Pathology 4\textsuperscript{th} grade
Liver lect 1

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The dominant primary diseases of the liver are

1. Viral hepatitis
2. Alcoholic liver disease (in the Western world; rare in Iraq)
3. Hepatocellular carcinoma
HEPATIC FAILURE
This is the gravest consequence of liver disease. It should be noted that 80% of hepatic functional capacity must be damaged before failure ensues. In many cases decompensation arises as a result of inter current diseases that place further burden on an already sick liver; these include
1. Gastrointestinal bleeding
2. Systemic infection
3. Electrolyte disturbances
4. Severe stress such as major surgery or heart failure.
The morphologic alterations that cause liver failure fall into three categories:

1. Massive hepatic necrosis; most often drug-induced, as from paracetamol overdose, halothane & antituberculous drugs (rifampin, isoniazid). Hepatitis A & hepatitis B infection, and other causes (including unknown) account for about one-third of the cases. Hepatitis C infection does not cause massive hepatic necrosis.
2. Chronic liver disease, which is the most common road to hepatic failure and is the endpoint of persistent chronic hepatitis ending in cirrhosis.

3. Hepatic dysfunction without overt necrosis: hepatocytes may be viable but unable to perform normal metabolic function, as with Reye syndrome, tetracycline toxicity, and acute fatty liver of pregnancy.
Regardless of cause, the clinical signs of hepatic failure are much the same. Jaundice is almost always present. Hypoalbuminemia, which predisposes to peripheral edema, and hyperammonemina, which may play a role in cerebral dysfunction, are extremely worrying developments. Fetor hepaticus (a characteristic musty body odor) occurs occasionally. Impaired estrogen metabolism and consequent hyperestrogenemia are thought to be the causes of

a. palmar erythema and spider angiomas of the skin
b. hypogonadism and gynecomastia in males
highly susceptible to failure of multiple organ systems. Thus, respiratory failure with pneumonia and sepsis combine with renal failure to claim the lives of many patients.

A coagulopathy develops due to impaired hepatic synthesis of blood clotting factors. The resultant bleeding tendency can lead to massive gastrointestinal bleeding as well as petechiae elsewhere.
Intestinal absorption of blood places a metabolic load on the liver, which worsens the extent of hepatic failure. The outlook of full-blown hepatic failure is grave: A rapid downhill course is usual, & without liver transplantation, death occurs within weeks to a few months in about 80% of cases
Two particular complications signal the gravest stages of hepatic failure
1. Hepatic encephalopathy, which is manifested disturbances of consciousness with rigidity, hyperreflexia, and tremor. It is regarded as a disorder of neurotransmission in the central nervous system and neuromuscular system and appears to be associated with elevated blood ammonia levels, which impair neuronal function and promote generalized brain edema.
2. Hepatorenal syndrome refers to the appearance of renal failure in patients with severe chronic liver disease, in whom there are no intrinsic morphologic or functional causes for the renal failure. Sodium retention, impaired water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities. There is oliguria associated with rising blood urea nitrogen and creatinine. The prognosis is poor, with a median survival of only 2 weeks in the rapid onset form and 6 months with the insidious-onset form.
CIRRHOSIS

Cirrhosis is the end-stage of chronic liver disease & is defined by three characteristics:

1. Bridging fibrous septae in the form of delicate or broad bands of fibrosis that link portal tracts with one another and portal tracts with centrilobular veins.

2. Parenchymal nodules containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small micronodules to large macronodules.

3. Disruption of the architecture of the entire liver
Classification of cirrhosis

The only satisfactory classification of cirrhosis is based on the underlying etiology.

The descriptive terms "micronodular" and "macronodular" should not be used as primary classifications. Many forms of cirrhosis are initially micronodular (nodules < 3 mm), but there is a tendency for nodules to increase in size; thus converting it to mixed (micro- & macronodular) & eventually to macronodular form (nodules > 3 mm).

The etiology of cirrhosis varies both geographically and socially. The following are established causes of cirrhosis:
1. Alcoholic liver disease (70% in Western countries)
2. Viral hepatitis (a very common cause in our country)
3. Biliary diseases
4. Primary hemochromatosis
5. Wilson disease
6. $\alpha_1$-Antitrypsin deficiency
7. Cryptogenic cirrhosis
Infrequent types of cirrhosis also include those complicating galactosemia and tyrosinosis in infants and children, and drug-induced cirrhosis, as with α-methyldopa (aldomet). After all the categories of cirrhosis of known causation have been excluded, a substantial number of cases remain (15%) & is referred to as cryptogenic cirrhosis. It is possible that many of these cases are due to undiagnosed nonalcoholic fatty liver disease. Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone.
Pathogenesis of cirrhosis

The central pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver. In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts. New vascular channels in the septae connect the vascular structures in the portal region (hepatic arteries and portal veins) and terminal hepatic veins (centrilobulat & larger veins), shunting blood around the parenchyma.
Continued deposition of collagen in the space of Disse is accompanied by the loss of fenestrations in the sinusoidal endothelial cells. As a result, hepatocellular secretion of proteins (e.g., albumin, clotting factors, and lipoproteins) is greatly impaired.
Throughout the process of liver cell damage and fibrosis, remaining hepatocytes are stimulated to regenerate and proliferate as spherical regenerative nodules within the confines of the fibrous septae. The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely impaired, as is the ability of hepatocytes to secrete substances into plasma. Disruption of the interface between the parenchyma and portal tracts obliterates biliary channels as well.
Thus, the cirrhotic patient may develop jaundice and even hepatic failure, despite having a liver of normal mass. In cirrhosis death is usually due to one or more of the following:

1. Progressive liver failure
2. Portal hypertension related complications
3. The development of hepatocellular carcinoma
PORTAL HYPERTENSION
Increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into prehepatic, intrahepatic, and posthepatic causes.

Prehepatic conditions include
1. Portal vein thrombosis & narrowing
2. Massive splenomegaly through shunting excessive blood into the splenic vein.

Posthepatic causes are
1. Severe right-sided heart failure
2. Constrictive pericarditis
3. Hepatic vein outflow obstruction.
Intrahepatic causes:

1. Cirrhosis is the dominant cause accounting for most cases of portal hypertension.
2. Schistosomiasis
3. Massive fatty change
4. Diffuse fibrosing granulomatous disease such as sarcoidosis and miliary tuberculosis
5. Diseases affecting the portal microcirculation, exemplified by nodular regenerative hyperplasia
Portal hypertension in cirrhosis results from increased resistance to portal flow at the level of the sinusoids, and compression of terminal hepatic veins by perivenular scarring and expansile parenchymal nodules. Anastomoses between the arterial and portal systems in the fibrous septa also contribute to portal hypertension by imposing arterial pressure on the low-pressure hepatic venous system.
The four major consequences of portal hypertension in the setting of cirrhosis are

1. Ascites
2. The formation of portosystemic venous shunts leading to esophageal varices & hemorrhoids
3. Congestive splenomegaly
4. Hepatic encephalopathy
Ascites refers to the collection of excess fluid in the peritoneal cavity. It usually becomes clinically detectable when at least 500 mL has accumulated, but many liters may collect and cause massive abdominal distention. It is generally a serous fluid having less than 3 gm/dL of protein (largely albumin) as well as the same concentrations of solutes such as glucose, sodium, and potassium as in the blood. Influx of neutrophils suggests secondary infection, whereas red cells point to possible disseminated intra-abdominal cancer. With long-standing ascites, seepage of peritoneal fluid through transdiaphragmatic lymphatics may produce hydrothorax, more often on the right side.
The pathogenesis of ascites
This is complex, involving the following mechanisms:
1. Sinusoidal hypertension, altering Starling's forces and driving fluid into the space of Disse, which is then removed by hepatic lymphatics; this movement of fluid is also promoted by hypoalbuminemia.
2. Percolation of hepatic lymph into the peritoneal cavity: normal thoracic duct lymph flow approximates 800 to 1000 mL/day. With cirrhosis, hepatic lymphatic flow may approach 20 L/day, exceeding thoracic duct capacity.
3. Intestinal fluid leakage: portal hypertension also causes increased perfusion pressure in intestinal capillaries. This promotes movement of additional fluid out of intestinal capillaries into the abdomen.

4. Renal retention of sodium and water due to secondary hyperaldosteronism