PATHOLOGY TEAM 436

MEDICINE
KING SAUD UNIVERSITY

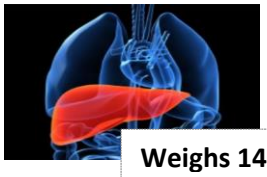
Liver Cirrhosis

Objectives:-

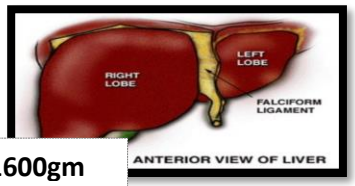
Upon completion of **Liver Cirrhosis** lecture students will be able to:

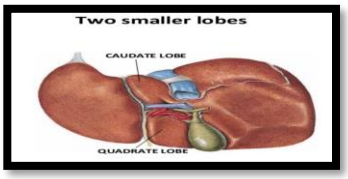
- Define Cirrhosis.
- Recognize the types of cirrhosis.
- Recognize the causes and the pathogenic mechanisms leading to cirrhosis.
- Describe the pathological findings in cirrhotic livers.

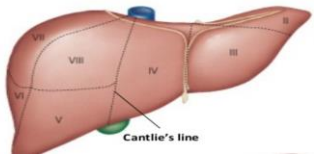
● Black: Doctor's slides. ● Red: Important! ● Green: Doctors' notes. ● Grey: Extra. ● *Italic black: New terminology.*

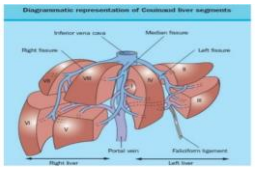


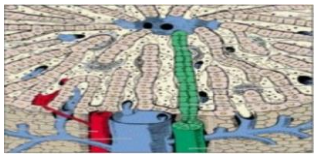
Weighs 1400 to 1600gm



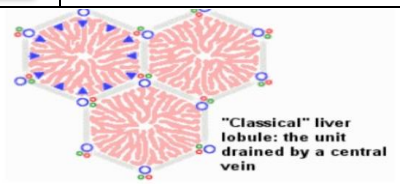








- The blood flows from periphery to centre.
- Bile flows from centre to periphery.



- Define Cirrhosis.

Liver Cirrhosis: تليُّف الكبد

- Cirrhosis refers to the diffuse transformation of the liver into regenerative parenchymal nodules surrounded by fibrous bands
- It is among the top 10 causes of death in the Western world.
- It is the end-stage of chronic liver disease. Only if patient survived enough
- The chief worldwide causes are:
  1. alcohol abuse
  2. viral hepatitis (chronic eg : hepatitis B,C virus).
     - Other causes include:
  1. biliary disease
  2. iron overload
- **Cirrhosis is defined by three characteristics**

Cirrhosis By Osmosis (9min)
HIGHLY recommended

Cirrhosis By Pathoma (20min)

Watch till min 7:00 - Cirrhosis - alcohol liver disease - Nonalcoholic liver disease

then watch from 14:10 to 16:18 - Primary biliary cirrhosis - Primary sclerosing cholangitis

1-Fibrosis in the form of delicate bands or broad scars/septae.(crossing the liver everywhere)

It's not any fibrosis, it's BRIDGING (broad) responding to the injury. يقسم الكبد الى ندبولز

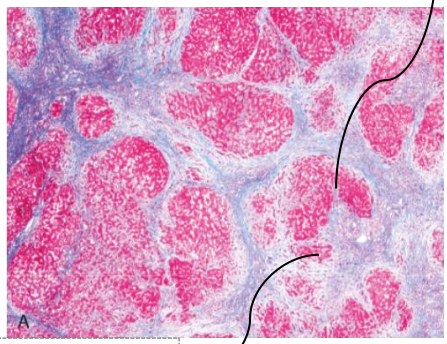
2-Nodules containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small (<3 mm, micronodules) to large (several centimeters, macronodules).

3-Disruption of the architecture of the entire liver.لازم يكون داخل الكبد عشان يكون تليف مو بس بالخارج

If it was focal disruption we can't call it cirrhosis!

- **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

Hepatocyte aggregation (pink circles) surrounded by fibrosis (blue areas)



- Recognize The Types Of Cirrhosis.

Classification of Cirrhosis:

1. The classification is based on the underlying etiology.
2. Many forms of cirrhosis (particularly alcoholic cirrhosis) are initially micronodular, but there is a tendency for nodules to increase in size with time.

We classify cirrhosis according to either (MORPHOLOGY) or (Etiology\Cause).

According to morphology:

Micronodular \ macronodular

According to cause are these 7 causes.

- **Classification of cirrhosis based on causes:**

1.	Alcoholic liver disease	60% to 70%
2.	Viral hepatitis	10%
3.	Biliary diseases	5% to 10%
4.	Primary hemochromatosis	5%
5.	Wilson disease(copper accumulation)	Rare
6.	α1-Antitrypsin deficiency	Rare
7.	Cryptogenic (Idiopathic) cirrhosis	10% to 15%

These 3 are the most common

- **Other infrequent types of cirrhosis:**
- The cirrhosis developing in infants and children with galactosemia and tyrosinosis[1]
- drug-induced cirrhosis. (Inherited metabolic disorders)
- Severe fibrosis can occur in the setting of cardiac disease; called "cardiac cirrhosis"

(Long time heart failure), with time there will be resistance then portal hypertension leading to injury and "cardiac cirrhosis"

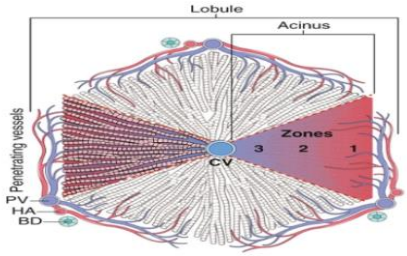
- In some cases there is no cause and these are referred to as "cryptogenic cirrhosis"
- Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone. اذا التليف انتهى صعب نعرف السبب الرئيسي من مجرد النظر اليه

[1] a condition characterized by abnormally large amounts of tyrosine in the urine, caused by faulty metabolism

- Recognize The Causes And The Pathogenic Mechanisms Leading To Cirrhosis.

Pathogenesis of cirrhosis:

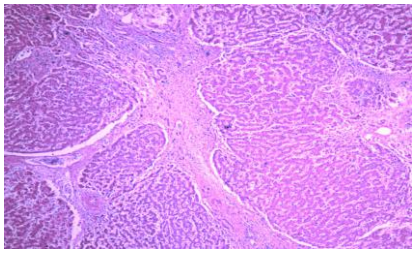
- The pathogenic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver



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

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

بالتالي يأثر على sinusoids وتقفل وبالتالي تتأثر السيركيوليشن .

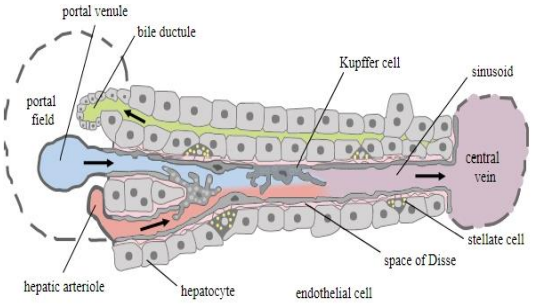


There is loss of fenestrations in the sinusoidal endothelial cells (capillarization of sinusoids, that is the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma)

- The major source of excess collagen in cirrhosis is the perisinusoidal stellate cells (Ito cells), which lie in the space of Disse. space of disse is an exchange area

Although Ito cells normally function is a vitamin A fat-storing cells, during the development of cirrhosis they become activated and transform into myofibroblast-like cell

Deposition of collagen blocks the exchange يعني يصير الكبد ينقل الدم فقط بدون تصفية السموم

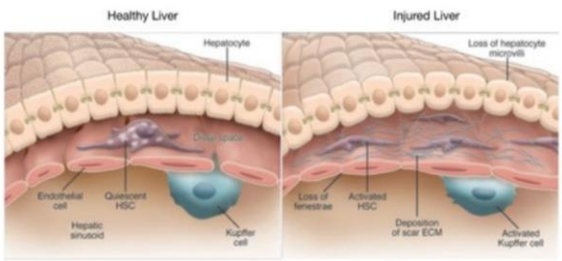


chronic inflammation and release of مع وجود ال injury يحصل cytokines بالتالي تتحفّز الأتو سلز وتسوي لي deposition of fibers in the perisinusoidal space وبالتالي تقفل لنا الفتحات الموجودة في الساينوسويد.

ويصير الساينوسويد مثله مثل الكبلري بس ينقل الدم مثل ماهو الويست حقته لباقي الجسم بدون ما ينظفه لما يمر الكبد.

طبعا كل هالسالفة تاخذ وقت عشان تحصل وما تحصل بسرعة لأن اكبد عضو كبير ويقدر يقاوم.

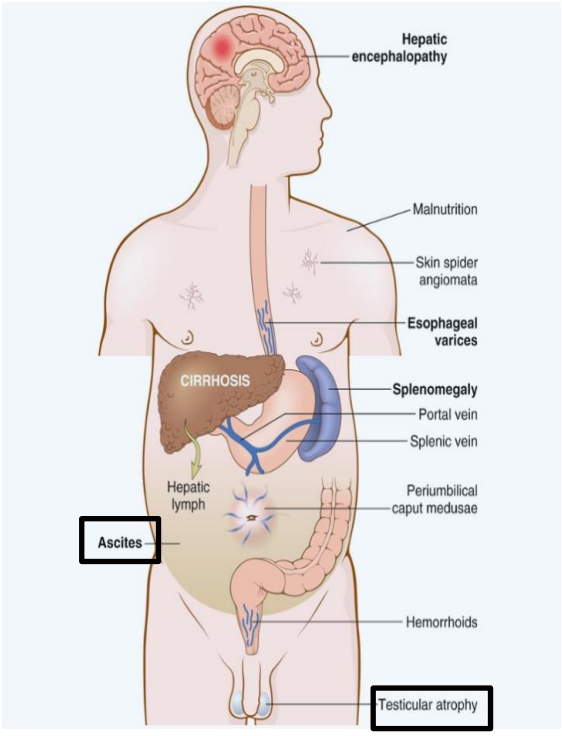
نصيحة شوفوا فيديو osmosis اللي فوق من عند الدقيقة ٢ وبتفهموا كل هالسالفة!



• Describe The Pathological Findings In Cirrhotic Livers.

- **Collagen synthesis is stimulated by:**

1. Chronic inflammation, with production of inflammatory cytokines.
2. Cytokine production by activated endogenous cells (*Kupffer cells*[2], endothelial cells, hepatocytes, and bile duct epithelial cells).
3. Disruption of the normal extracellular matrix.
4. Direct stimulation of stellate cells by toxins



Clinical Features

- All forms of cirrhosis may be clinically **silent**.

As we said before: liver is guit big organ and rich in vessels

and blood supply (It's has dual supply by both portal and hepatic veins).

- When symptomatic they lead to nonspecific clinical

manifestations: anorexia, weight loss, weakness,

osteoporosis, and, in advanced disease, frank debilitation.

- **Jaundice**. دائما الجندس يطلع في النهاية في كل انواع السروسز

Icterus which is yellowing of the sclera اللي هو الاصفرار وبين jaundice فرّقوا بين

- Incipient or overt hepatic failure may develop.
- cholestasis: deposition of bile salt in the tissues
- ascites: fluids accumulation in the free spaces in the body

caused by portal hypertension leading to increase hydrostatic pressure (lymph nodes become overwhelmed and cant drain all these fluids)

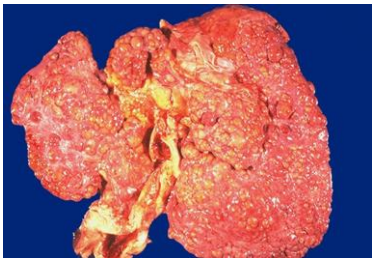
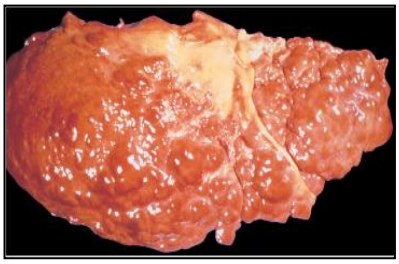
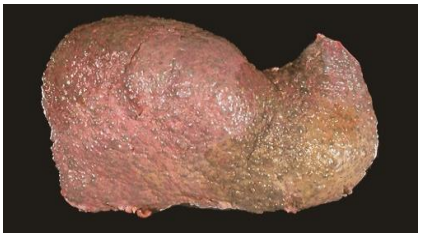
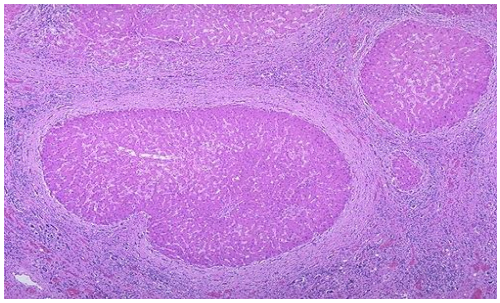
- splenomegaly caused by portal hypertension
- Testicular atrophy is caused by disruption in the metabolism of estrogen (estrogen is metabolized in the liver)

- **The ultimate mechanism of most cirrhotic deaths is :**

1. progressive liver failure
2. a complication related to portal hypertension (most common ex : bleeding)
3. the development of hepatocellular carcinoma

[2] Liver microphages

Morphology:

<table>
<tr>
<td><u>Gross Features</u></td>
<td>  
The nodules seen here are larger than 3 mm and, hence, this is an example of "macronodular" cirrhosis.</td>
<td> 
Micronodular cirrhosis : The regenerative nodules are quite small, averaging less than 3 mm in size. The most common cause for this is chronic alcoholism.</td>
</tr>
<tr>
<td><u>Under microscope :</u></td>
<td colspan="2"> 
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.</td>
</tr>
</table>

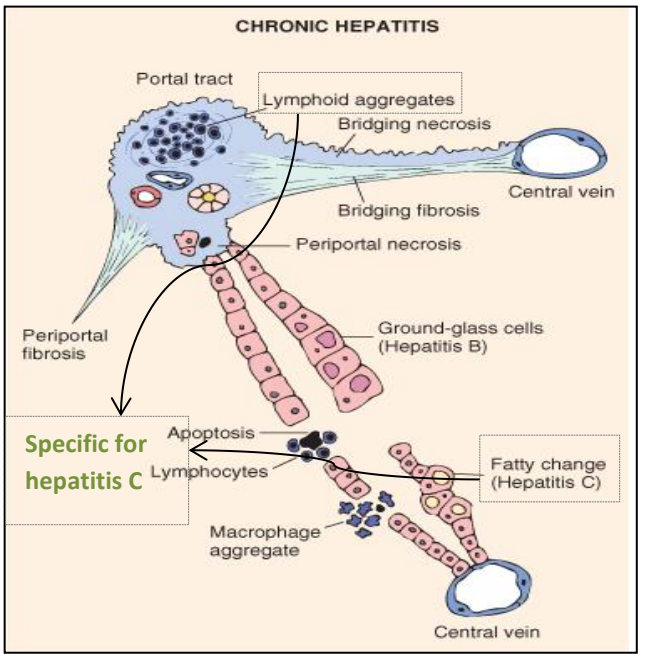
Causes of liver cirrhosis

- **Chronic Viral Hepatitis (hepatitis B and C virus*)***
- **Autoimmune hepatitis**
- **Biliary Cirrhosis**
  - **secondary biliary cirrhosis**
  - **primary biliary cirrhosis**
  - **primary sclerosing cholangitis**
- **Alcoholic liver disease**

1. Chronic Hepatitis:

morphology Some changes are shared with acute hepatitis.

- Hepatocyte injury, necrosis, and regeneration
- Sinusoidal cell reactive changes
- Portal tract يبدأ هنا بعدها يطلع على الهيباتوسايتس Inflammation:
  - Confined to portal tracts or
  - Spillover into adjacent parenchyma, with necrosis of hepatocytes ("**interface hepatitis**") or
  - **Bridging inflammation and necrosis**
- Fibrosis:
  - continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
  - HBV: "ground-glass" hepatocytes, "sanded" nuclei
  - HCV: bile duct damage, lymphoid aggregate formation
- **Cirrhosis: The end-stage outcome** **Stage 4**

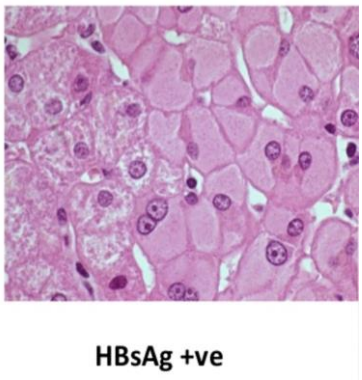
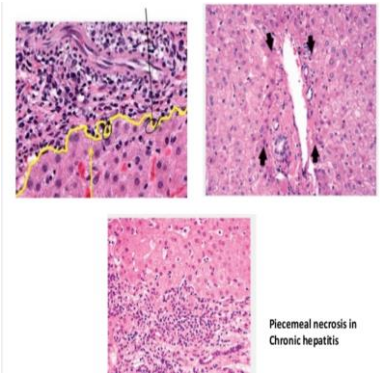
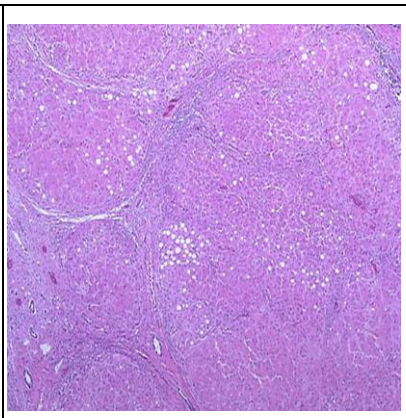
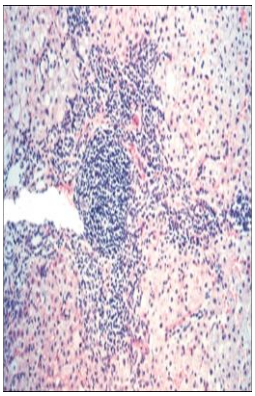


اذا الانفلاميشن طلع برا التراكت نسميها علطول grade 2

اذا الفايبروسس طلع برا البورتال تراكت نسميه stage 2

Fat inside cell = steatosis
Fat inside cell + inflammation in the lobules = steatohepatitis
Stage 1 = fibrosis inside portal tract
Stage 3 = bridging fibrosis between portal tract and central vein
Stage 4 = nodules = cirrhosis

Grading: درجة الانفلميشن
Staging: the advancement of the fibrosis
ما نستخدم grading and staging الا مع نوع الهيباتايتس سروسز اما باقي الأنواع مافيها
اهم شي نعرف ان السروسز يعتبر قريد ٤ الباقي لمعلوماتكم فقط

 HBsAg +ve	 Piecemeal necrosis in Chronic hepatitis		
	Spillover into adjacent parenchyma, with necrosis of hepatocytes "interface hepatitis"	Viral hepatitis C which is at a high stage with extensive fibrosis and progression to macro nodular cirrhosis, as evidenced by the large regenerative nodule at the center right.	Chronic hepatitis , morphology

2. Autoimmune hepatitis:

هو نوع من الهيباتايتس لكن الفرق ان هنا ماعندي فايرس ولما تسوي سيرولوجي رح تطلع نقتف ورح نلاقي increased titer of autoantibodies وهذا يعني انها قاعدة تشتغل على جسمك

It is a chronic hepatitis with histologic features like that of chronic viral hepatitis. This disease may run an indolent or severe course**.**

Features include the following:

- Female predominance, particularly in young and premenopausal women.
- **Absence of viral serologic markers**
- Elevated serum IgG and γ-globulin levels (>1.5 times normal)
- High serum titers of autoantibodies in 80% of cases, including **antinuclear (ANA),** antismooth muscle (SMA), 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.

3. Intrahepatic Biliary Tract Disease

Three disorders of intrahepatic bile ducts:

A. Secondary biliary cirrhosis شيء خارجي
B. Primary biliary cirrhosis من البايل نفسها
C. Primary sclerosing cholangitis من البايل نفسها

A. Secondary biliary cirrhosis **the doctor focused on laboratory findings**

يجي سيناريو فيه ابستركشن سبب كرونك انفلميشن وقتها لازم تحطوا ببالكم انه رح يصير فيه تحفيز لل events of cirrhosis

It is caused by 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[3], cystic fibrosis, choledochal cysts (A cystic anomaly of the extrahepatic biliary tree)

[3] narrowing (small ductules) or absence of biliary duct

Morphology:

- 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 of the biliary tree (*ascending cholangitis*), which aggravates the inflammatory injury. Enteric organisms such as coliforms and enterococci are common cause.

SUMMARY

Etiology	Extrahepatic bile duct obstruction: biliary atresia, gallstones, stricture, carcinoma of pancreatic head
Sex predilection Symptoms and signs	None. 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

B. Primary biliary cirrhosis **the doctor focused on laboratory findings**

Primary biliary cirrhosis (AKA: primary biliary cholangitis. autoimmune disease.) 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, inflammatory destruction of medium-sized intrahepatic bile ducts.*
- Cirrhosis develops only after many years.
- middle-aged women,
- **female : male predominance (6:1).**

Pathogenesis: autoimmune etiology, 90% of patients have circulating **"antimitochrondrial antibodies" AMA**

Clinical features

- *Pruritus*[4], jaundice, hepatomegaly. *Xanthomas*[5] 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.** (Increase serum level of alkaline phosphate indicate injury of bile duct)
- 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

(At the end, cirrhosis is cirrhosis) في النهاية ما تقدر تفرق اذا كان برايمري ولا سكندري

SUMMARY

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

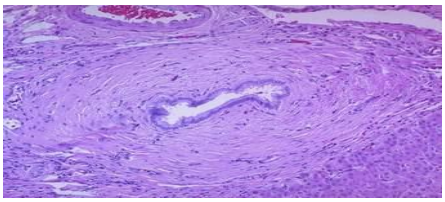
[4] حكة caused by deposition of bile salts

[5] deposition of cholesterol بقع بيضاء حول العين

C. Primary sclerosing cholangitis

Primary sclerosing cholangitis is characterized by *inflammation and obliterative fibrosis* اللي فوق كانت دايركت *of intrahepatic and extrahepatic bile ducts* اللي فوق كانت انترا , with dilation of preserved segments. دستركشن Characteristic "**beading**"= "شكل السبحة" 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.

Males predominate 2:1



Periductal portal tract fibrosis **(onion-skin fibrosis)**

Pathogenesis: unknown

Morphology:

- Primary sclerosing cholangitis is a 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 مرة ثانية يقول لنا ما نقدر نفرق بينهم

SUMMARY

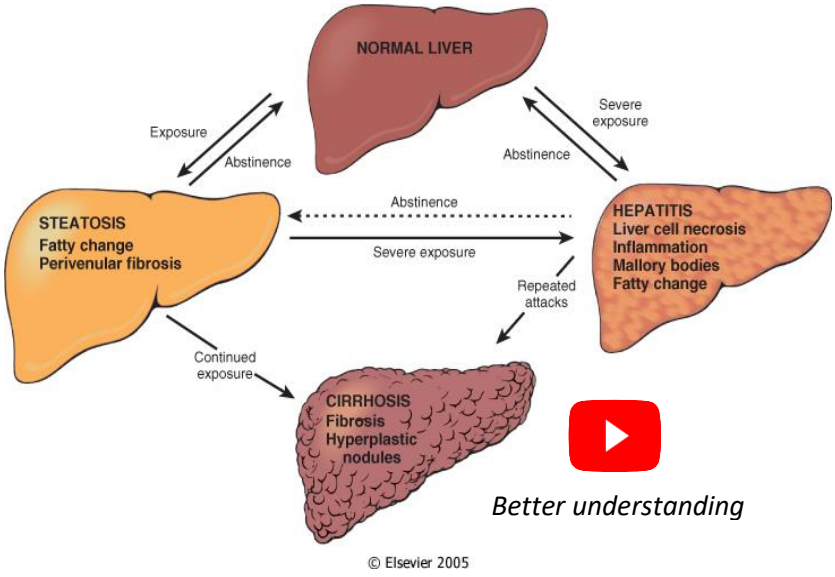
Etiology	Unknown, possibly autoimmune; 50-70% associated with inflammatory bowel disease
Sex predilection Symptoms and signs	Female to male: 1:2 Same as secondary biliary cirrhosis; insidious onset
Laboratory findings	Same as secondary biliary cirrhosis, plus elevated serum IgM, hypergammaglobulinemia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

4. Alcoholic liver disease

Three features:

1. Steatosis (fatty change)
2. Hepatitis (steatohepatitis)
3. Fibrosis

هنا الكبد يا انه يصير لها steatosis ثم Hepatitis
أو أحيانا في حالة severe exposure تتحول الى hepatitis دايركتلي
وبالنهاية يصير cirrhosis

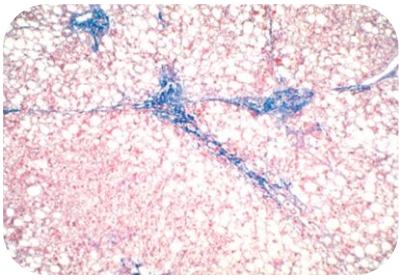


Better understanding

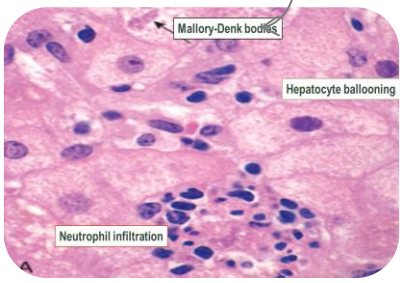
The causes of death are:

- Hepatic failure
- Massive gastrointestinal hemorrhage
- Intercurrent infection (to which affected individuals are predisposed)
- Hepatorenal syndrome
- Hepatocellular carcinoma (3%–6% of cases)

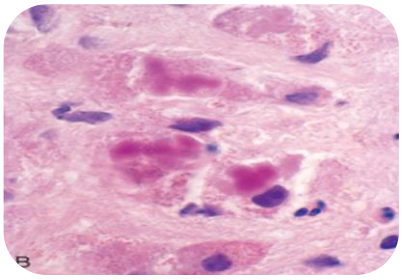
Mallory-Denk bodies (not specific)



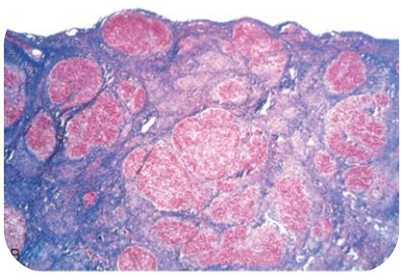
Alcoholic liver disease: macrovesicular steatosis, involving most regions of the hepatic lobule. The intracytoplasmic fat is seen as clear vacuoles. Some early fibrosis (stained blue) is present (Masson trichrome).



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*).



Eosinophilic Mallory bodies are seen in hepatocytes, which are surrounded by fibrous tissue (H&E).



The microscopic view shows **diffuse nodules of varying sizes entrapped in blue-staining fibrous tissue.** The liver capsule is at the top (Masson trichrome).

Summary

1. Cirrhosis is the transformation of normal liver into Regenerative Parenchymal Nodules surrounded by Fibrosis and usually it is the end stage of Chronic Liver Disease.
2. The most common causes are Alcohol abuse and viral hepatitis.
3. The diagnostic features of Liver Cirrhosis 1- FIBROSIS 2- NODULES 3- DISTORTION OF THE ARCHETICTURE OF THE ENTIRE LIVER.
4. Pathogenesis of Liver cirrhosis is deposition of COLLAGEN TYPE 1 AND 3 in the Lobule produced by ITO CELLS.
5. The specific clinical features are JAUNDICE AND MAY PROGRESS TO HEPATIC FAILURE.
6. Under the microscope there will be regenerative hepatic nodules surrounded by fibrous bands.
7. Morphology of Chronic hepatitis Portal tract inflammation that nay spillover into adjacent parenchyma with bridges of necrosis , the Fibrosis depends on the etiology if it is caused by HBV (there will be Grounded-Glass Hepatocyte and Sanded Nuclei) or if it is caused by HCV (there will be bile duct damage and lymphoid aggregation) .
8. Autoimmune Hepatitis there will be increase IgG and gamma-globulin with increase ANTINUCLEAR ANTIBODIEAS (ANA).
9. Secondary biliary cirrhosis is due to due to obstruction of extrahepatic biliary tree and the most common cause is Gallstones. There will be increase ALKLINE PHOSPHTASE.
10. Primary biliary cirrhosis characterized by destruction of intrahepatic bile duct and there will be ANTIMITOCHONDRIAL ANTIBODIES (AMA).
11. Primary sceloroting cholangitis characterized by obletrative fibrosis of INTRA and EXTRA hepatic bile ducts and it is associated with ulcerative colitis , Under the Microscope there will be ONION SKIN FIBROSIS .
12. Alcoholic liver disease characterized under the microscope by 1-MALLORY BODIES 2- BALLOONIG HEPATOCYTE 3- NEUTROPHILS .

Questions

1- A previously healthy, 38-year-old lady has become increasingly dulled in the past 4 days. On physical examination, she has icterus, and abdominal fluid wave. Laboratory findings show a prothrombin time of 38 seconds, high levels of ALT and AST. Which of the following will most likely be abnormal in her case?

A) Alkaline phosphate.
B) Ammonia.
C) Amylase.
D) Antinuclear antibody (ANA).

ANS: B. D is less likely since Autoimmune hepatitis is not likely to produce a fulminant hepatitis.

2- Which of the following is the most likely cause of death of a patient with cirrhosis?

A) Caput medusa.
B) Ascites.
C) Hepatocellular carcinoma.
D) Esophageal varices.

ANS: D

3- Interface hepatitis refers to which of the following?

A) Fibrosis septa.
B) Regenerative hepatocytes.
C) Spillover inflammation to parenchyma from portal tracts.
D) Bridging necrosis and fibrosis reaching the central veins.

ANS: C

4- A 26-year-old Lady experienced progressive tiredness for the past 2 months. Lab tests showed normal albumin levels but increased ALT and AST. Alkaline phosphatase levels we normal. Serology was negative for HBV, and HCV. After another test the doctor diagnosed her case to be autoimmune hepatitis. Which of the following is true in her case?

A) Positive Anti-Mitochondrial Antibodies.
B) Positive Anti-Nuclear Antibodies.
C) Decreased Gamma globulin levels.
D) Decreased ammonia levels.

ANS: B

5- Which of the following is False about patients with autoimmune hepatitis?

A) Similar histological features with viral hepatitis.
B) Predominant in males.
C) Treated through autoimmune therapy.
D) Usually associated with other autoimmune diseases.

ANS: B

6- A 39-year-old Gentleman presented with severe itchiness, dark urine, and tiredness. Physical examination showed hepatomegaly, splenomegaly and jaundice. Which of the following is expected in his case?

A) Low ALT levels.
B) Decreased bile acids.
C) High Alkaline phosphatase.
D) Decreased cholesterol.

ANS: C

7- Anti-Mitochondrial antibodies are important of diagnosing which of the following?

A) Autoimmune hepatitis.
B) HBV.
C) Primary sclerosing cholangitis.
D) Primary biliary cirrhosis.

ANS: D

8- 38-year-old lady presented to the hospital with pain in the upper right abdomen, abdominal swelling. Physical examination revealed hepatosplenomegaly. The doctor asked for liver function tests which revealed raised alkaline phosphatase. After that he asked for a biopsy of the liver which showed periductal portal tract fibrosis (onion-skin fibrosis). What is the most likely diagnosis?

A) Secondary biliary cholangitis.
B) Cirrhosis caused by HBV.
C) Primary biliary cirrhosis.
D) Primary sclerosing cholangitis.

ANS: D

9- Glass hepatocytes histologic feature is specific to which of the following?

A) HBV.
E) Primary biliary cirrhosis.
B) Primary sclerosing cholangitis.
C) HCV.

ANS: A

حسبي الله لا إله إلّا هو عليه توكلت وهو رب العرش العظيم

القادة	الأعضاء
مها الغامدي	عبد الكريم الحربي
حنين السبكي	صقر التميمي
عبدالله أبو عمارة	ريان القرني
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References: Doctor's slides + notes, Robbins basic pathology ١٠th edition.