Pathology

Doctor 2017 | Medicine | JU | GI

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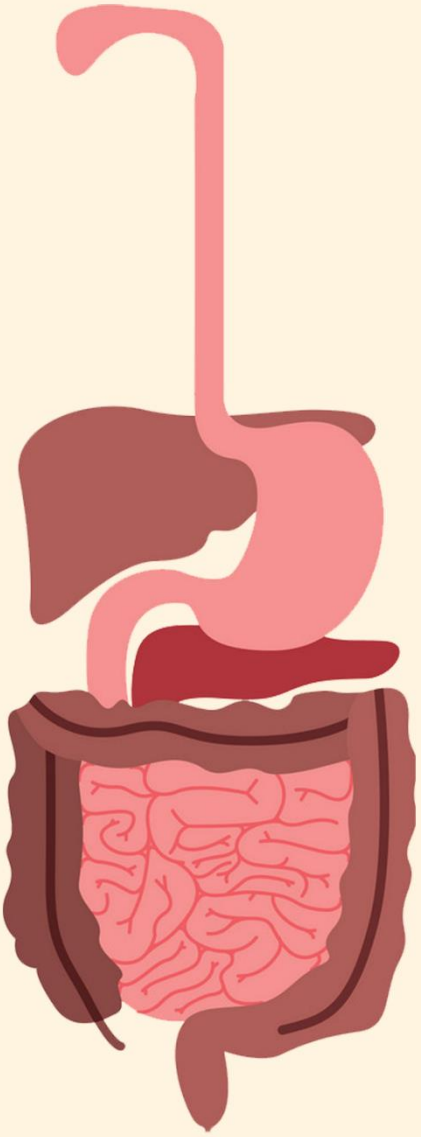


2nd system - GI

In this lecture we'll discuss one of the most prominent outcomes of the liver disease cirrhosis, Portal Hypertension, as well as two other forms of liver disease, Drug-induced liver injury and Viral Hepatitis.

Portal Hypertension:

Portal hypertension (PHTN) arises when there is reduced flow through the portal venous system. This can occur because of obstruction at the:

1. Prehepatic level:
    - Portal vein thrombosis
    - Massive splenomegaly
2. Intrahepatic level:
    - **Cirrhosis**
    - Schistosomiasis
    - Massive fatty change
    - Diffuse granulomatosis (sarcoidosis, TB)
    - Disease of portal microcirculation as nodular regenerative hyperplasia
3. Post-hepatic level:
    - Severe Rt.- sided heart failure
    - Constrictive pericarditis
    - Hepatic vein out flow obstruction

Note: Splenomegaly can cause PHTN; and can also be caused by PHTN! Read below!

The cause that concerns us most here is cirrhosis.

Cirrhosis causes nodules to develop, which are islands of parenchyma surrounded by fibrous tissue. Fibrosis can also surround the central vein in lobules (*perivenular fibrosis*), compressing the vein and increasing the resistance to the portal blood flow → Portal Hypertension (PHTN).

There are four very important clinical consequences of PHTN; ascites, portosystemic shunts, hepatic encephalopathy, and splenomegaly.

- Ascites: is the collection of excess fluid in peritoneal cavity. Normally, fluid in the peritoneal cavity is very minimal. If it builds up, it becomes clinically detectable when at least 500 ml have accumulated, but ascites patients usually have litres of fluid accumulated, and that causes abdominal distension.
  - Features of this fluid include:
    - Serous
    - Low in protein
    - Contains some electrolytes like K^+ and Na^+
    - Has some mesothelial cells and lymphocytes

Procedures of management include tapping (emptying) of this fluid, this relieves the abdominal pressure and allows the opportunity of monitoring or analysing this fluid, **if neutrophils were detected → sign of infection** (remember that cirrhosis patients are more liable to infections), **if blood or RBCs were detected → sign of disseminated cancer (metastasis)**. Malignancy is associated with bleeding.

- How does PHTN cause ascites? The **pathogenesis** of ascites in relation to cirrhosis presents through the following:
    - Increased sinusoidal BP 'pushes' fluid to exit into the ECF around the hepatocytes, which then moves into the abdomen.
    - Loss of liver function → ↓ production of albumin → hypoalbuminemia in blood → ↓ osmotic pressure in blood → fluid is 'pushed' into the ECF.
    - Increased lymph flow causes lymph to leak directly into the abdominal cavity. Normally, only 1L per day flows through the thoracic duct, but in cirrhotic patients this number rises to about 20 L/d!
    - Renal retention of Na+ and water due to 2^{ry} hyperaldosteronism.
- Portosystemic shunts: develop when blood flow is reversed from the portal to systemic circulation wherever the systemic and the portal circulations share common capillary beds, the most clinically important of which are:
    - Esophagogastric varices: often cause massive, frequently fatal (50%) hematemesis (65% of cirrhosis patients develop oesophageal varices).
    - Haemorrhoids: around & within the rectum (Haemorrhoids can be caused by cases other than cirrhosis though).
    - Caput medusae: periumbilical & abdominal wall collaterals dilations due to increased pressure in the falciform ligament.
    - Retroperitoneum (but usually don't bleed so not that clinically significant).
- Hepatic encephalopathy:
    - Describes many different disturbances in consciousness ranging from subtle behavioural abnormalities → to confusion and stupor → to coma and death.
    - Encephalopathy may develop over days, weeks, or a few months after acute *OR* chronic hepatic failure.
    - **Neurologic signs** include: rigidity, hyperreflexia, nonspecific EEG, seizures, and **asterixis**. Physical signs include brain oedema and astrocytosis. NO INFLAMMATION IN THE BRAIN.

Asterixis: a nonrhythmic rapid extension-flexion movement of the head and extremities, best seen as "flapping" of the hands when the arms are held in extension with dorsiflexed wrists (recall the demonstration in Clinical 1).

- **Pathogenesis**: cirrhosis → loss of liver function → accumulation of ammonia (**NH_3**) in the blood → toxicity to brain + oedema → pathologic neurologic signs.

Note from Awaisheh: the Dr explains in her lecture that hepatic encephalopathy is a result of PHTN, but according to all other sources and the logic of her explanation itself, it is due to any form of liver failure.

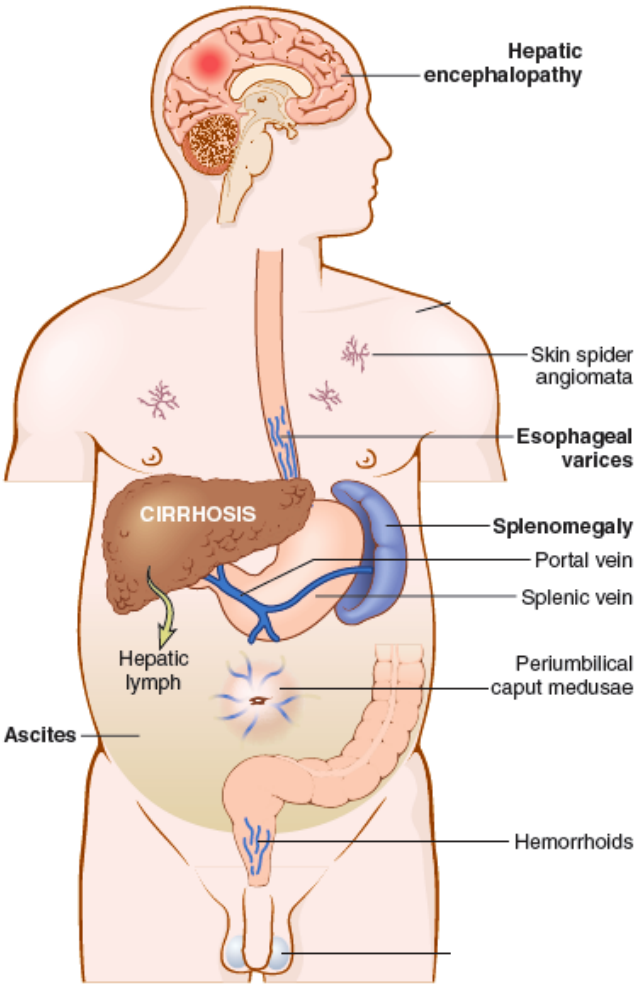


Fig. 16.7 Major clinical consequences of portal hypertension in the setting of cirrhosis, shown for the male.

- Splenomegaly: the spleen normally weighs around 300g, but splenomegaly confers the meaning that its weight has risen to around 1000g. **This increased size can make the spleen palpable, which is one of the most important tests for one of the earliest manifestations of liver disease.**

  An important outcome: we know that one of the spleen's functions is to filter and breakdown old blood cells, as a result, splenomegaly → increased size and blood capacity → increased blood capacity reduces blood flow → reduced blood flow gives more time for the spleen to breakdown blood cells (*hypersplenism*) → **pancytopenia**.

  Pancytopenia is a condition that occurs when a person has low counts for all three types of blood cells: red blood cells, white blood cells, and platelets.

  Hypersplenism occurs when there is an exaggerated increase in the spleen's function.

Drug/Toxin Induced Liver Injury

Since drugs/toxins can cause liver damage, **history of any drug/toxin use by the patient should always be used for differential diagnosis of any liver disease**. The form of liver disease observed varies based on many factors as well as between individuals, as does the severity of this disease. Liver disease caused by drugs/toxins is usually acute unless administration of the agent was over many months or years, but the liver commonly regenerates completely once the agent is removed.

Drug-induced chronic hepatitis is clinically & histologically indistinguishable from chronic viral or autoimmune hepatitis.

Injury may result from:

- **Direct toxicity**: the drug/toxin can be directly damaging or be converted into a toxic metabolite. Ex. acetaminophen, CCl4, mushroom toxins.
- **Immune mediated toxicity**: produced by immune mechanisms when drugs/toxins change the antigenicity of cellular proteins of hepatocytes → immune attack against hepatocytes → liver damage.

Patterns of injury:

- Hepatocellular necrosis
- Cholestasis
- Steatosis
- Steatohepatitis

} Remember these, be familiar with the rest

- Fibrosis
- Vascular lesions
- Granuloma
- Neoplasms benign & malignant

Diagnosis of drug or toxin-induced liver injury may be made on the basis of:

(a) Observed symptoms or signs starting after taking the drug/toxin.
(b) Recovery if the drug/toxin was stopped/removed.
(c) Exclusion of other potential causes.

} Just understand these

Reactions to the drug/toxin can be:

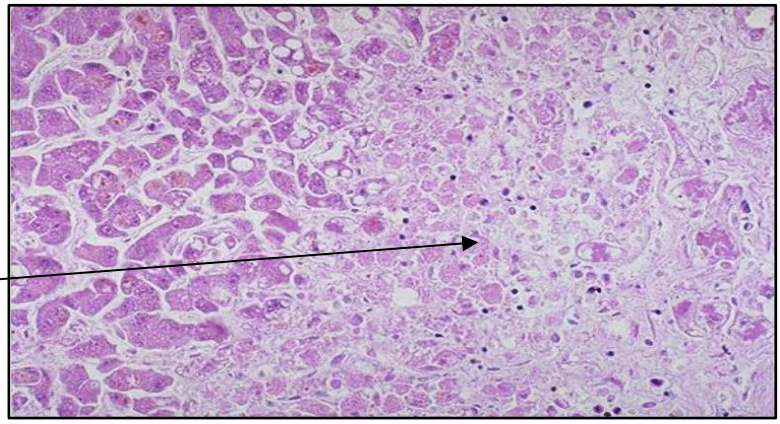
- Predictable (intrinsic): depends on the dose (dose-dependent)
  Ex. *Acetaminophen*, *Tetracycline*, *Antineoplastic agents*, CCL4, Alcohol.
- Unpredictable (idiosyncratic): is due to an unpredicted or uncommon immune response of the drug/toxin at first exposure. Varies between individuals based on rate of metabolism and sensitivity of the immune system.
  Ex. *Chlorpromazine*, *Halothane*, Sulphonamides, *Methyldopa*, *Allopurinol*.

Drugs that may cause acute liver failure:

1. *Acetaminophen*: most common
2. *Halothane*
3. Antituberculotic drugs like *Rifampin* and *Isoniazid*
4. Antidepressant monoamine oxidase inhibitors
5. Toxins as CCL4 & mushroom poisoning

Morphology of drug/toxin induced liver injury: **Necrosis**; can be massive, sub-massive, or patchy.

Note the necrosis on the right of the pic. Features observed are the loss of basophilia, loss of trabeculae, and loss of nuclei.



Viral Hepatitis

There are 5 clinical outcomes for most viral infections, and we'll discuss them in the context of viral hepatitis A, B, C, D, and E:

1. Asymptomatic: show very minimal manifestations, common with **C** in adults, where they later develop chronic hepatitis. Also common in children but with the A and B strains. When the child is infected with HAV or HBV, their weaker immunity shows no manifestations but at the same time the virus is cleared with time and they gain immunity to the microbe, unlike C which persists in the body and develops into chronic hepatitis.

   Note: that is why it is rare for adults to get infected with HAV in regions where HAV is endemic (developing countries). In developed countries, HAV in adults is more common and induces a stronger immune rxn → worse disease manifestations.

2. Acute symptomatic: **A, B, C, D, and E** can cause acute liver disease, and they usually present with the nondifferential symptoms of malaise and fever (within 6 months) that are common in any viral infection, though development of jaundice is possible.

   There are three phases for acute symptomatic infections:

   I. Incubation period: varies between strains.
   II. Symptomatic pre-icteric (pre-jaundice) phase: symptoms are not specific. They include fever, malaise, general fatigue, nausea, loss of appetite, headaches, myalgia, diarrhoea, and especially in HBV, serum sickness.
   III. Symptomatic icteric phase: jaundice is present and can even lead to pruritis (itching) when severe. Most commonly reached in B, C, and A in adults.

3. Fulminant hepatitis: a very severe and quick (2-3 weeks) acute reaction to the causative agent → severe destruction + severe **necrosis** of the liver → severe manifestations. Most common with **D superinfections, B**, and can occur with **A but only in adults**. Causes of fulminant hepatitis:

   - **Viral hepatitis 50 – 65%** (B twice as common as C)
   - **Drugs & chemicals 25- 50%**
     Ex. *Isoniazid*, *halothane*, *methyldopa*, & *acetaminophen*.
   - **Obstruction of the hepatic vein**
   - Wilson's disease
   - Acute fatty change of pregnancy
   - Massive tumour infiltration
   - Reactivation of chronic hepatitis B
   - Acute immune hepatitis

   Morphology: necrosis, collapsed reticulin tissue, inflammatory infiltrate, fibrosis, and decreased liver mass to about 600g.

4. Chronic:

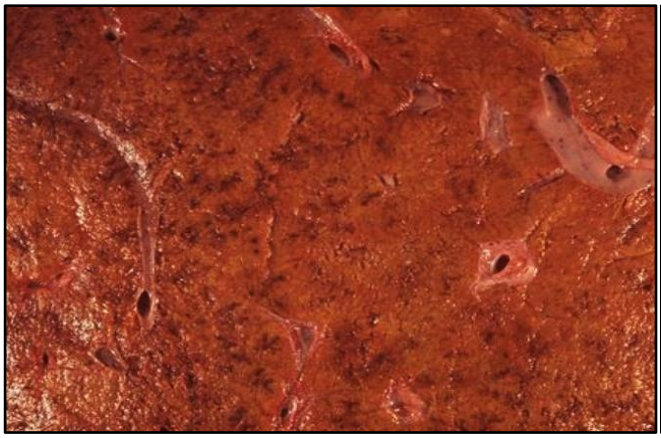
   - Aids the progression of cirrhosis, most common in **B , C, and D superinfection**.
   - Associated with abnormal liver function and serology.
   - Depending on the level of fibrosis, this state can be:
     i. Progressive chronic: occurs in severe chronic cases where damage is not limited to the portal area but extends to involve the parenchyma as well.
     ii. Non-progressive chronic: in mild chronic cases, damage is limited to the portal area

   Development into either state cannot be accurately predicted.

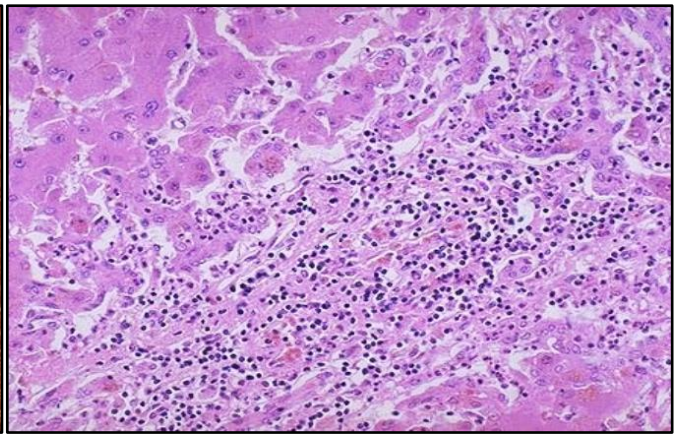
- **Treatment** of chronic hepatitis is only directed to limit the manifestation and further development.
- **Morphology** of chronic hepatitis from mild to most severe:

More severe ↓

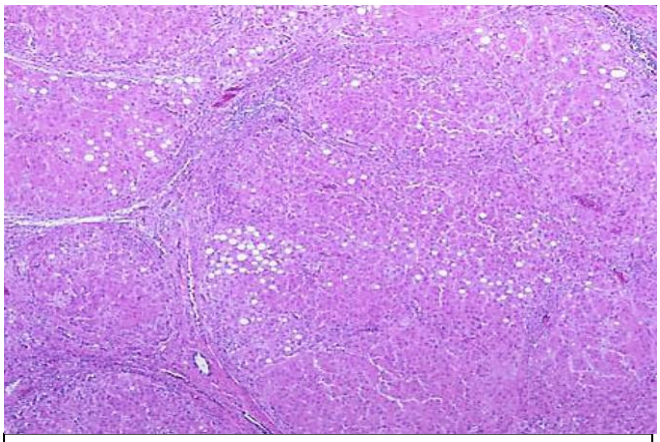
- Portal inflammation (mildest)
- Lymphoid aggregate
- Necrosis of hepatocytes- councilman bodies
- Bile duct damage (HCV)
- Steatosis (HCV)
- Interface hepatitis
- Bridging necrosis & fibrosis
- Fibrosis
- Ground-glass appearance (HBV)
- Sanded nuclei
- Lobular disarray (most severe)



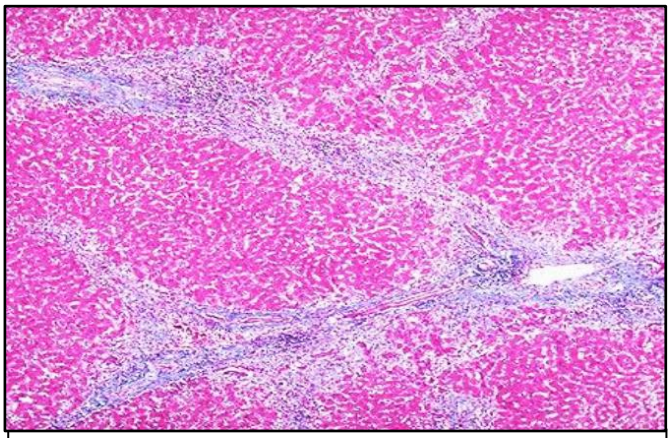
Necrosis is shown in the darker spots.



The dark spots show lymphocytes → chronic hep.



Fibrotic bands producing nodules.



Fibrous bands (blue) shown by trichrome stain.

5. Carrier: carriers show no symptoms and their liver function and structure is normal, but they shed the virus. Must be isolated or treated to reduce risk on the community. This state is common in areas where the virus is endemic, and transmission is associated with vertical transmission from mother to child. 95% of babies born to infected mothers develop the carrier state. HBV and HCV carriers are the most common so screening for these two viruses is recommended. Lastly, immunodeficient persons are more susceptible to the carrier state.