بسم الله الرحمن الرحيم

WORSHIP THE CREATOR, NOT HIS CREATIONS.
Metabolic liver disease
Metabolic liver disease

Group of diseases due to disorders of metabolism

- Acquired
  - Inherited

A- Acquired
  - Non alcoholic fatty liver disease

B- Inherited
  - Hemochromatosis
  - Wilson disease
  - A\textsubscript{1} antitrypsin deficiency
Non alcoholic fatty liver disease (NAFLD)

Non alcoholic fatty liver disease (NAFLD) – group of conditions:

Include;

1. Simple hepatic steatosis (fatty liver)
2. Steatosis accompanied by non specific inflam
   (stable conditions with out significant clinical problems)
3. Non alcoholic steatohepatitis (NASH)

- Individuals with No H/o alcohol consumption / take very small quantity - < 20 gm of ethanol / week
Non Alcoholic Steatohepatitis - NASH

NASH:
• A condition with hepatocyte injury –
• may progress to cirrhosis - in 10 – 20 % cases .

Main components are:

• Hepatocyte ballooning
• Lobular inflammation
• Steatosis

Progression of disease – fibrosis

Men = women
Non Alcoholic Steatohepatitis - NASH...

Ass. with; obesity & other components of metabolic synd. – as.

• Dyslipidemia,
• Hyperinsulinemia
• Insulin resistance

➢ 70% of obese individuals - NAFLD;

➢ Most common cause of cryptogenic cirrhosis –
  (cirrhosis of unknown origin)
➢ contribute to progression of other liver diseases – HCV infectopn, & HCC.
Pathogenesis;

Pathogenesis;

• Has two sequential events:

(1) Hepatic fat accumulation &
(2) Hepatic oxidative stress.

Oxidative stress - acts upon accumulated hepatic lipids, - leads to

• Lipid peroxidation &
• Release of lipid peroxides, - produce reactive oxygen species.
Obesity → Hepatic steatosis → NASH → Cirrhosis → HCC

- Obesity: 30-90%
- Hepatic steatosis: 10-20%
- NASH: 3-5% in 20 years
- Cirrhosis: ??%
Fatty liver - Morphology

Steatosis;
• Involves \( \geq 5\% \) of hepatocytes
  (rarely - \( > 90\% \))

• Micro & macro vesicular –
  (droplets of fat in hepatocytes)

In less severe disease –
• Only - Elevated liver enzymes

No inflam, hepatocyte death / scaring
Two patterns of hepatic steatosis

(1) **Micro vesicular steatosis:**
- **Cytoplasm** - replaced by bubbles of fat - do not displace the nucleus; &

(2) **Macrovesicular steatosis:**
- **Cytoplasm** - replaced by a large bubble of fat that displaces the nucleus to edge of cell.
Morphology

Steatohepatitis (NASH);

- Steatosis,
- Parenchymal inflam-
  - Multi focal, mainly neutrophils
- Mallory bodies –
- Hepatocyte death (ballooning degen & apoptosis),
- Fibrosis;
  - Sinusoidal,
  - In portal tract &
  - Around terminal hepatic V

- Cirrhosis - may develop after years
Steatohepatitis

Micro;

• Macro vesicular steatosis,

• Cytologic ballooning,

• Mallory bodies, and

• Scattered lobular inflam
Mallory's hyaline bodies:

- Pink filamentous structures, cytoplasmic inclusions in hepatocytes (ab. keratin, hyaline, & other pr).

- Consequence of cellular injury.

- Found in ballooned hepatocytes (black arrow)

- Morphologic hallmarks of alcoholic and nonalcoholic steatohepatitis.

Hepatocytes, - macro vesicular fat globules (white arrow), displacing nucleus (white arrowhead) to periphery
Steatohepatitis with cirrhosis.

- A nodule of liver tissue is circumscribed by scar tissue.
NASH

- Elevations in liver tests, ALT / AST
- **No apparent reason for liver disease** (medications, viral hepatitis, / alcohol)

- x rays or imaging studies - show fat, - suspect - NASH .
- Tissue shows fat without inflam / damage - **simple fatty liver / NAFLD**.
Clinical features

• Simple steatosis – asymptomatic

• Symptoms - Related to other metabolic derangements – (Obesity, insulin resistance and diabetes)

• General symptoms -
  • Fatigue
  • Right abd. Discomfort - due to hepatomegaly

• NASH with ass - dyslipidemia, hyperinsulinemia and insulin resistance –
  • Cardiovascular disease – frequent cause of death
Clinical features...

Diagnosis:
- Elevated serum AST & ALT – in 90% - pts with NASH
- Imaging studies – fat accumulation - in liver
- Liver biopsy – diagnostic tool for NASH.
  Determine the:
  - Extent of - steatosis,
  - Presence of - steatohepatitis and
  - Degree of - fibrosis

Goal of treatment to:
- Reverse steatosis and
- Prevent cirrhosis

Liver transplantation - only treat for advanced cirrhosis with liver failure,
Hemochromatosis
Hemochromatosis

Hemochromatosis – can be;

• **Primary**
  • An inherited disorder-
  • Caused by *excessive iron absorption*

• **Secondary** - acquired H./ hemosiderosis
  • Accumulation of iron in tissues - *due to parental administration of iron as* transfusion / other causes
Hemochromatosis

Ch by:

- Excessive accumulation of body iron, - in parenchymal organs – liver & pancreas. / heart, joints, endocrine organs

Normally:
- Total body iron pool -2-6 gm in adults.
- 0.5gm – in liver, 98% of this – in hepatocytes

In primary hemochromatosis:
- Total body iron - > 50 gm,
  - 1/3rd of which – in liver
Hemochromatosis...

Primary hemochromatosis:

- **Fully developed cases** show
  - Micronodular cirrhosis – in all pts
  - Diabetes mellitus – 75 – 80% of pts
  - Skin pigmentation – 75 - 80% pts

- **Iron accumulation** –
  - Is life long, but
  - Injury by excessive iron - slow & progressive so
  - Symptom - in 5\textsuperscript{th} – 6\textsuperscript{th} decades of life

- **Men** > women
Classification of Iron Overload

I. Hereditary Hemochromatosis
   • Mutations in genes

II. Hemosiderosis (Secondary Hemochromatosis)

   A. Parenteral iron overload
      • Transfusions
      • Long-term hemodialysis
      • Aplastic anemia
      • Sickle cell disease
      • Myelodysplastic syndromes
      • Leukemias
      • Iron-dextran injections

   B. Ineffective erythropoiesis with increased erythroid activity
      • β-Thalassemia

   C. Increased oral intake of iron
      • African iron overload (Bantu siderosis)

   D. Congenital atransferrinemia

   E. Chronic liver disease
      • Chronic alcoholic liver disease
      • Porphyria cutanea tarda

   F. Neonatal hemochromatosis

   • Sideroblastic anemia
   • Pyruvate kinase deficiency
Hemochromatosis

Pathogenesis.

• Total body iron - regulated by intestinal absorption

In hemochromatosis:

• Regulation of intestinal absorption of dietary iron is - lost – Net iron accum. - 0.5 to 1.0 gm/year mainly in liver.
• - After 20 gm of storage iron - Disease.
Pathogenesis...

*Excessive iron* - directly toxic to host tissues by;

1. Lipid per oxidation via iron-catalyzed free radical reactions
2. Stimulation of collagen formation
3. Interactions of reactive oxygen species & iron with DNA, lethal injury / hepatocellular carcinoma

- Process - *reversible in cells* - not fatally injured,
- Removal of excess iron by therapy - promotes recovery of tissue function
Pathogenesis...

- **Main regulators** of iron absorption is – [hepcidin](#) – pr. encoded by HAMP gene, produced by hepatocytes.

- Its production
  - Increased by - inflam cytokines & iron &
  - Decreased by - iron def, hypoxia & ineffective erythropoiesis.

- [Hepcidin](#) - prevents - release of iron from intestinal cells & macrophages – lowers plasma iron level

- Hepcidin level is regulated by;
  - [Hemojuvelin](#) ( Pr expressed by liver, heart & sk muscle)
  - Transferrin Receptor 2 - on hepatocytes
  - [HFE](#) - product of hemochromatosis gene
Pathogenesis...

Mutation of:

- **HAMP gene & hemojuvelin** — *Sever form* of hereditary *juvenile hemochromatosis.*

- **HFE & transferrin receptor 2** — *Classic form* of *mild* hereditary *adult hemochromatosis.*
Hereditary Hemochromatosis

**Morphologic Changes** - ch. by

- Deposition of hemosiderin - in dec. order of frequency in:
  - liver,
  - Pancreas,
  - Myocardium,
  - Pituitary gland,
  - Adrenal gland,
  - Thyroid, parathyroid,
  - Joints &
  - Skin

- Cirrhosis

- Pancreatic fibrosis

- "Hemosiderosis" - relatively benign accum. of iron.

- Hemochromatosis" - when organ dysfunction occurs.
Morphology...

• **Golden yellow** hemosiderin granules - of periportal hepatocytes – *(cytoplasm)*

• Stain **blue** with **Prussian blue stain**

**With increasing iron load** –

• Progressive involvement of - *rest of lobule*,

• Bile duct epith & Kupffer cell - pigmentation,

**At this stage;**

• liver – slightly enlarged, & **chocolate brown**.

**Fibrous septa** - slow –

• Micro nodular pattern of **cirrhosis** in intensely pigmented liver

**Prussian blue iron stain**

-Blue granules of hemosiderin in; hepatocytes & Kupffer cells.
Hemochromatosis

- A cross-section of a **normal, healthy liver**

Dark brown color of:
- **Liver**,  
- **Pancreas** (bottom center) &  
- **Lymph nodes** (bottom right) on sectioning - is due to – **extensive iron deposition**
Morphology…

• **Pancreas** –
  • Intensely pigmented,
  • Diffuse interstitial fibrosis,
  • Parenchymal atrophy.
  • **Hemosiderin** present both in acinar & islet cells & fibrous stroma

• **Heart** –
  • Enlarged,
  • Hemosiderin granules in myocardial fibers

• **Skin** - pigmentation

• **Pigmentation** of synovial lining, and testes
Hemochromatosis

- **Extensive fibrosis** with small nodules of hepatocytes **without** fatty change.

- **Iron stain of liver** - presence of **hemosiderin granules**.
Hemochromatosis

**Hepatocytes & Kupffer cells** –

- Granular brown deposits of **hemosiderin** –

Due to - accumulation of excess iron in the liver.
Clinical features

• Arthritis

• > in male,

• **Rare - < 40 y**

Presents as;

• Hepatomegaly-

• Abdominal pain,

• Skin pigmentations ,

• Diabetes mellitus - due to destruction of pancreatic islands,

• Cardiac dysfunction- (arrhythmias, cardiomyopathy),

**Classic triad**- late in the course;

1) Pigment cirrhosis with **hepatomegaly,**

2) Skin pigmentation,

3) Diabetes mellitus
Clinical features…

**Death** - may occur due to:

- Cirrhosis,
- Cardiac disease /
- Hepatocellular Ca

**Diagnosis:**

- **High serum iron** and **ferritin** levels,
- Exclusion of secondary causes of iron overload
- **Liver biopsy**
- **Prussian blue** histological reaction
- **Treatment:**
  Pre - cirrhotic stage - treated by **regular phlebotomy**
Wilson's disease
Wilson's disease / hepatolenticular degeneration

- An **autosomal recessive** disorder caused by **mutations in** (ATP 7B) **gene**. Resulting in;
  - **Impaired** - copper excretion into bile &
  - **Failure** to incorporate copper - **in ceruloplasmin**

- **Toxic levels** of copper accumulates in tissues & organs, esp
  - Liver,
  - Brain &
  - Eyes;
Wilson's disease

Normally:

• 40 -60 % of ingested copper (2 -5 mg /day)- **absorbed** in duodenum & proximal small intestine – **To portal circulation** - with **albumin** & histadine

• **Free copper** dissociates - & taken up by **hepatocytes** –

• **Incorporates in to enzymes** & **binds to apoceruloplasmin** to form **ceruloplasmin** – secreted in **blood**.

• **Excess copper** – transported **into bile**,  

• **90 – 95 %** of plasma copper – **ceruloplasmin** - eventually - **degraded by liver cells**

• **Released copper** is excreted into bile.

• **Total body copper** – **50 – 150 mg**
Wilson's disease

• **ATP 7B gene** – located on ch 13,

• **Encodes** - a trans memb. Copper transporting ATPase – expressed on hepatocyte canalicular memb.

• **Mutations** – def of - ATP7B pr. – decrease copper transport in bile

• **Impairs** - incorporation in cerulopl –
  - Dec cerulopl sec in blood –
  - Copper accum in liver – toxic liver inj
Liver - mainly effected,

Hepatic changes;
- minor to massive damage

- **Fatty change** - mild to moderate with;
- **vacuolated nuclei** and
- occasional **focal hepatocyte necrosis**

- **Acute hepatitis** –
  feature of - acute viral hepatitis with **fatty change**

A **bluish-coppery** colored liver,
Morphology...

**Chronic hepatitis** of Wilson disease –

- Moderate to severe inflammation
- Hepatocyte necrosis &
- Macro vesicular steatosis.
- Vacuolated hepatocellular nuclei and
- Mallory bodies –

**Progress to cirrhosis**

- Hepatic copper content -  > 250 µg / gm dry weight - most diagnostic
- **In the brain** - toxic injury to basal ganglia - atrophy / cavitation
Wilson's disease

**Eyes:**

- *Kayser-Fleischer rings* (KF rings)
- visible around the iris.
- Due to copper deposition in *descemet's memb of cornea*.

- *Golden Brown / copper-colored rings* - Kayser-Fleischer rings around - corneas
Clinical features

- **Symptoms** usually appear between 6 - 40 years

- Most common presentation – acute / chronic liver disease

Neuropsychiatric manifestations including:

- Mild behavioral changes,
- Frank psychosis or
- Parkinson disease – like syndrome e.g. tremors
Clinical features...

**Biochemical diagnosis** of Wilson disease is based on:

- **Decreased** - serum ceruloplasmin,
- **Increased** - hepatic copper content & - (most sensitive test)
- **Increased** - urinary excretion of copper- (most sp. Screening test)

- **Serum copper level** – low / normal / elevated
  depending on the stage of disease - **not diagnostic**

Pts with hepatitis / cirrhosis- **liver transplantation** –
Alpha 1-antitrypsin deficiency
Alpha antitrypsin-1 deficiency

- **Autosomal Recessive Disorder** –
- **Very low levels** of **Alpha 1 – antitrypsin** - a **plasma glycoprotein** - synthesized by hepatocytes

- **Major function** of this protein –
  - **Inhibition of proteases** -
    esp neutrophil elastase, cathepsin G & protinase 3 – normally released from neutrophils at sites of inflam.
Alpha antitrypsin-1 deficiency

- **Alpha antitrypsin-1 deficiency** – cause – *pulmonary emphysema* due to *unopposed* destructive proteases

- Also causes:
  - Liver disease due to accum of this pr in hepatocytes
  - Cutaneous paniculitis,
  - Arterial aneurysm,
  - Bronchiectasis and
  - Wegener’s granulomatosis.

**Defective secretion** of Alpha-1 antitrypsin by hepatocytes –
- Chronic active hepatitis,
- Cirrhosis,
- HCC in child
Alpha-1 antitrypsin deficiency

**Normal**
- **Lung**
  - Alpha-1 antitrypsin coats lungs, protecting them from neutrophil elastase.
- **Liver**
- **Blood Vessel**
  - Alpha-1 antitrypsin Protects lungs from neutrophil elastase.
  - Neutrophil elastase
    - Produced by white blood cells to break down harmful bacteria.
    - Potentially damaging to lungs if exposed.

**Alpha-1 Antitrypsin Deficiency**
- **Lung**
  - Lungs lack alpha-1 antitrypsin coating, leaving them open to damage by neutrophil elastase
- **Liver**
  - Alpha-1 antitrypsin
    - Trapped in liver, causing liver damage
- **Blood Vessel**
  - Neutrophil elastase
    - Uninhibited, causing lung damage.
  - White blood cell (neutrophil)
Alpha 1-antitrypsin deficiency - Morphology

Hepatic pathology – Range from:

- Neonatal hepatitis with / without cholestasis & fibrosis to childhood cirrhosis /

- Chronic active Hep / Cirrhosis - appears late in life

Distinctive feature of hepatic diseases;

- PAS positive globules, - (Mostly only distinctive feature)
- Fatty change &
- Mallory bodies
Alpha-1-antitrypsin deficiency

- **Morphology:**

  - **Round - oval** cytoplasmic **globular inclusions**

- Mostly, in hepatocytes, surrounding the portal tracts

- **Acidophilic** in H&E,
- **PAS** – **positive**.
Alpha-1-antitrypsin deficiency

- Large globules in the liver cells (PAS positive granules)
- On the right - normal liver cells
Alpha 1-antitrypsin deficiency

C/F;

- **Neonatal** - hepatitis & jaundice – 10 – 20% of newborns with antitrypsin deficiency

- **In adolescence** – symptoms of hepatitis / cirrhosis

- Hepatitis – may subside with recovery or
- chronic H - cirrhosis in middle to latter life

- 2 - 3% of adults develop HCC

- Treatment – Liver transplantation
Intrahepatic biliary disease
Intrahepatic billiary disease

Disorders of intrahepatic bile ducts

1. Secondary billiary cirrhosis
2. Primary billiary cirrhosis
3. Primary sclerosing cholangitis

• **Secondary billiary cirrhosis** - uncorrected obst. of extra hepatic billiary tree

• **Primary billiary cirrhosis** – destructive disorder of intrahepatic billiary tree

• **Primary sclerosing cholangitis** - involves both extra hepatic & intra hepatic billiary tree
## Primary biliary cirrhosis / Secondary biliary cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Primary biliary cirrhosis</th>
<th>Secondary biliary cirrhosis</th>
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</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>autoimmune</td>
<td>extra hepatic bile duct obstruction; biliary atresia, gall stones, stricture, ca head of pancreas</td>
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<tr>
<td><strong>Sex predilection</strong></td>
<td>6 : 01</td>
<td>None</td>
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<tr>
<td><strong>Symptoms / signs</strong></td>
<td>pruritus, jaundice, malaise, dark urine, light stools, hepatosplenomegaly, - insidious onset</td>
<td>same as primary biliary cirrhosis</td>
</tr>
</tbody>
</table>
| **Lab findings**       | • Conjugated hyperbilirubinemia ,  
                          |   • Increased serum alk. Phosphatase, bile acids, cholesterol,  |
|                        |   • IgM auto antibodies                                          | • Conjugated hyperbilirubinemia  
                          |   • Increased serum alk. Phosphatase, bile acids, cholesterol,  |
| **Important pathological findings- before cirrhosis develops**  | Dense lymphocytic infiltrate in portal Tracts with  
                          | Granulomatous destruction of bile ducts                          | • Prominent bile stasis in bile ducts,  
                          | • Bile ductular proliferation with surrounding neutrophils,  |
|                        |                                                                  | • Portal tract edema                                              |
Primary biliary cirrhosis

Ch by:

Destruction of bile ductules within triads of liver.

- Dense chronic inflam. Infilt. With loss of bile ductules in portal tract.

- Periductal epithelioid granulomas.

- Micro nodular cirrhosis.
Secondary biliary cirrhosis

Characterized by:

- **Regeneration nodules**, surrounded by coarse fibrous septa.

- **Regenerating hepatocytes** are disorderly disposed.

- **Fibrous septa** - inflam. infiltrate
  
  *(lymph, macrophages)*
Secondary biliary cirrhosis

Embedded in septa are:

• Small & large bile ducts (prolif / distended) –

• Bile stasis - as bile thrombi (brown-green, amorphous).

• Bile retention - in the parenchyma, as "bile lakes".
Tumors of Liver
Tumors of Liver

Non-Neoplastic

1. Cystic masses
   • Abscess (pyogenic / amebic)
   • Hydatid cyst
   • Polycystic liver disease
   • Caroli Disease

2. Solid
   • Nodular hyperplasia

Neoplastic

1. Benign
   • Adenoma
   • Hemangioma

2. Malignant
   • Hepatoblastoma
   • Hepatocellular ca.
   • Fibro lamellar ca.
   • Cholangio ca.
   • Angio sarcoma

3. Metastatic
Hepatocellular carcinoma

- Usually after 5th decade,

- $M > F$ – (2.4 : 1)

- More common in Africa & South east Asia

  (with high rates of chronic HBV).
Pathogenesis

Four major etiologic factors – ass. with HCC;

1. Chronic viral infection (HBV, HCV)
2. Chronic alcoholism
3. Non alcoholic steatohepatitis (NASH)
4. Food contaminants - Aflatoxins

Aflatoxin:

A toxin produced by fungus (aspergillus flavus) - contaminate peanuts & grains –

(aflatoxins bind with cellular DNA – cause specific mutation in p53)
Pathogenesis

Other predisposing conditions:

1. **Tyrosinemia** - rare – 40% pts develop HCC despite dietary control
2. Glycogen storage disease
3. Hereditary hemochromatosis
4. Non alcoholic fatty liver disease
5. α₁ anti trypsin deficiency
6. Other contributing factors include;
   - Genetic factors,
   - Age, gender,
   - Chemicals, hormones
Pathogenesis

1. **In countries with high prevalence regions of HBV infection** – main cause
   - Begins in **infancy** from **infected mother** –
   - **200 times increased risk** for HCC - by adulthood
   - **Cirrhosis** - absent in **50 % pts**
   - Cancer occurs **at 20 – 40 yrs of age**

2. **In western world (where HBV – not prevalent)**
   - Ass with other Ch. Liver diseases e.g.
     - Alcoholism
     - Non alcoholic steatohepatitis
     - Ch. HCV infection
     - Hemochromatosis
   - **Cirrhosis** present in **75 – 90 %**

3. **In china & southern Africa (HBV – endemic)** – **aflatoxins**
Pathogenesis…

Events in pathogenesis:

• **Ch. Hepatitis** - from any cause –
  • Repeated cycles of **cell death & regeneration** – imp – in pathogenesis of HCC.

• Resulting accum. of **mutations** may
  • Damage - **DNA repair mechanisms**,
  • Transform hepatocytes. – Preneoplastic - **dysplasia**

- **Progression to HCC** - may occur from **point mutations** of different genes
Pathogenesis…

In HBV infected individuals-

- **Viral integration** - precedes / accompanies – transforming event – disrupt cell genome

  - Depending on **integration sites**, HBV may;
    - Activate - proto – oncogenes – **tumorigenic** or
    - Transform- **HBV–X–protein** , a **transcriptional activator** of many genes,

**HCV** - RNA virus

- **Does not** disrupt DNA / produce oncogenic proteins,

- **May participate** via -**HCV core & NS5A**- protein of hepatitis C virus - to develop HCC
Hepatocellular carcinoma

Grossly:

Liver **enlarged** – tumor;

- **Unifocal** – usually **large mass**, 
- **Multifocal**, widely distributed **nodules** of variable size
- **Diffusely infiltrative ca.** - may involve **entire liver** – in **cirrhotic background**

- **Paler** than surrounding liver,
- **Green hue** - when composed of **well diff. hepatocytes** - **secreting bile**

Hepatocellular carcinoma with a **greenish yellow hue.**
Hepatocellular carcinoma...

Multinodular.

- Unifocal
Hepatocellular carcinoma...

• Diffuse

Hepatocellular ca **in cirrhosis**
Morphology

• All patterns may **invade**;
  • Vascular structures – extensive **intrahepatic metastasis**,  
  • Portal vein / inferior venacava - may extend to right heart

• Metastasis outside the liver – - **Via**;
  • Hematogenous – to **lung**,  
  • Lymphatics - **lymph node** –(perihilar, peripancreatic & para-aortic nodes) **above & below the diaphragm**
Hepatocellular carcinoma

• **May spread** extensively within the liver by;
  • Contiguous growth &
  • By development of **satellite nodules** - driven from parent tumor

**Satellite nodules** – represent either;

• **Intrahepatic spread** of tumor or

• **Multicentric origin** of tumor.
**Morphology…**

**Microscopically ;**

**HCCs** range – well diff - highly anaplastic / undiff lesions.

**Well diff & moderately diff tumors ;**

- Recognizable hepatocytes
- > than 2 cell thick plates forming
  - Trabeculae ,
  - Solid / tubular structures
  - Acinar / pseudo glandular pat.

**Well diff T** - composed of liver cords –
- wider than two cells thick
- Loss of lobular architecture,
- Vascular structures - present.
Morphology…

• **Important clues** are
  • **Atypical** mitotic figures,
  • **Cluster** of **enlarged hyper chromatic nuclei**
  • Blood vessel with thrombi.
  • **Intra nuclear / cytoplasmic inclusion** may be seen.

• **Cytoplasm** may show **Mallory’s hyaline bodies, / bile pigment**.
• **Kupffer cells** - **scant and irregularly scattered**.

• **CEA** -negative / focally positive
• **AFP** - specific but insensitive,
Morphology...

Well differentiated ca.

Tumor cells –
• Resemble hepatocytes,
• Form cords & nests,
• May contain bile pig. in cytoplasm

• Malignant cells (mostly on right) – interdigitate with

• Normal, larger hepatocytes (mostly at left).
Hepatocellular carcinoma

**Poorly diff T-**

Tumor cells;

- **Pleomorphic** with **numerous anaplastic giant cells,**

Or
- **Small & completely undiff,**
  - May resemble **spindle cell sarcoma**

**Poorly diff** (upper right), **developed on liver cirrhosis.**
- Discohesive, pleomorphic, anaplastic, giant cells.
- **Scant stroma and central necrosis** because of the poor vascularization.
• Poorly diff - hepatocellular carcinoma.
Hepatocellular carcinoma

• **Cytoplasm** showing --- *bile pigment.*

• **Hepatocellular Ca.**
  **in lymphatic vessels**
Fibro lamellar Carcinoma

Fibro lamellar carcinoma -

- A variant of HCC, -(5% of HCC)
- Young males & adult females
- Equal incidence
- No underlying ch. Hepatic disease
- Etiology – unknown
- Presents as ;
  - Single, large, hard ‘scirrhous’ tumor with fibrous bands coursing through it
- Prognosis – better than HCC
Fibro lamellar Carcinoma

Microscopically – composed of;

- Well diff polygonal cells - in nests / cords
- Separated by lamellae of dense collagen bundles

- Tumor cells have
  - Abundant eosinophilic cytoplasm &
  - Prominent nucleoli
Clinical Features of HCC

Often masked by that of cirrhosis / ch. Hepatitis

Mostly pts. have

- ill defined upper abdominal pain,
- Malaise
- Fatigue
- Wt. loss
- Abdominal mass / fullness
- Jaundice
- Fever
- GI / esophageal variceal bleeding
Clinical Features

Lab findings - helpful but rarely conclusive

• **Serum α–feto pr** – elevated - 50% cases

**GLYPICAN-3** – (GPC-3) is a **heparin sulphate proteoglycan** & an oncofetal protein.

• **Useful serum marker** in pts with hepatocellular ca
• **GPC3 immunohistochemistry** (IHC) - used to distinguish early HCC from dysplastic nodule
Clinical Features

**Diagnosis** - ultrasound, hepatic angiography, MRI,

**Natural course:**
progressive enlargement of primary mass – disturbs hepatic function / metastasizes – first to lungs, than - other sites

**Death may occurs** from
- Cachexia,
- GI / esophageal variceal bleeding,
- Liver failure with hepatic coma,

**5 – yr survival rate;**
- With large tumor - < 2 yrs
- Detection of Tumor < 2cm – excision – good prognosis
Cholangiocarcinoma
Cholangiocarcinoma

• Malignancy of biliary tree, arising from bile ducts within & outside the liver

Risk factors include;

• Primary sclerosing cholangitis,

• Congenital fibro polycystic disease of biliary system
  (esp choledochal cysts & Caroli disease - rare inherited disorder, ch by dilatation of intrahepatic bile ducts)

• HCV infection &

• Previous exposure to Thorotrast (for radiography of biliary disease).
Cholangiocarcinoma…

Acc to location are classified in

- Intrahepatic &
- Extra hepatic CCA

**Extra hepatic - 80 – 90 % - including:**
- Perihilar (Klatskin tumors) – at the jn of Rt & Lt hepatic ducts &
- Distal bile duct tumors,
  - Subgroup - tumors near ampulla of Vater.
  - Periampullary ca - also include ;
    - Adeno. ca of duodenal mucosa and
    - pancreatic ca
Cholangiocarcinoma...

- Survival only 15% - at 2 yrs after diagnosis

- **Intrahepatic CCAs** - diagnosed
  - late - after obstruction of bile flow or
  - As liver mass

- **Hilar and distal tumors** - present with symptoms of:
  - biliary obst,
  - cholangitis and
  - right upper quadrant pain
Morphology

Extrahepetic CCAs

- **Small lesions** at the time of diagnosis
- Firm, gray nodules within bile duct wall
- Diffusely infiltrating, / papillary / polypoid lesions
- Most – Adeno ca - with / without mucin secretion
- Squamous features, present - **rare**
- Epith prolif. with abundant fibrous stroma

Klatskin tumors ( hilar cholangiocarcinoma);

- Have **slower growth** than other CCAs
- Show prominent fibrosis &
- Have distant metastasis
Cholangiocarcinoma...

Ca of **extrahepatic bile ducts**.

- tumor extends from the **junction of the cystic and hepatic ducts** –
- to the **ampulla of Vater**.
Cholangiocarcinoma...

**Intrahepatic CCAs**

- Occur in **non cirrhotic liver**, 
- Track along intrahepatic portal tract system – **create tree like mass** or

- **Massive tumor nodule** develops
- Vascular invasion & propagation along portal lymphatics – **prominent** –

- Extensive **intrahepatic metastasis**
Cholangiocarcinoma...
Cholangiocarcinoma…

Microscopy:

- Cholangio ca - resemble adeno ca of other sites

- Mostly well to moderately diff sclerosing adeno ca with

- Glandular and tubular structures lined by cuboidal to low col epith

- Markedly desmoplastic – dense collagenous stroma separating the glandular element – tumor extremely firm & gritty
Cholangiocarcinoma...

**Metastasis:**
- Lymphatic – lymph nodes,
- Hematogenous - lungs and bones, adrenals and brain

**Mixed variants** occur in which elements of both HCC & CCA are present
- 3- forms recognized;
  1. Separate tumor masses of HCC & CCA within same liver
  2. ‘Collision tumors’: tumorous masses of HCC & CCA co-mingle at, identifiable interface
  3. Tumors in which elements of HCC & CCA - mixed at microscopic level
Cholangiocarcinoma...
Cholangiocarcinoma...

Cholangio ca, well diff

intrahepatic CCA - adeno ca showing:

• Tubular and / or papillary structures
• Lined by anaplastic cuboidal to low columnar epithelial cells.

• Variable fibrous stroma.

• Cholangio ca, moderately diff
Metastatic Carcinoma
Metastases to the liver

- Numerous mass lesions of variable size.

- Some of the larger ones demonstrate central necrosis.
Metastatic carcinoma

Cross section of liver, showing:

• Multiple tumor deposits of Adeno ca - body of the pancreas.
Metastatic carcinoma

- *Metastatic infiltrating ductal carcinoma from breast*, with

- *Normal liver parenchyma.*
Thank you