TUMORS & HEPATIC NODULES

+ The liver & lungs are the most commonly involved organs by metastatic cancer

secondaries.

+ indeed, the most common hepatic tumors are metastatic carcinomas, mainly from

colon + lung + breast primaries.

<table>
<tr><td colspan="2">The main two primary liver cancers are</td><td colspan="2">Two rare primary liver tumors (not discussed further)</td></tr>
<tr><td>(1) hepatocellular carcinomas (HCC),</td><td>(2) cholangiocarcinomas</td><td>Hepatoblastoma</td><td>Angiosarcoma</td></tr>
<tr><td>which is the most common primary hepatic malignancy</td><td>cholangiocarcinomas → bile duct epithelium</td><td>childhood hepatocellular tumor</td><td>of blood vessels that is associated with exposure to vinylchloride & arsenic, & Thorotrast</td></tr>
<tr><td colspan="4">Clinically, hepatic masses may :
(1) cause epigastric fullness,
(2) be detected by routine physical ex
(3) be incidental finding during X-ray ex. for other indications.</td></tr>
</table>

Hepatocellular Nodules

Solitary or multiple benign hepatocellular (H) nodules which may develop in the liver

are of 3 types:

(I) focal nodular hyperplasia	(II) macroregenerative	(III) dysplastic nodules.
***Is not a tumor,** but a **nodular regeneration**. *Is a localized, well-demarcated, but poorly encapsulated lesion, consisting of hyperplastic H nodules with a central fibrous scar, may reach up to many cm in *Occurs in response to **local vascular injury**, & in about 20 % of cases, it coexists with **hepatic cavernous hemangiomas** . * Occurs usually as an **incidental finding,** commonly in **women of reproductive age.**	*larger than surrounding cirrhotic nodules * but do not display atypical .features *Nodules contain more than one portal tract, have an ‹intact reticulin framework .	***Nodules **less than 1 mm** in * The H in dysplastic nodules & in smaller lesions called dysplastic foci, are highly proliferative * **Show low or high grade atypical features,** i.e., crowding & pleomorphism**.** *Are often monoclonal, & may contain chromosome aberrations similar to those present in HCC. * Dysplastic nodules are subdivided into small-cell & large-cell dysplastic nodules or foci. *H in large-cell dysplastic lesions are apparently have reached replicative senescence.
Nodules **appear in noncirrhotic livers.**	Appear in cirrhotic livers	that **appear in cirrhotic liver.**
Does not carry a risk for cancer .	are not precursors of cancer	+ **High-grade dysplastic lesions are considered to be precursors of HCC** **Only small-cell dysplasias are precursors to HCC**

Benign Tumors

Cavernous hemangioma	**Hepatic Adenoma**
*is the commonest BT of the liver. * Well-circumscribed lesions , consist of EC-lined vascular channels & intervening stroma . * Appear as discrete red-blue, subcapsular, soft nodules, less than 2 cm in dimeter . * Clinical significance: (A) blind percutaneous needle biopsy may cause severe intra-abdominal bleeding (B) importance of not mistaking them for metastatic cancer.	*BT of H, usually occurs in **women** of childbearing age who have **used oral contraceptive steroids,** & it may regress on discontinuance of hormone use. * These T may be yellow-tan pale, or bile-stained, well-demarcated nodules found anywhere in the hepatic substance but, **often subcapsular.** ***They may reach 30 cm** . • *H, **composed of sheets & cords of cells that resemble normal H. Portal tracts are absent ; instead, prominent arteries & veins are distributed through the tumor.** *Clinically, **hepatic adenomas are significant for 3 reasons**: (1)**They may be mistaken for HCC** ==> اول اشي بتتوقعه metastasis لأنه ال فلازم تتأكد و تستثني الاحتمالات (2) **Subcapsular** adenomas are at risk for **rupture** , particularly during pregnancy (under estrogenic stimulation), **causing life - threatening intra - abdominal hemorrhage .** (3) Although adenomas are not considered precursors of HCC, **adenomas carrying β - catenin mutations carry a risk of developing into cancers.**

Hepatocellular Carcinomas (HCC)

+ Epidemiology, worldwide, HCC (also known as **liver cell carcinoma** or, erroneously, hepatoma , constitutes 5.4% of all cancers, but the incidence varies

widely in different areas of the world.

+ **More than 85% of cases** occur in countries with high rates of **chronic HBV infection.**

Highest incidences	Low incidence
are found in Asian countries (Southeast China, Korea,& Taiwan) & African countries such as Mozambique, in which HBV is transmitted vertically, & in which carrier state starts in infancy Moreover, many of these populations are exposed to aflatoxin, which, combined with HBV infection, the risk of HCC development by more than 200 - fold over non infected, non exposed populations .	HCC incidence is rapidly in the West It tripled in the US during the last 25 years, but it is still much lower (8- to 30 fold) than the incidence in some Asian countries.
The peak incidence of HCC in these areas is between 20- 40 years of age,	In the West, HCC is rarely present before age 60
In almost 50% of cases, the HCC appear in the absence of cirrhosis!	in 90 % of cases, HCC develop in persons with cirrhosis!
There is a marked male preponderance of HCC throughout the world;	
M: F = 8:1	M:F = 3:1
These differences may be related to the greater prevalence of HBV infection, alcoholism, & chronic liver disease among males	

Pathogenesis of HCC

****3 major etiologic associations have been established**:

*HBV or HCV infection

*Chronic alcoholism

*Aflatoxin exposure

**Other conditions include hemochromatosis & tyrosinemia .

****Many variables** , including age, gender, chemicals, viruses, hormones, alcohol, &nutrition, **interact in the development of HCC** , e.g., t**he disease most likely to give rise to HCC is, in fact, the extremely rare hereditary tyrosinemia**, in which 40% of patients develop HCC despite dietary control.

+The development of **cirrhosis seems to be an important**, but not requisite,contributor to the emergence of HCC.

+Carcinogenesis is greatly enhanced in the presence of cell injury & replication, as occurs in chronic viral hepatitis.

In many parts of the world, including **Japan & Central Europe**	**In China & South Africa**
chronic HCV infection is the greatest risk factor in the development of liver cancer	*where **HBV** is endemic *there is also high exposure to **dietary aflatoxins** derived from the fungus **Aspergillus flavus**. These carcinogenic toxins are found in "moldy" grains & peanuts. Aflatoxin can bind covalently with cellular DNA & cause a mutation in p53.
HCC in patients with hepatitis C occurs almost exclusively in the setting of C.	

+Despite the detailed knowledge about the etiologic agents of HCC, t**he pathogenesis of HCC is still uncertain .**

Origin :

HCC seems to arise from both:

1- **mature hepatocytes**

2- progenitor cells (known as **ductular cells or oval cells**).

+ **In most cases, it develops from small - cell, high ‑ grade dysplastic nodules in cirrhotic livers** , these nodules may be monoclonal & may contain chromosomal aberrations similar to those seen in HCC.

+ **Distinguishing high-grade dysplastic nodules from early HCC is difficult** even in biopsies, because there are **no molecular markers specific for these stages**.

+ **An important criterion of HCC is tumor nodule vascularization** , visualized By **imaging (U/S)**, which is almost always a clear indication of malignancy.

+ An almost **universal feature of HCC** is the presence of structural & numeric chromosomal abnormalities. The precise origin of HCC genetic instability is not known.

Pathogenesis

+ Cell death, H replication, & inflammation seen in all forms of chronic hepatitis, are believed to be main contributors to DNA damage .

► Poor regulation of H replication can occur by:

(1) point mutations

(2) overexpression of specific cellular genes (such as β -catenin)

(3) mutations or loss of heterozygosity of tumor suppressor genes (such as p53)

(4) methylation changes

(5) constitutive expression of Gfs

(6) Defects in DNA repair, particularly those in repair systems for double-stranded

DNA breaks, perpetuate DNA damage & may cause chromosome defects.

Neither HBV nor HCV contains oncogenes, & the tumorigenic capacity of these viruses probably relates primarily to their capacity to cause continuing cell death, regeneration & chronic inflammation.

Morphology:

**HCC may appear grossly as a :

(1) **Unifocal**	(2) **Multifocal**	(3) **Diffusely infiltrative** cancer
single massive tumor	made of multiple nodules of variable size	which may involves the entire liver.
	In the latter two patterns it may be difficult to distinguish regenerative nodules of cirrhotic liver from cancer nodules of similar size!	
Tumor masses are grossly yellow-white, punctuated sometimes by bile staining & areas of hemorrhage or necrosis.		

****Vascular invasion : all HCC have a strong propensity** for invasion of vascular channels, resulting in:

1- extensive intrahepatic metastases

2- occasionally s**nakelike cancer masses** invade the **portal vein** (causing occlusion) or the **inferior vena cava**,extending into the right side of the **heart**!

**H, HCC range from:

1-well-differentiated T that reproduce H arranged in cords, trabeculae or glandular patterns

2- to poorly differentiated T, often composed of large multinucleate anaplastic T giant cells.

****In the better differentiated variants,**

+ **Globules of bile** may be found within the cytoplasm of cells & in pseudocanaliculi between cells, & acidophilic hyaline intracytoplasmic inclusions **(Mallory bodies)** may be seen.

** There is **surprisingly scant stroma** in most HCC, explaining the soft consistency of these T.

Fibrolamellar carcinoma

is a distinctive clinicopathologic variant of HCC

Fibrolamellar carcinoma	Usual HCC
occurs **in young** (20-40 years of age)	Details above
with **equal sex** incidence	Male more
has **no association with cirrhosis or other risk factors,**	**3 major etiologic associations have been established**: *HBV or HCV infection *Chronic alcoholism *Aflatoxin exposure **cirrhosis seems to be an important**
usually consists of a single large, hard "scirrhous" tumor with fibrous bands coursing through it, resembling focal nodular hyperplasia. H, composed of well-differentiated polygonal cells growing in nests or cords & separated by parallel lamellae of dense collagen bundles.	There is **surprisingly scant stroma** in most HCC, explaining the soft consistency of these T.

Clinical Features

1- Although HCC may present with **silent hepatomegaly**

2- HCC are often **encountered in individuals with cirrhosis** who already have symptoms of it.

3- In cirrhotic persons:

a- a rapid increase in liver **size**

b- sudden worsening of **ascites**

c- the appearance of **bloody ascites**

d- **fever, & pain**

call attention to the development of HCC.

Diagnosis

**Laboratory studies are helpful but not diagnostic .

***50 % of patients have elevated serum α - fetoprotein**.

1-However, this T "marker" lacks specificity, because **modest elevations** are also encountered in other conditions, such as cirrhosis,, chronic hepatitis, normal pregnancy, fetal distress

or death, & gonadal germ cell T.

2- **Very high levels (> 1000 ng/mL), however, are rarely encountered except in HCC.**

****Final diagnosis is by histopathological examination of liver biopsy .**

Prognosis of HCC is grim

** **But** it is significantly better for individuals who have a

single tumor less than 2 cm in diameter & good liver function.

▼The **median survival is 7 months,** with **death from**:

(1) Profound cachexia

(2) Bleeding esophageal varices

(3) LF with hepatic coma

(4) rarely Rupture of the tumor with fatal hemorrhage.

Treatment

** **Early detection** of HCC is **critical** for successful treatment.

**The most effective therapies are

1- surgical resection of smaller T detected by U/S

2- screening of persons with chronic liver disease

3- **liver transplantation** for patients with small tumors & good liver function.

**T recurrence rate is greater than 60% at 5 years.

****Best hope** for preventing HCC in regions endemic for HBV infection is a comprehensive anti - HBV immunization program.