree or head of the pancreas and strictures resulting from previous surgical procedures. Obstructive conditions in children include biliary atresia, cystic fibrosis, choledochal cysts (a cystic anomaly of the extrahepatic biliary tree).

Secondary inflammation resulting from biliary obstruction initiates periportal fibrosis, which eventually leads to hepatic scarring and nodule formation, generating secondary biliary cirrhosis.

Subtotal obstruction may promote secondary bacterial infection (originally GI infection/normal flora) of the biliary tree (*ascending cholangitis*), which aggravates the inflammatory injury. Enteric organisms such as coliforms and enterococci are common culprits.

Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head
Sex predilection	None.
Symptoms and signs	Pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly
Laboratory findings	Conjugated hyperbilirubinemia, increased serum alkaline phosphatase, bile acids, cholesterol
Important pathologic findings before cirrhosis develops	Prominent bile stasis in bile ducts, bile ductular proliferation with surrounding neutrophils, portal tract edema

Primary biliary cirrhosis:

Is a chronic, progressive, and often fatal cholestatic liver disease, characterized by the destruction of intrahepatic bile ducts, portal inflammation and scarring, and the eventual development of cirrhosis and liver failure.

The primary feature of this disease is a nonsuppurative (chronic-lymphocytes) inflammatory destruction of medium-sized intrahepatic bile ducts & granuloma formation.

Cirrhosis develops only after many years.

Sex and age predilection:

- middle-aged women,
- female:male predominance (6:1).

Pathogenesis: autoimmune etiology.

Clinical features include pruritus, jaundice, hepatomegaly. Xanthomas and xanthelasmas arise owing to cholesterol retention. . Over a period of time patients develop portal hypertension and hepatic encephalopathy.

Serum alkaline phosphatase and cholesterol are elevated; hyperbilirubinemia is a late development . 90% of patients have circulating "antimitochrondrial antibodies."

Morphology:

During the precirrhotic stage, portal tracts and bile ducts are infiltrated by lymphocytes and may exhibit noncaseating granulomatous inflammation. There is bile duct destruction.

With time, there is bile ductular proliferation, inflammation, and necrosis of the adjacent periportal hepatic parenchyma.

Over years to decades, relentless portal tract scarring and bridging fibrosis lead to cirrhosis.

In most cases, the end-stage picture is indistinguishable from secondary biliary cirrhosis or the cirrhosis that follows chronic hepatitis from other causes

Etiology	Possibly autoimmune
Sex predilection Symptoms and signs	Female to male: 6:1 Same as secondary biliary cirrhosis
Laboratory findings	Same as secondary biliary cirrhosis, plus elevated serum autoantibodies (especially antimitochondrial antibody-AMA)
Important pathologic findings before cirrhosis develops	Dense lymphocytic infiltrate in portal tracts with granulomatous destruction of bile ducts

Primary sclerosing cholangitis:

Is characterized by inflammation and obliterative fibrosis of the intrahepatic and extrahepatic bile ducts, with dilation of preserved segments.

Characteristic "beading" of a barium column in radiographs of the intrahepatic and extrahepatic biliary tree is attributable to the irregular strictures and dilations of affected bile ducts.

It is commonly seen in association with inflammatory bowel disease, particularly chronic ulcerative colitis

*in general any chronic inflammation leads to fibrosis & scarring OR cancer

males predominate 2:1

Pathogenesis: unknown.

Morphology:

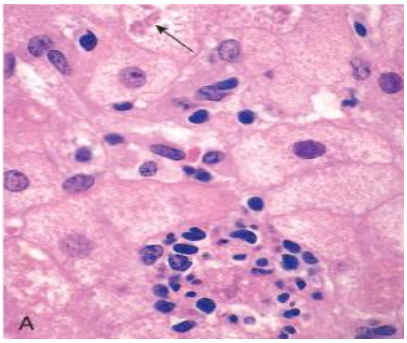
fibrosing cholangitis of bile ducts, with a lymphocytic infiltrate, progressive atrophy of the bile duct epithelium, and obliteration of the lumen.

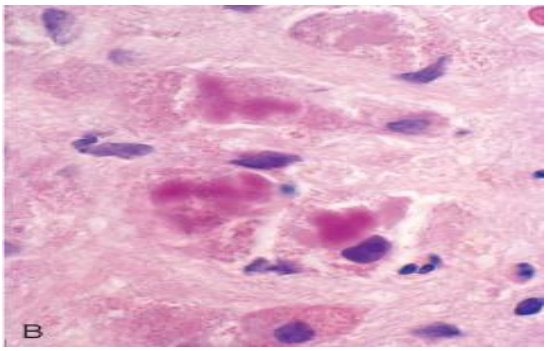
The concentric periductal fibrosis around affected ducts ("onion-skin fibrosis") is followed by their disappearance, leaving behind a solid, cordlike fibrous scar.

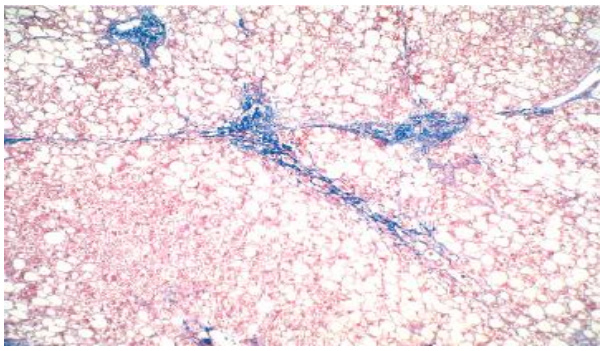
As the disease progresses, the liver becomes cirrhotic like that seen with primary and secondary biliary cirrhosis

Etiology	Unknown, possibly autoimmune; 50-70% associated with inflammatory bowel disease
Sex predilection	Female to male: 1:2
Symptoms and signs	Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Same as secondary biliary cirrhosis, plus elevated serum IgM, hypergammaglobulinemia
Important pathologic findings before cirrhosis develops	Periductal portal tract fibrosis, segmental stenosis of extrahepatic and intrahepatic bile ducts

Alcoholic liver disease:







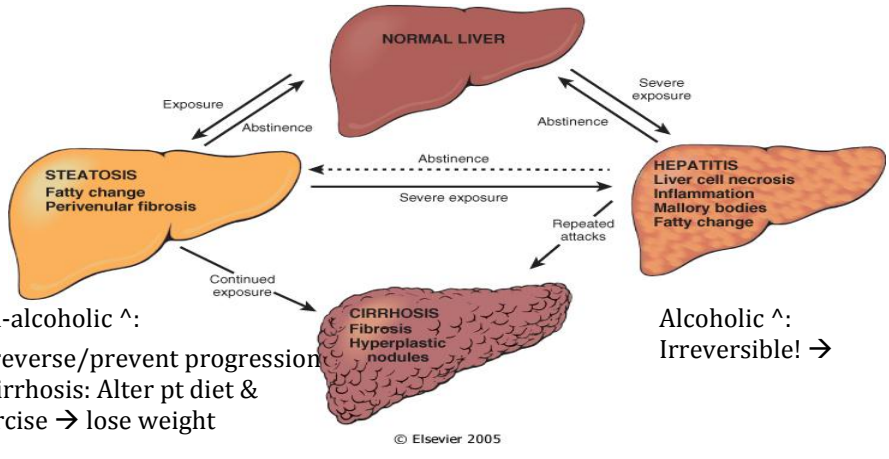
Alcoholic liver disease:

Macrovesicular steatosis, involving most regions of the hepatic lobule. The intracytoplasmic fat is seen as clear vacuoles. Some early fibrosis is present (stained blue with Masson trichrome stain).

Alcoholic hepatitis.:
A, The cluster of inflammatory cells marks the site of a necrotic hepatocyte. A Mallory body is present in a second hepatocyte (*arrow*).
B, Eosinophilic Mallory bodies are seen in hepatocytes, surrounded by fibrous tissue (H&E).

Alcoholic cirrhosis:

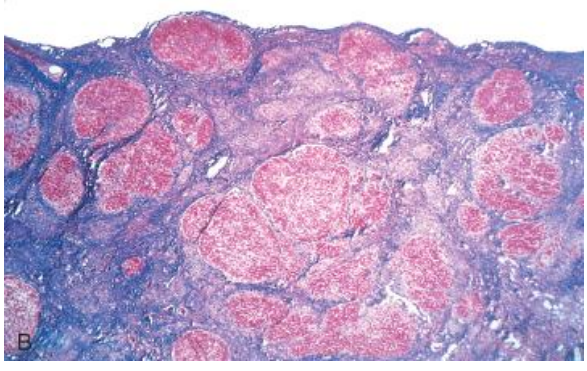
A, The characteristic diffuse nodularity of the surface reflects the interplay between nodular regeneration and scarring. The greenish tint of some nodules is due to bile stasis. A hepatocellular carcinoma is present as a budding mass at the lower edge of the right lobe (lower left of figure). *B*, The microscopic view shows nodules of varying sizes entrapped in blue-staining fibrous tissue. The liver capsule is at the top (Masson trichrome).



Non-alcoholic ^:

To reverse/prevent progression to cirrhosis: Alter pt diet & exercise → lose weight

Alcoholic ^:
Irreversible! →



Questions:

1) All of the following are morphological characteristics of liver cirrhosis except:
a. fibrous tissue
b. micronodules
c. infiltration of inflammatory cells
d. disruption of architecture

2) What is the major source of collagen in a cirrhotic liver?
a. Ito cells
b. endothelial cells
c. inflammatory cells
d. hepatocytes

3) Primary Biliary Cirrhosis can be characterized by ……. ?
a. Hyperamylasemia
b. Elevated serum IgG and γ-globulin levels
c. Elevated Antimitochrondrial antibodies (AMA)
d. High Albumin level

4) Which of the following is considered as the highest cirrhotic related mortality causing event?
a. Complications of hepatocellular carcinoma
b. Progressive liver failure
c. Complications of Portal Hypertension
d. Autoimmune disease

5) Liver Cirrhosis occurring mostly as a complication of ….. ?
a. Viral hepatitis
b. Alcoholic liver disease
c. Primary hemochromatosis
d. Biliary diseases

Answers:
c, a, c, c, b.