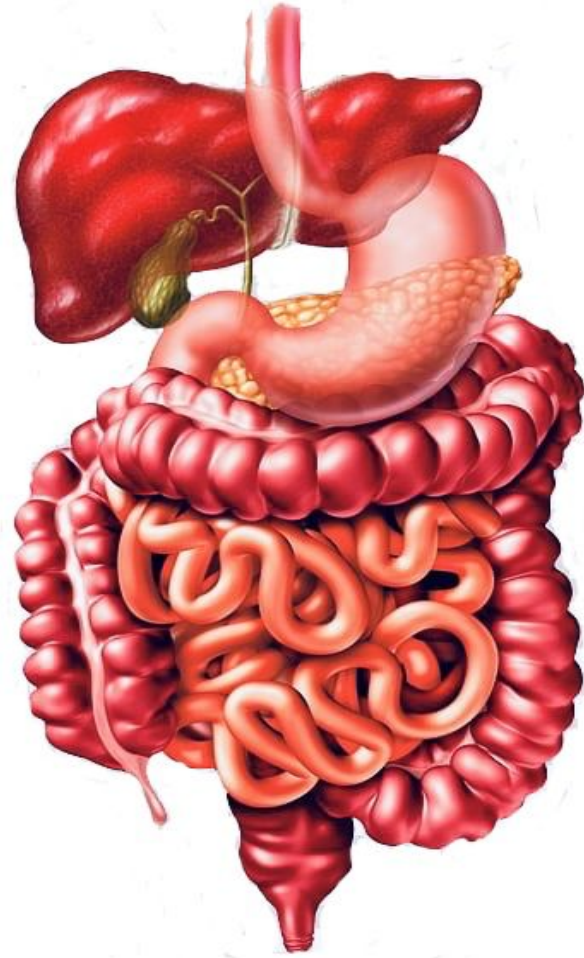


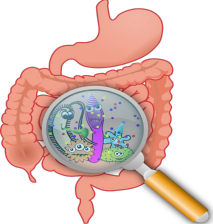
هذه المحاضرة هي تكريم لكل من يعمل ولا
يكرّم، لكل من يعمل بالخفاء، لكل ايادي تدفعنا
من ظهورنا لا نرى وجوه اصحابها



Cancers of the liver and pancreas

Objectives:

1. Describe **hepatocellular** and **cholangiocarcinoma**.
2. Understand the frequency of **metastatic** disease to the liver.
3. Recognize the rarity of **primary liver neoplasms** in children.
4. Recognize all aspects of **pancreatic carcinoma**.



Describe hepatocellular and cholangiocarcinoma

Malignant tumors of the liver

The most common malignant tumors in the liver are metastatic
The most common primary tumor in the liver is hepatocellular carcinoma

- The **liver** and **lungs** are the visceral organs that are **most often involved by metastatic tumors**.
- **Primary** carcinomas of the liver are relatively **uncommon**.
- Most arise from hepatocytes and are termed **hepatocellular carcinoma (HCC)**. Much less common are carcinomas of bile duct origin, cholangiocarcinomas.
- There are two rare forms of primary liver cancer hepatoblastomas and angiosarcomas (neoplasm arising from the blood vessels).

Hepatocellular Carcinomas HCC

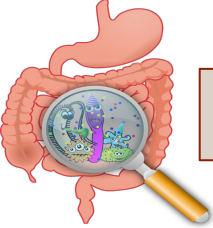
- Most common primary liver cancer
- **Male** predominance in western countries it's nine times more common in male, but in other part of the world like Asia and Africa it's less, three times more common.
- Peaks around **fifth and sixth decades** (older age group).
- More than 85% of cases of HCC occur in countries with high rates of **chronic HBV infection**.
- In these regions, the HBV carrier state begins in infancy following vertical transmission of virus from infected mothers, conferring a 200-fold increased risk for HCC by adulthood especially in Africa, there will be aspergillus (fungus) that grow in saved peanuts for long time in wet countries which produce aflatoxin and this toxin in presence of HBV will help to develop HCC.
- In the Western world where HBV is not prevalent, **cirrhosis** is present in 85% to 90% of cases of HCC, usually in the setting of other chronic liver diseases **Because they drink alcohol**

Pathogenesis of HCC

The following have been implicated in human hepatocarcinogenesis:

1. Postnecrotic cirrhosis due to **chronic HCV (most common cause)** and **HBV** (3rd most common cause)
2. **Alcoholic cirrhosis** (2nd most common cause of HCC)
3. Food contaminants : **Aflatoxins** (from **Aspergillus flavus** mold in grains and peanuts) in association with HBV infection.
4. Hereditary hemochromatosis, Wilson disease
5. PBC, AAT* deficiency, tyrosinemia (*): **alpha one antitrypsin**.
6. Metabolic syndrome e.g. obesity, **diabetes mellitus**, and NAFLD**, all of which increase the risk for HCC (**): **non alcoholic fatty liver disease**.

Robbins: Aflatoxin can bind covalently with cellular DNA, resulting in mutations in genes such as TP53.

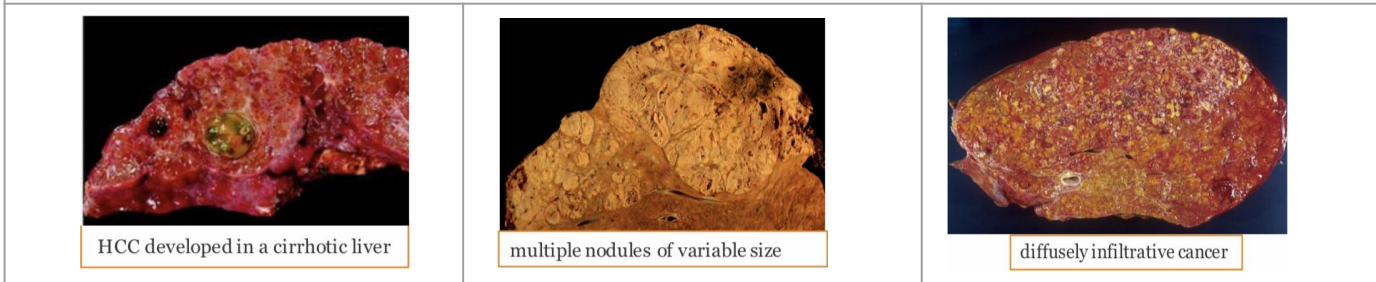


Describe hepatocellular and cholangiocarcinoma

Morphology of HCC

Unifocal mass	Multifocal <i>When you see multifocal think about metastasis because it's more common</i>	Diffusely infiltrative cancer
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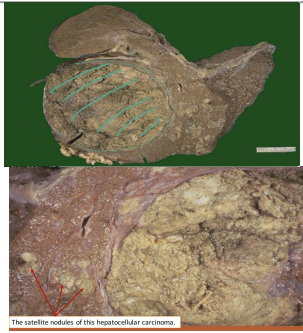
All three patterns may cause liver enlargement. All patterns of hepatocellular carcinomas have a strong propensity for **invasion of vascular channels**.



Hepatocellular carcinoma

Such liver cancers usually arise in the setting of cirrhosis.
Could HCC arise from non cirrhotic liver.

- Worldwide, viral hepatitis is the most common cause, but in the U.S., chronic alcoholism is the most common cause.
- The neoplasm is large and bulky and has a **greenish cast because it contains bile**. **To the right of the main mass are small satellite nodules.**



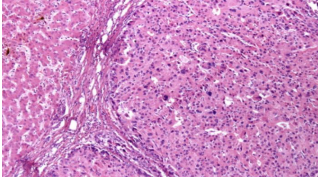
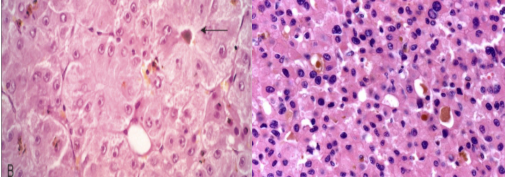
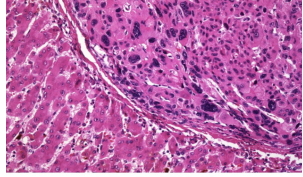
Extensive intrahepatic metastases may occur:

- Tumor may **invade the portal vein** (with occlusion of the portal circulation) or inferior vena cava, extending even into the **right side of the heart**.
- Lymph node metastases to the perihilar, peripancreatic, and para-aortic nodes above and below the diaphragm can be present.
- Hepatocellular carcinomas range from well- differentiated to highly anaplastic undifferentiated lesions.

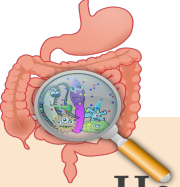
The golden greenish color is due to bile pigment, also note the nodules

Robbins: HCC has a strong propensity for vascular invasion

In well-differentiated and moderately well-differentiated tumors, cells that are recognizable as hepatocytic in origin. **Bile pigment is usually present**. The malignant cells may be **positive for alpha-fetoprotein**. *Well-differentiated tumor have the capacity to produce the original function.*
 In poorly differentiated forms, tumor cells can take on a pleomorphic appearance with numerous anaplastic giant cells, can become small and completely undifferentiated cells.

well-differentiated tumors	HCC with bile pigment	Poorly-differentiated tumors
		 <p>Poorly differentiated HCC (Right)</p>

**Robbins: false-positive results are obtained in yolk-sac tumors, many non-neoplastic conditions such as cirrhosis, chronic hepatitis, normal pregnancy, massive liver necrosis*



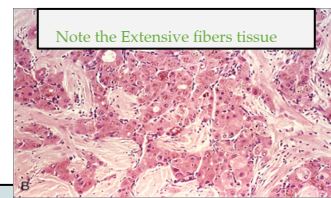
Describe hepatocellular and cholangiocarcinoma

Hepatocellular carcinoma Variant: Fibrolamellar carcinoma

<p>A distinctive variant of hepatocellular carcinoma</p>	<p>This tumor occurs in young male and female adults (20 to 40 years of age),</p>	<p>It has no association with HBV or cirrhosis, and often has a better prognosis.</p>
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microscopic examination

it is composed of well-differentiated polygonal cells growing in nests or cords and separated by **parallel lamellae of dense collagen bundles** (fibrous tissue arranged in layers) and it has mild degree of polymorphism.



Gross appearance

It usually presents as single large, hard "scirrhous" tumor with **fibrous bands** from its name coursing through it.



Clinical Features

Ill-defined upper abdominal pain, malaise, fatigue, weight loss, and feeling of abdominal fullness.

In many cases, the enlarged liver can be felt on palpation. Jaundice and fever are uncommon.

Laboratory studies: **Elevated levels of serum α -fetoprotein** are found in **50% to 75% of patients with HCC**. It's (not specific) biomarker normally found in fetus.

Hepatocellular Carcinoma

Overall, death usually occurs from

- 1) cachexia
- 2) **gastrointestinal or esophageal variceal bleeding** Most common complication of portal hypertension.
- 3) liver failure with hepatic coma
- 4) rupture of the tumor with fatal hemorrhage. **If it's large.**

Pic mnemonic I didn't found one so I created one



It's a fibrolamellar so we draw a J imagine that J is a piece of lettuce ,you will notes that J is the fiber part of that piece of lettuce. The sun ☀ resembles the better prognosis of the tumor

Note the alpha-fetus climbing the J tree

We will have elevation of alpha-fetoprotein

the -YOUNG -yang tells you that the tumor affect Young .

Now let's discuss the gross appearance :see the **black alone scary house** next to the tree,grossly the tumor present as "scirrhous" single large.

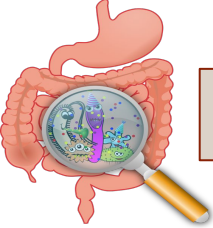
Note some fibrous part from the tree in a shape of a bands directed to it "**fibrous bands coursing through it.**"

Above that scary house there is two signs "hippies are not allowed! Cirrhosis are not allowed" ممنوع التصوير فيه صورة كاميرا there is no association with HBV or cirrhosis

The two GIT red folds in both sides of scary house mouth tells you about the dangerous GI and esophageal bleeding

Note The brownish rupture at the corner of the house ,rupture of the tumor may lead to fatal hemorrhage

Now let us discuss microscopy see the polygonal shaped eggs surrounded by the nest and separated by collagenes blue lines you will notes also that some "poly"of the eggs "gone"from the nest hence it's name polygonal ,On microscopic examination, it is composed of well-differentiated polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagen bundles

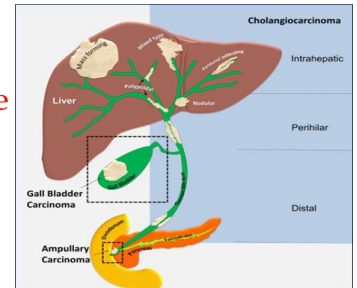


Describe hepatocellular and cholangiocarcinoma

Cholangiocarcinoma

Robbins: Extrahepatic cholangiocarcinomas constitute approximately two thirds of these tumors and may develop at the hilum known as Klatskin tumors

- liver after HCC Cholangiocarcinoma is a malignancy of the **biliary tree**, arising from bile ducts within and outside of the liver **cholangio means bile duct** .
- It is the **second most common primary malignant tumor of the liver**
- occur in non-cirrhotic livers
- may track along the intrahepatic (it can grow along the tree of the bile duct spreading to the liver) portal tract system or produce a single massive tumor

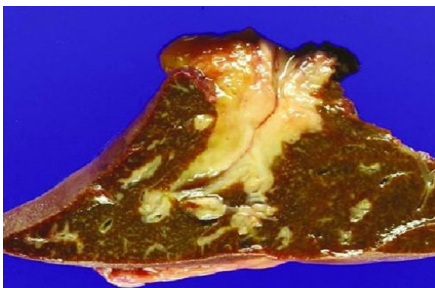


The risk conditions for development of cholangiocarcinoma include

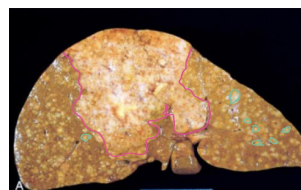
- **Primary sclerosing cholangitis.**
- Congenital fibropolycystic diseases of the biliary system (particularly **Caroli** disease and choledochal cysts).
- Previous exposure to Thorotrast (formerly used in radiography of the biliary tract).
- In the Orient, the incidence rates are higher, and it is due to chronic infection of the biliary tract by the liver fluke *Opisthorchis sinensis*. *This is all parasitology !*

Morphology

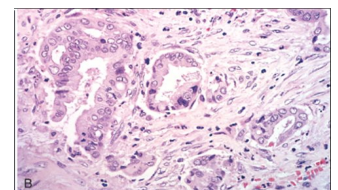
Intrahepatic cholangiocarcinomas occur in the **non-cirrhotic liver** and may track along the intrahepatic portal tract system to create a **treelike** tumorous mass within the liver or a massive tumor nodule. **Lymphatic and vascular invasion are common.**



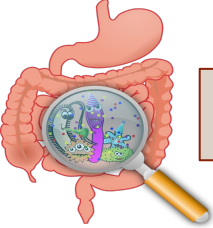
- well to moderately differentiated, growing as **glandular**/tubular structures lined by malignant epithelial cells surrounded by marked **desmoplasia** of the stroma.
- mucin-producing adenocarcinomas **invasive glands which produces mucin because adenocarcinoma**
- in the hcc there will be production of bile**



See the small dots they are also cancer! not only the big mass



You can see Desmoplasia,, what is the type of the tumor? Adenocarcinoma

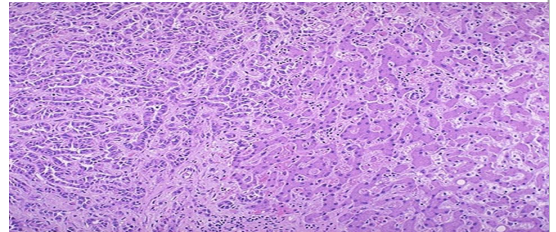


Describe hepatocellular and cholangiocarcinoma

Cholangiocarcinoma

Morphology

The carcinoma at the left has a glandular appearance. Cholangiocarcinomas **do not make bile, but the cells do make mucin**, and they can be almost impossible to distinguish from metastatic **adenocarcinoma** on biopsy or fine needle aspirate



- Mixed variants occur, in which elements of both hepatocellular carcinoma and cholangiocarcinoma are present.
- **Hematogenous metastases** to the lungs, **bones** (mainly vertebrae), adrenals, brain. Lymph node metastases to the regional lymph nodes are also found

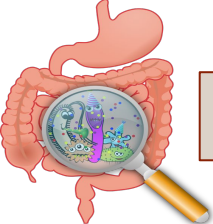
Clinical Features

- Intrahepatic cholangiocarcinoma is usually **detected late** in its course, either as the result of obstruction to bile flow through the hilum of the liver or as a symptomatic liver mass.
- Prognosis is poor. The median time from diagnosis to death is 6 months. **Aggressive surgery** remains the only treatment offering hope for long-term survival.
- **Alpha-fetoprotein is not elevated.**

Liver shaped tree :tree like tumor
 Glands appearance tree:the tumor has a glandular appearance
 No cirrhosis sign لا تصور :occurs in non cirrhotic liver
 Primary defense sclerosing fence:primary sclerosing cholangitis is A risk factor
 Curly hair like folds on the liver shaped tree :caroli disease
 Alpha fetus down:there is no elevation of alpha-fetoprotein
 Moon:poor prognosis because it's detected late remember that the sun resembled good prognosis in the previous sketch
 Grave:leads to death within 6 month
 Lymph nodes and blood vessels invades the tree :lymphatic and vascular invasion is common
 Brownish apples on the tree :massive tumor nodules
 Metastasis to brain, adrenal glands ,vertebrae ,bones is hematogenous so we draw a red line opposite to these organ in the sketch
 In lymph nodes we draw a green line opposing it to remember lymphatic spread
 Greenish not Yellowish Apple's dropped from the tree:secretes mucin not bile
 Apple factory car takes apple from tree:Tumor treated by aggressive surgery

Pic mnemonic you need another one?



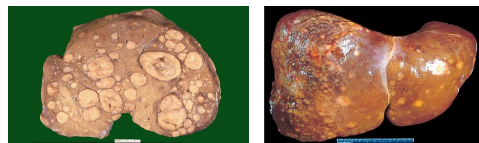


Understand the frequency of metastatic disease to the liver

1-Metastatic tumors:

Numerous mass lesions of variable size. Some of the larger ones demonstrate central necrosis. The masses are metastases to the liver.

Collapse mass = umbilication



Metastatic involvement of the liver is far more common than primary neoplasia. (most common sites for metastasis are liver and lung)

Although the most common primaries producing hepatic metastases are those of the breast, lung, and colon, any cancer in any site of the body may spread to the liver, including leukemias and lymphomas. Typically, multiple nodular metastases are found that often cause striking hepatomegaly and may replace over 80% of existent hepatic parenchyma. The liver weight can exceed several kilograms.

2- Angiosarcoma

Not that common
Just to remember it
Remember risk factors
And it's related with blood vessels and it is not necessarily a cirrhosis patient

Grow as small blood vessels

This consists of pleomorphic endothelial cells with large hyperchromatic nuclei, giant cells in frequent mitosis and irregular anastomosing vascular channels. The cells may appear spindle shaped.

Cirrhosis is present in 20% to 40% of the cases. These have also been linked to **vinyl chloride** and **thorotrast exposure**.

3- Hepatocellular Adenomas

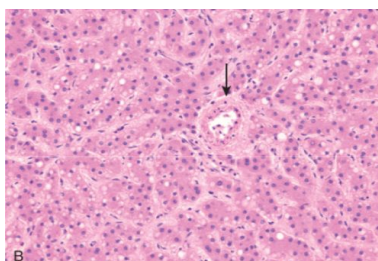
Not common,remember risk factors,related to medications,steroids and contraceptive ,is this tumor benign or malignant?

Benign glandular neoplasms developing from hepatocytes

- Sex hormone exposure(**oral contraceptive pills, anabolic steroids**)

markedly increases the frequency of hepatic adenoma

- They may be detected incidentally as a hepatic mass on abdominal imaging or when they cause symptoms.
- The most common symptom is **pain**, occasionally rupture, an event that may lead to life-threatening intra-abdominal bleeding **shock**



Microscopic view showing cords of hepatocytes, with an arterial vascular supply (arrow) and no portal tracts. **No central vein**



Recognize all aspects of pancreatic carcinoma, Morphology, clinical features

Robbins: the most common antecedent lesions of pancreatic cancer arise in small ducts and ductules, and are called pancreatic intraepithelial neoplasias (PanINs)

Pancreatic carcinoma

Pancreatic cancer has one of the **highest** mortality rates of any cancer. It is carcinoma of the **exocrine pancreas**. It arises from **ductal epithelial cells**. It occurs in the **6th to 8th** decade, blacks more than whites, **males more** than females, **diabetics more** than non-diabetics.

Risk factors

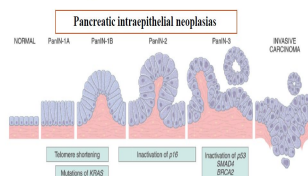
1. **Smoking**, which doubles the risk
2. Long-standing chronic pancreatitis and diabetes mellitus
3. Germ line mutations of the familial breast/ovarian cancer gene BRCA2 **seen also in breast cancer** are seen in approximately 10% of cases arising in individuals of Ashkenazi origin.

Clinical features

- **Jaundice**, weight loss, pain, massive metastasis to liver and migratory **thrombophlebitis**. **Most pancreatic cancers are diagnosed at an advanced stage, accounting for the high mortality rate**

Pathogenesis for the development of pancreatic cancer

Pancreatic cancer arises as a consequence of inherited and acquired mutation in cancer-associated genes



Four genes are most commonly affected by somatic mutations in this neoplasm: KRAS, CDKN2A/p16, SMAD4, and TP53

The genes are important !! KRAS is early
TP53 is a tumour suppressor gene and it's late

Location of pancreatic carcinoma

1. **Head of the pancreas**: 60%
2. The body of the pancreas: 15%
3. The tail of the pancreas: 5%
4. The neoplasm diffusely involves the entire gland: 20%

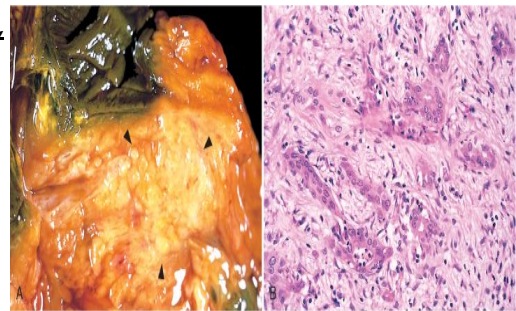
Morphology

Carcinomas of the pancreas are usually **hard, stellate, gray-white, poorly defined masses**.

Majority of carcinomas are ductal adenocarcinomas.

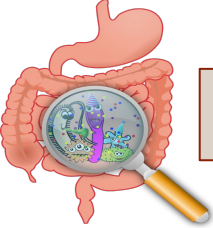
Two features are characteristic:

1. It is **highly invasive** it is **very aggressive tumor**.
2. It elicits an intense non-neoplastic host reaction called a "desmoplastic response".



Metastasis to:

- **Lymph nodes**: Peripancreatic, gastric, mesenteric, omental, and portohepatic lymph nodes are **frequently** involved.
- Distant metastases: to the lungs and bones **and peritoneal cavity**.
- Less common variants of pancreatic cancer include acinar cell carcinomas, adenosquamous carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells. تذكروا الاسماء بس ما بندخل بالديتيلز



Pathoma

12

Cancer of liver and pancreas

PANCREATIC CARCINOMA

- A. Adenocarcinoma arising from the pancreatic ducts
 - 1. Most commonly seen in the elderly (average age is 70 years)
- B. Major risk factors are smoking and chronic pancreatitis.
- C. Clinical features (usually occur late in disease)
 - 1. Epigastric abdominal pain and weight loss
 - 2. Obstructive jaundice with pale stools and palpable gallbladder; associated with tumors that arise in the head of the pancreas (most common location)
 - 3. Secondary diabetes mellitus; associated with tumors that arise in the body or tail
 - 4. Pancreatitis
 - 5. Migratory thrombophlebitis (Trousseau sign); presents as swelling, erythema, and tenderness in the extremities (seen in 10% of patients)
 - 6. Serum tumor marker is CA 19-9.
- D. Surgical resection involves en bloc removal of the head and neck of pancreas, proximal duodenum, and gallbladder (Whipple procedure).
- E. Very poor prognosis; 1-year survival is < 10%.

Liver

XI. HEPATIC ADENOMA

- A. Benign tumor of hepatocytes
- B. Associated with oral contraceptive use; regresses upon cessation of drug
- C. Risk of rupture and intraperitoneal bleeding, especially during pregnancy
 - 1. Tumors are subcapsular and grow with exposure to estrogen.

XII. HEPATOCELLULAR CARCINOMA

- A. Malignant tumor of hepatocytes
- B. Risk factors include
 - 1. Chronic hepatitis (e.g., HBV and HCV)
 - 2. Cirrhosis (e.g., alcohol, nonalcoholic fatty liver disease, hemochromatosis, Wilson disease, and α_1 AT deficiency)
 - 3. Aflatoxins derived from *Aspergillus* {induce p53 mutations}
- C. Increased risk for Budd-Chiari syndrome
 - 1. Liver infarction secondary to hepatic vein obstruction
 - 2. Presents with painful hepatomegaly and ascites
- D. Tumors are often detected late because symptoms are masked by cirrhosis; poor prognosis
- E. Serum tumor marker is alpha-fetoprotein.

XIII. METASTASIS TO LIVER

- A. More common than primary liver tumors; most common sources include colon, pancreas, lung, and breast carcinomas.
- B. Results in multiple nodules in the liver
- C. Clinically may be detected as hepatomegaly with a nodular free edge of the liver

Questions



1. Which of the following is the most common to develop Hepatocellular carcinoma:

- A. HAV
- B. HBV
- C. HCC
- D. a+c

2. Which of the following is the most common malignant tumor of the liver:

- A. cholangiocarcinoma
- B. metastatic tumors
- C. primary HCC

3. A male patient complained of upper abdominal pain, fatigue and weight loss he was diagnosed with Hepatocellular carcinoma which one of the following may be positive?

- A. Alpha fetoprotein
- B. Alpha 1 acid glycoprotein
- C. Beta-2 microglobulin

4. The most common carcinomas of the liver will arise from:

- A. Bile ducts
- B. Hepatocytes
- C. Blood vessels

5. Which of the following is a laboratory finding in cholangiocarcinomas?

- A. Alpha-fetoprotein is not elevated
- B. Alpha-fetoprotein is elevated
- C. Alpha-fetoprotein is decreased

6. A distinctive variant of hepatocellular carcinoma is the:

- A. Fibrolamellar carcinoma
- B. Hepatic Adenoma
- C. Hepatocellular Carcinomas

7. What is the common etiology for Hepatic adenoma?

- A. HBV & HCV
- B. Primary sclerosing cholangitis
- C. Oral contraceptive drugs

Answers

- 1- B
- 2- B
- 3- A
- 4- B
- 5- A
- 6- A
- 7- C

كل الشكر والتقدير للجهود العظيمة من قبل أعضاء فريق علم الأمراض الكرام

قادة فريق علم الأمراض

شيرين العكيلي

فايز غياث الدرسوني

اعضاء فريق علم الأمراض

رزان الزهراني
لين الحكيم
عهد القرين
وجدان الشامري
غرام جليدان
ليلى الصباغ
ريناد الغريبي

مها العمري
مجد البراك
بتول الرحيمي
منيرة المسعد
مشاعل القحطاني
رناد الفرغ
غادة الحيدري
دانة القاضي
مها بركة

راكان محمد الغنيم
سلطان ناصر الناصر
عادل عبدالعزيز السحيباني
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تركي عيد الشمري
عبدالجبار اليماني
عبدالله المعيدر
منصور العبرة
خالد العقيلي
تركي آل بنهار
عبدالعزیز الضرعام
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