الجهاز الهضمي

علم الأمراض

رقم المحاضرة : 6

الكتّاب : سُرى علي وحلا موسى

المدقق : زهراء الحدّاد

الدكتور : مها شوماف

Doctor's words → RED Slides → BLACK Important → PURPLE Extra info → BLUE

Budd – Chiari Syndrome

Caused by:

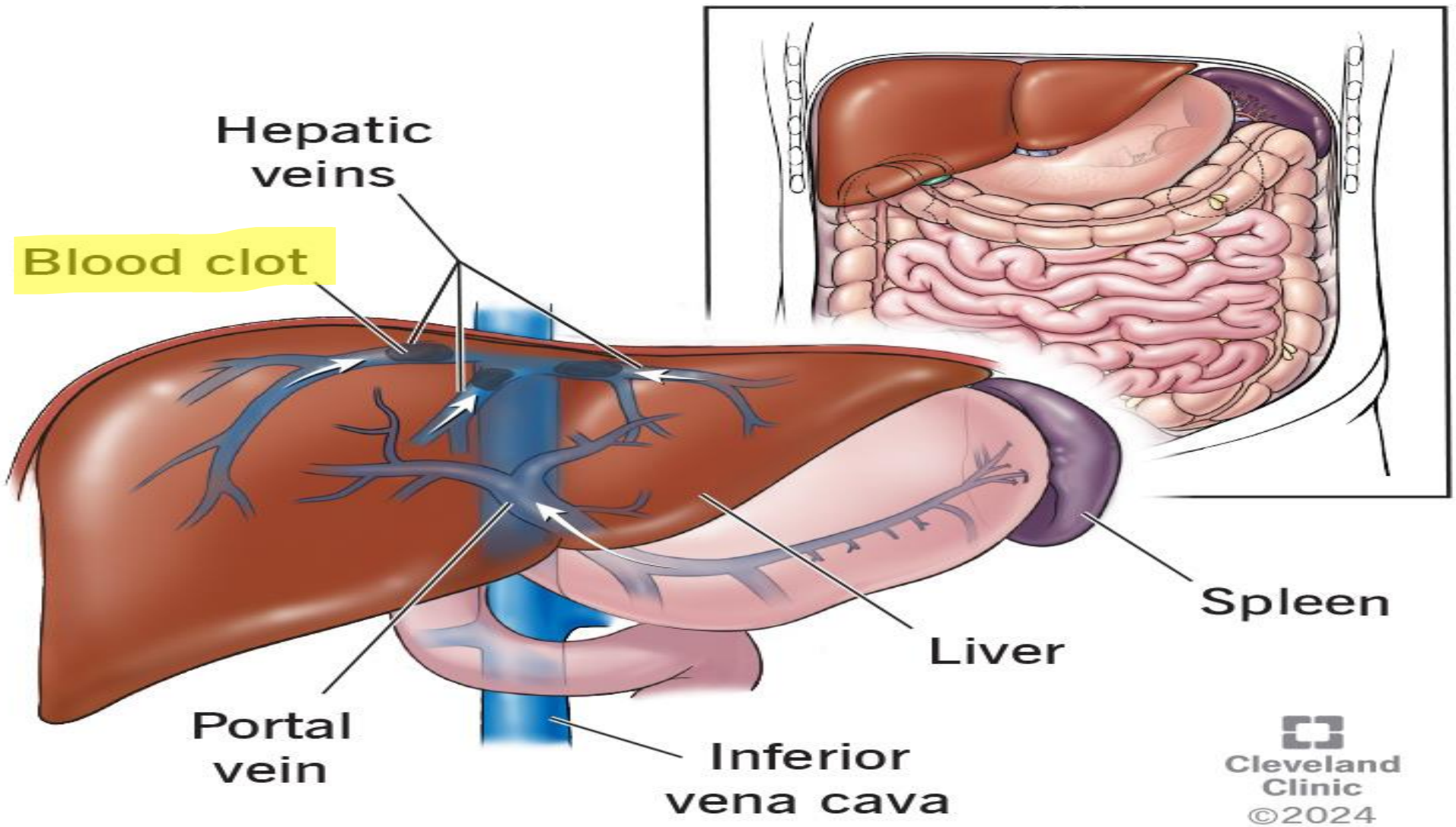
-**Traumatic** thrombotic occlusion of the hepatic vein.

*Any condition that is associated with increased risk of thrombosis, can later complicate into Budd-Chiari syndrome
*This process can be an acute or chronic.
If It's chronic, It can develop the following manifestations:

-Hepatomegaly (Enlargement of liver)
-Weight gain
-Ascitis
-Abdominal Pain and tenderness

Budd-Chiari syndrome is a condition that can be seen in other diseases. It's one of the complications that can occur in patients that have other problems. So, when a patient starts to develop manifestation, remember that it could be a possible complication later.

Budd-Chiari syndrome



✓ Thrombus → blood clot which is formed intravascularly .
✓ Normally, the blood in the circulation should be liquid without having any clots.

- If someone gets injured, a small red mass will be formed at the site of injury, this red mass is the clot.
- In Budd-Chiari → the clot forms within the blood vessels.
- The clot circulates until it reaches a vessel with suitable diameter to close it, leading to obstruction.
- There are many disease and causes that increase the risk of obstruction due to thrombus formation. [will be viewed in the next slide]

The following causes or diseases are characterized by increased risk of developing thrombosis (which, again, leads to Budd-Chiaria), some of them are vascular diseases, some are other conditions:

1-PCV (polycythemia vera) → is a malignancy of RBCs → having tendency of forming clots.

2-Pregnancy

3-Postpartum

Females during pregnancy and postpartum period have high risk of developing thrombus due to hormonal effect.
↑ Progesterone → stasis of blood and dilation of vessels walls.

4-Females using oral contraceptive

5-PNH paroxysmal nocturnal hemoglobinuria)
is a form of hemolytic anemia.

6-Mechanical obstruction of vessels

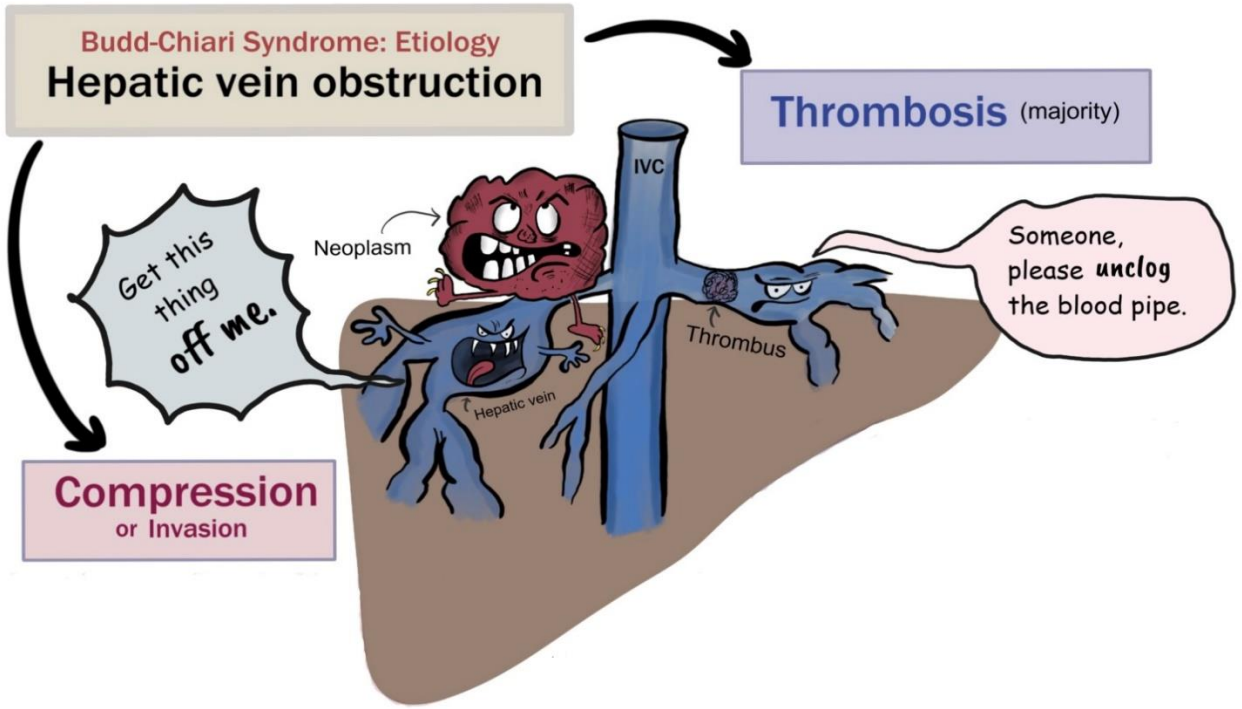
The obstruction can result from compression by the surrounding tissue, ex :(tumor, stricture ...Etc)

Obstruction+stasis of the blood → very important for clot formation.

7- Tumors as HCC

Tumors enlarge and compress the surrounding tissue.

- ❑ The tumor can be anatomically close to the portal vein and compress it from outside.
- ❑ Hepatocyte carcinoma tends to infiltrate the vessel and the tumor growth can go within the vessel.



8- idiopathic in 30% of the cases (not a small percentage)

Additional information

PCV (polycythemia vera) is type of blood cancer that causes overproduction of red blood cells. → Hyperviscousity of blood (hypercoagulability) → Thrombosis

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Oral contraceptives → They contain chemically produced hormones that mimic women's natural cycle (Estrogen) → Causes hypercoagulability state → Thrombosis

YOU CAN SKIP THIS SLIDE

(interesting info though!)

What do we expect to see in Budd-Chiaria patients?

- Morphology

-Swollen liver and enlarged, red, with tense capsule

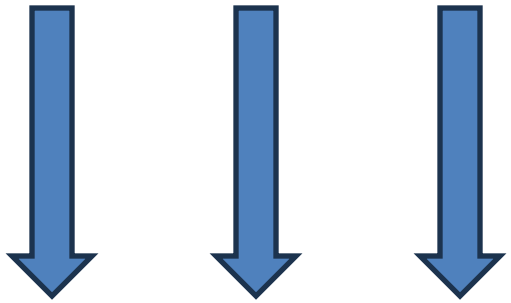
-Centrilobular congestion & necrosis

-Fibrosis

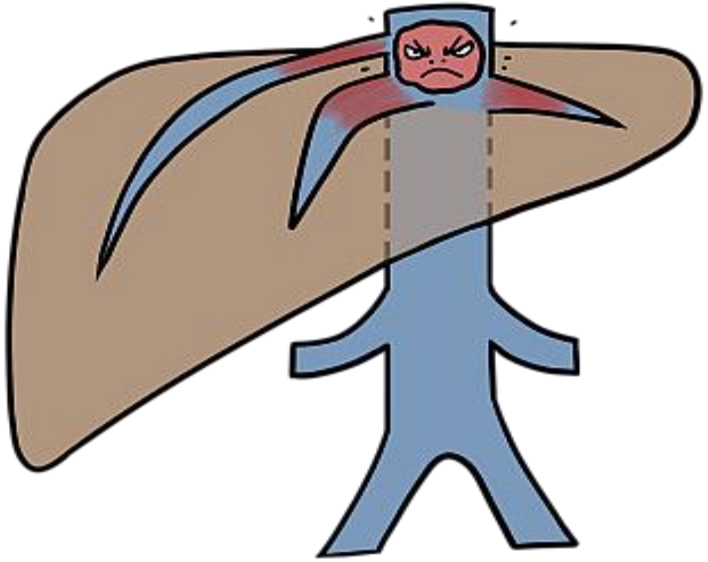
-Thrombi

The condition is serious, and It can cause liver failure and death if it is not recognized early .

- Clinically
- Mortality rate is high if not treated



- Microscopically, there is congestion in the central veins because they are tributaries to the portal vein.
- pressure in these veins → they become dilated because they are congested and stuffed with blood.
- This depends on the severity and acuteness of the condition and might result in necrosis. Why? Central vein engorged (filled with blood) → compression in the surrounding hepatocyte → necrosis.
- It can be acute or prolonged (chronic)
- chronic → might induce fibrosis around central veins.
- Diagnosis is clinical and by suspicion → because all manifestations are non-specific.



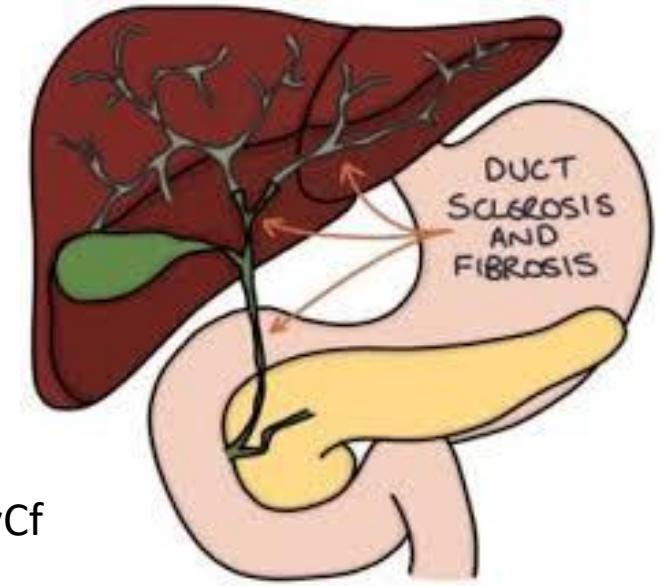
Primary sclerosing cholangitis

This is an example on a condition that affects the primary biliary tract of the liver. It's not so frequent but it's important.

It is characterized by:

- -Inflammation
- -Obliterative fibrosis
- -Segmental dilation of the obstructed intra hepatic & extra hepatic bile ducts

- -In PSC, UC coexists in 70% of patients
- -in patients of UC, 4% develop PSC
- -Usually in first 3-5 the decades
- -M: F 2:1

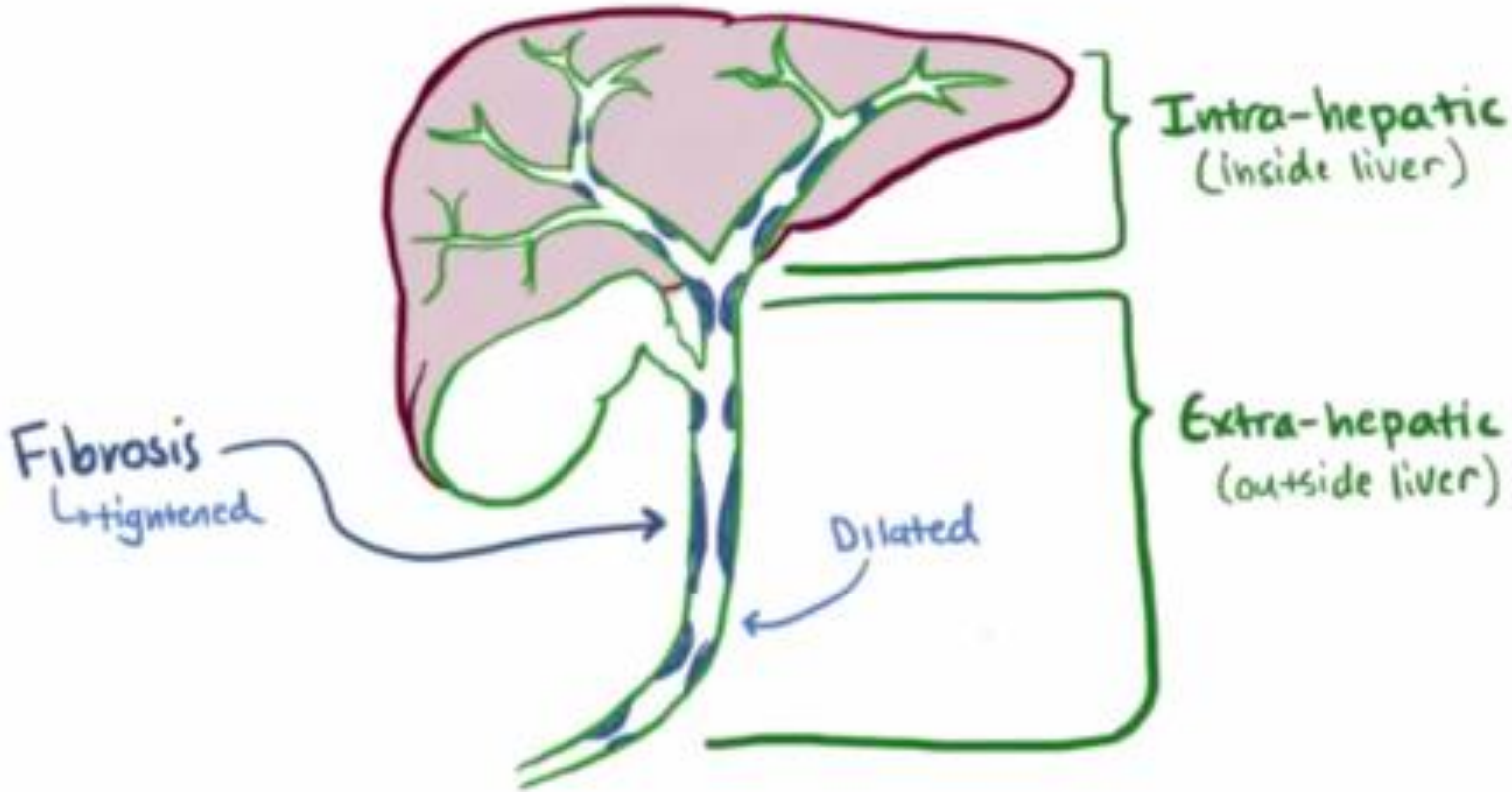


https://youtu.be/ZXs6FkjnBIs?si=yB0CkltFEc264yCf

- PSC (primary sclerosing cholangitis) is characterized by inflammation with fibrosis that primarily affects the biliary tract.
- This fibrosis that surrounds the bile tract produces segmental dilation of the biliary system → gives characteristic appearance of hepatocyte. This process involves both intra- and extrahepatic biliary system, inducing this condition
- It is associated with ulcerative colitis (UC) in severe cases (chronic inflammatory bowel disease). If a patient presents with PSC, there is a high possibility of having ulcerative colitis.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

- PRIMARY: not caused by something else
- SCLEROSING: Hardening of tissue
- CHOLANGITIS: Inflammation
- (PSC)



-Asymptomatic patients.

-Depending on the severity.

-Persistent ↑serum alkaline phosphatase.

-**Manifestations:**

Fatigue, pruritis (severe itching due to deposition of different bile salts in the skin),

Jaundice (obstruction of biliary system),

weight loss, ascites, bleeding,

encephalopathy (extreme condition when there is a severe biliary system damage and development of fibrosis and cirrhosis)

Characteristic test: liver function test on the enzyme alkaline phosphatase (ALP) . Alkaline phosphatase is a reflection of biliary system

In general, If ALP is increased, we should think of primary biliary system because It is execrated by the epithelium lining the biliary system when injured (damage, disease).

❖ Characteristic of this disease: It is an autoimmune disease,

So we perform screening tests to check which Abs are prominent.

❖ Characteristic antibodies:

-Antimitochondrial Abs < 10% of cases

-Antinuclear cytoplasmic Abs in 80% of cases

Antimitochondrial Abs are less because they are characteristics of other autoimmune disease.

Morphology

Is characteristic

If we examine liver biopsy, we notice that the target of the inflammation is the bile duct

-Around the bile duct there is **concentric periductal onion-skin fibrosis** (layers) **& lymphocytic infiltrate.**

-**Atrophy & obliteration of bile ducts** → Disappearance is a characteristic

-Dilation of bile ducts inbetween areas of stricture

-Cholestasis(because the biliary system is the target) & fibrosis

-Cirrhosis, cholangiocarcinoma (10 – 15%)

بتكون الbile duct بالنص و حولها طبقات من Fibrosis و هاي الطبقات على شكل onion

Fibrosis produces segmental obstruction (not along the whole tube, but on the sides). And between two adjacent obstruction there is dilatation of bile duct which gives the characteristic appearance of the biliary system.

Pathogenesis, due to:

-Exposure of the biliary system to gut normal-flora-derived toxins.

-Immune attack targeting bile duct

-Ischemia of biliary tree

All of these can be a cause of this destructive inflammation.

Secondary biliary cirrhosis

It is called secondary because it's cirrhosis developed from other biliary diseases, all of which are characterized by having abnormality(narrowness) in bile duct, sectioning of the bile duct leading to exposure of hepatocytes/liver's parenchyma to the bile's toxins.
Biliary cirrhosis can be primary (without obvious causes).

-Prolonged obst. To extrahepatic biliary tree

-Causes:

1-cholelithiasis

- Stones that are formed in the bile ducts, can cause obstruction.
- Obstruction in the biliary system means that all the bile is stagnant (راكد)within the duct which in turn produces damage effect in hepatocytes.
- If It is left untreated→ development of cirrhosis

2-biliary atresia

- Narrowing of the biliary system→ can be intra- or extrahepatic

→ The most common: atresia in common bile duct

تكملة لل
causes of secondary biliary cirrhosis

3-malignancies **Obstruction >can be primary or secondary(causing pressure from outside)**

4-stricutres

May be congenital or produced by different surgeries.
In surgeries: formation of fibrous bands → contraction → entrapping the common bile duct.

All the diseases that cause secondary biliary cirrhosis are characterized by having an abnormality of the bile duct, narrowing, obstruction or bleeding because of the exposure of hepatocytes to toxins in the bile.

Primary biliary Cirrhosis

Characteristic: presence of non-suppurative granuloma

-Chronic, progressive & often fatal cholestatic liver disease

-Non-suppurative granulomas associated with destruction of medium-sized intrahepatic bile ducts, in the presence of portal inflammation & scarring

This type of cirrhosis is related to biliary inflammation, biliary destruction

-Age 20-80yrs. Peak: middle aged(40-50yrs)
-F>M
-Insidious onset
-Pruritis, jaundice
-Cirrhosis over 2 or more decdes

Prolonged process, needs time to develop. It also develops in stages.

- ❑ Development of cirrhosis in patients presents late in the process (because It is a prolong process) .
- ❑ It starts from non-specific features of liver until there is cirrhosis, the process is graded

↑Alkaline phosphatase & cholesterol (is execrated through bile)

Characteristic

Remember in primary sclerosing cholangitis, ALP is raised in a patient with ulcerative colitis.

-Hyperbilirubinemia = hepatic decompensation

The process is prolonged, and they will develop jaundice.

-Antimitochondrial Abs > 90%

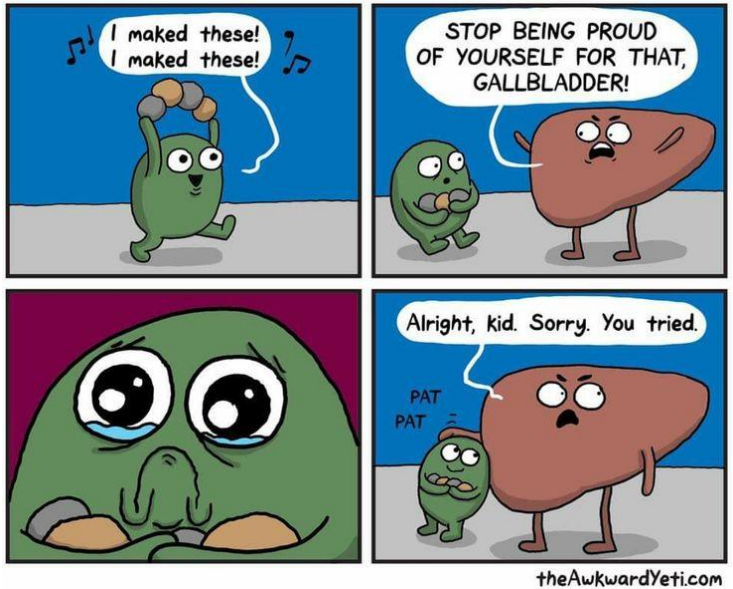
-Antimitochondrial pyruvate dehydrog

Also characteristic

-Associated conditions: Sjogren synd. Scleroderma thyroiditis, RA, Raynaud's phenomenon. MGN, celiac disease.

- **Morphology**

- ❑ In this condition the target is > interlobular bile ducts are absent or severely destructed (florid duct lesion)
- ❑ Intra epithelial inflammation
- ❑ Granulomatous inflammation (Surrounding the biliary system)
- ❑ Bile ductular proliferation
- ❑ Cholestasis (Extensive)
- ❑ Necrosis of parenchyma (Depending on parenchyma involvement)
- ❑ Cirrhosis



Another form of vascular diseases is, which is not frequent but you should be aware of:

Sinusoidal Obstruction Syndrome
(Veno-occlusive disease)

Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids (toxic)

-This occurs in the first 20-30 days after bone marrow transplantation.

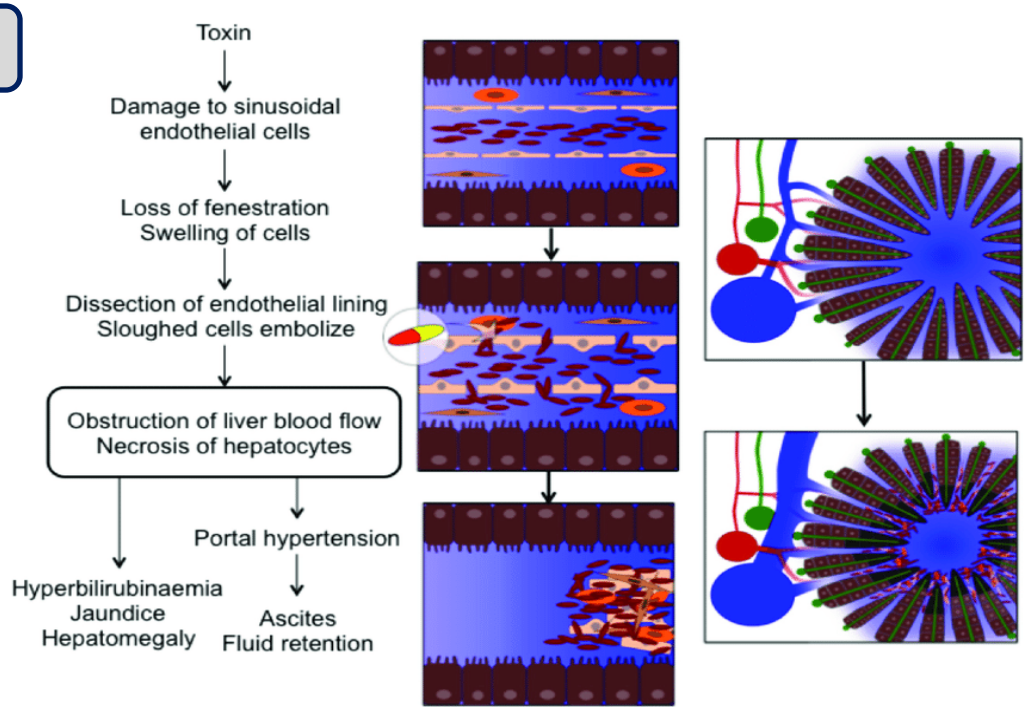
Which is caused by:

1-Drugs as cyclophosphamide

2-Total body radiation

It's not frequently encountered, except in patients with malignancies. A rare, but well-known cause of this syndrome is the toxicity due to consumption of alkaloids, but it now occurs primarily in cancer patients (especially leukemia) who receive bone marrow transplantation. Prior to transplantations, patients undergo total body irradiation to destroy their diseased bone marrow (to give them a fresh one). But unfortunately this process introduces some damages to sinusoids. Moreover, chemotherapy can induce injuries to multiple sites including sinusoids.

Additional:



.Incidence

-20% in recepients of allogeneic marrow transplant

Because in process of preparation, cells are damaged.

-Clinical presentation

Mild – severe

Death, if it doesn't resolve in 3 months

However, in acute conditions, it can be very severe.

Mechanism

Toxic injury to sinusoidal endothelium

→emboli

→blockage of bl. Flow

Passage of blood into space of Disse

→↑stellate cells → fibrosis

Toxicity and injury by the aforementioned factors causes death of the endothelial lining of sinusoids leading to desquamation and separation of cells as clusters. As sinusoids are very delicate structures, clustering of cells within will induce obstruction and blood flow impedance. Therefore, blood will leak into spaces of disse which stimulates stellate cells (fibroblasts) to produce fibrosis.

Another form of vascular diseases is:

Peliosis Hepatis

-sinusoidal dilatation, caused by:

1-anabolic steroids (used for muscle building)

2-oral contraceptive (females)

3-danazol (a drug)

-Pathogenesis Unknown

-Some patients are
Asymptomatic

May lead to:
-Intra abdominal hemorrhage
-Liver failure
If the underlying cause is corrected, it can be
reversible

Dilation of sinusoids causes the liver to be engorged with blood, which can leak into abdomen, causing hemorrhage.

Additional table from Robbins:

Table 16.3 Patterns of Injury in Drug- and Toxin-Induced Hepatic Injury

Pattern of Injury	Morphologic Findings	Examples of Associated Agents
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids, antibiotics, HAART
Cholestatic hepatitis	Cholestasis with lobular necrosis and inflammation; may show bile duct destruction	Antibiotics, phenothiazines, statins
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldopa, phenytoin
	Massive necrosis	Acetaminophen, halothane
	Chronic hepatitis	Isoniazid
Fatty liver disease	Large and small droplet fat	Ethanol, corticosteroids, methotrexate, total parenteral nutrition
	"Microvesicular steatosis" (diffuse small droplet fat)	Valproate, tetracycline, aspirin (Reye syndrome), HAART
	Steatohepatitis with Mallory-Denk bodies	Ethanol, amiodarone
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Alcohol, methotrexate, enalapril, vitamin A and other retinoids
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, amiodarone, isoniazid
	Fibrin ring granulomas	Allopurinol
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusive disease): obliteration of central veins	High-dose chemotherapy, bush teas
	Budd-Chiari syndrome	Oral contraceptives
	Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	Anabolic steroids, tamoxifen

Liver tumors are either benign or malignant. The most common liver tumor is liver metastasis

Liver tumors

- Benign
- Most common is cavernous hemagioma **(tumor of blood vessles)**
- Usually <2cm
- Subcapsular

A liver hemangioma is a benign mass made up of swollen blood vessels that are prone to rupture and bleeding, especially due to being subcapsular, which increases the chance to hemorrhage following procedures to take biopsies or surgeries.

Another tumor is:

- Liver cell adenoma (adenoma means tumor of glands or secretory cells; hepatocytes)
- Young female
- Hx of oral contraceptive intake
- May rupture (subcapsular) esp. during pregnancy causing severe intraperitoneal hemorrhage
- Rarely may contain HCC
- Misdiagnosed of HCC

Characteristic, hormone-dependent.

Liver is a common site of metastasis, that's why any emerging mass in the liver must be diagnosed cautiously to identify its nature, whether neoplastic or non-neoplastic. If neoplastic, further analysis must be done to find out if it's malignant or benign.

Liver Nodules

Focal noudular hyperplasia

- **Well demarcated hyperplastic hepatocytes with central scar. (Also forms a mass)**
- **Non-cirrhotic liver (nodules are localized not diffuse)**
- **Not neoplasm (won't turn into a malignant mass) but nodular regeneration**
- **Local vascular injury**
- **Females of reproductive age**
- **No risk of malignancy**
- **20% of cases have cavernous hemagnioma**

Caused by a focal injury to the liver which disrupts the normal architecture leading to parenchymal degeneration followed by fibrosis .

Macroregenerative Nodules

- Cirrhotic liver
- Larger than cirrhotic nodules
- No atypical features,
- Reticulin is intact
- No malignant potential (no neoplastic features)

In the case of macroregenerative nodules (in the previous slide ⬆️), the liver already has nodules due to cirrhosis, but some nodules appear way larger and outstanding, which arouses suspicion of malignancy . But under microscopic investigations, no dysplasia is present and that proves those suspicions wrong.

In other presentations, microscopic observations may unfortunately prove the presence of dysplasia within some nodules in a cirrhotic liver, thus these nodules are called dysplastic nodules. (Check the next slide ⬇️)

Dysplastic nodules

- Larger than 1 mm
- Cirrhotic liver
- Atypical features (potentially malignant), pleomorphism and crowding
- High proliferative activity
- High or low dysplasia
- Precancerous (monoclonal, +ve gene mutations similar to mutations present in cancer cells)
- Types:

1. Small – cell dysplastic nodules
2. Large – cell dysplastic nodules

Hepatocellular carcinoma

The most common malignant liver tumors are liver metastasis (secondary, spread from other organs, especially colon cancer).
Primary tumors are rare, but it also depends on the geographical area.

- **5.4% of all cancers**
- **Incidence:**

<5/100000 population in N&S America
N& central Europe
Australia

15/100000 population in Mediterranean

36/100000 population in Korea, Taiwan
mozambique, china

- **Blacks > white**
- **M:F ratio**
  3:1 in low incidence areas. >60yr
  8:1 in high incidence areas. 20-40yr

Age of high incidence areas is less than the age of low incidence areas due to different development conditions

Predisposing Factors

1. Hepatitis B carrier state
   Most common route of developing carrier states is through vertical transmission (during delivery)
   increases the risk 200X (important)!!!
   cirrhosis may be absent,
   they are healthy carriers
   and show no symptoms
   unless changes occur
   young age group (20-40yr)
2. >85% of cases of HCC occur in countries with high rates of chronic HBV infection

3. Cirrhosis (degenerative-regenerative process)
   In western countries cirrhosis is present in 85-90% of cases
   >60yr
   HCV(transmitted through different ways. It's harder to control than HBV, and it's more common) & alcoholism
4. Aflatoxins (a toxin produced by a fungus, mutate tumor suppressor genes :p53, especially in Africa where early exposures are higher)
5. Hereditary tyrosinemia (an abnormality in metabolism of the amino acid 'tyrosine') (in 40% of cases)
6. Hereditary hemochromatosis (carcinogenic genetic disorder)

Pathogenesis

1. Repeated cycles of cell death & regeneration
   HBC, HCV, gene mutations, Genomic instability
2. Viral integration
   HBV DNA intergration which leads to clonal expansion
3. HBV DNA intergration which leads to genomic instability not limited to integration site.

HBV can integrate with the DNA of the host, instabilizing genes or producing new proteins and new functions leading to an uncontrolled proliferation of cells.

4. HBV

X-protein which leads to transactivation of viral & cellular promoters,

Activation of oncogenes by

acting as a promoter ,

Inhibition of apoptosis

5. Aflatoxins (fungus Aspirgillus flavus)

mutation of p53 (tumor suppressor gene)

6. Cirrhosis

HCV Alcohol

Hemochromatosis

Tyrosinemia (40% of pts. Develop HCC despite adequate dietary control

All are related to the process of carcinogenesis

Morphology

1. HCC (most common primary malignant tumor)
2. CC (cholangiocarcinoma, a billiary carcinoma which is an adenoma arising from billiary epithelium)
3. Mixed

- Unifocal (most of primary tumors)
- Multfiocal (usually in metastasis)
- Diffusely infiltrative

- Vascular invasion is common in all types.
- Well ---- Anaplastic

HCCs metastasize through the hematogenous route and may lodge in vessles ; hepatic vein or IVC, causing obstruction.

- **A form of liver cancer: Fibrolamellar**

Carcinoma **(different from that of primary)**

-20-40 yr. M=F. Young individuals

-No relation to HBV or cirrhosis

-better prognosis than HCC

-single hard scirrhous tumor

Why is this important? When a tumor is found within the area of abdomen and forming severe dysplasia, we have to think of biliary system or pancreas, these are characteristically desmplastic tumors

Cells are large and the cytoplasm is eosinophilic, background: fibrosis (hence the name).

- Cholangiocarcinoma are chraracteristically desmoplastic (tumor is associated with fibrosis, tumor cells are spread within a fibrous tissue produced by these tumor cells. So, for example, if we find a tumor in the abdomen causing severe dysplasia, we should think of the biliary system, the pancreas)

metastasis

Vascular – lungs, bones, adrenals, brain,
in 50% of cholagiocarcinoma

- C/P
  abd. Pain, malaise, wt. loss
  Characteristic to primary liver tumors :
  increase α-feto protein in 60 – 75% of pts
  (tumor marker, but unspecific in which it can rise in several conditions; pregnancy).

- α-feto protein increases also with:
  1-yolk sac tumor
- 2- cirrhosis,
- 3-massive liver necrosis,
- 4-chronic hepatitis,
- 5-normal pregnancy,
- 6-fetal distress or death
- 7- fetal neural tube defect.

Even though, if a patient has a predisposition and a liver proplem, α-feto protein can further indicates the presence of primary tumors, also it's used to differentiate between primary and secondary tumors.

Prognosis

Very bad

- Death within 7 -10 months or a year
- **Causes:**

1 Cachexia (severe weight loss)

2GI bleeding 3-

Liver failure

4-Tumor rupture and hemorrhage

SUMMARY

LIVER TUMORS

- The liver is the most common site of metastatic cancers from primary tumors of the colon, lung, and breast.
- **Hepatocellular adenomas** are benign tumors of hepatocytes. Most can be subclassified on the basis of molecular changes with varying degrees of malignant potential. They are associated with use of oral contraceptives and androgens.
- The two main types of malignant tumors are **hepatocellular carcinomas and cholangiocarcinomas**; HCCs are much more common.
  - HCC is a common tumor in regions of Asia and Africa, and its incidence is increasing in the United States.
  - The main etiologic agents for HCC are hepatitis B and C, alcoholic cirrhosis, hemochromatosis, and exposure to aflatoxins. In the Western population, about 90% of HCCs develop in cirrhotic livers; in Asia, almost 50% of cases develop in noncirrhotic livers.
  - The chronic inflammation and cellular regeneration associated with viral hepatitis are predisposing factors for the development of carcinomas.
  - HCC may be unifocal or multifocal, tends to invade blood vessels, and recapitulates normal liver architecture to varying degrees.
  - Cholangiocarcinoma is a tumor of intrahepatic or extrahepatic bile ducts that is relatively common in areas where liver flukes, such as *Opisthorchis* and *Clonorchis* species, are endemic.

ختامًا، شكرًا لثقتكم ودعمكم للفريق. وكونوا على علمٍ أن مهنة التفريغ هذه سامية، من الطالب إلى الطالب، لذا حرصنا دومًا على شمولية المحتوى العلمي، راجين من الله التوفيق في ذلك.
وأشمل الكثير من زملائي الكُتّاب والمدققين عندما أقول أنَّ هذا العمل انزرع في قلوبنا، وأنه من أفضل القرارات التي اتخذناها. لذا، نشجعكم دومًا على الانخراط في مثله. سواءً بشكل فرديٍّ أو جماعيّ، لذة العمل التطوعي حاضرة أينما استشعرتموها.
بالتوفيق، ودمتم بخيرٍ سالمين.

Always remember, to enjoy what you're doing. You're going to be a doctor someday (insha'Allah), enjoy the process, even if it gets hard. Remember that it's all going to be part of the magnificent story you'll tell to inspire others, and there are more exciting parts to on the way!! Wherever you end up, enjoy medicine :))

"صامدون،
ثابتون،
مرابطون"

~الطبيب الشهيد
عدنان البرش

يسعدنا أخذ آرائكم واقتراحاتكم فيما يتعلق بتفريغات الفريق، عبر الرابط التالي:
https://docs.google.com/forms/d/1bYOyNKJYSANwKYaC-YqrUdzHWwwPO36-Cfpf0r4TRSQ/edit#responses