Pathology

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Lecture 2

Diseases of the liver

Autoimmune hepatitis

-It is a chronic progressive disorder with features that include **genetic** predisposition, an association with **other autoimmune** diseases, presence of **autoantibodies** and therapeutic **response** to immunosuppression. It is characterized by:

- **Female** predominance
- **Absence** of serologic markers of viral infection
- Elevated serum **IgG**
- High serum titers of **autoantibodies**
- The presence of other forms of **autoimmune diseases** e.g.; rheumatoid arthritis

*Autoimmune hepatitis is a risk factor for cirrhosis

*The histological features of autoimmune hepatitis overlap with acute and chronic hepatitis of other etiologies.

Alcoholic and nonalcoholic fatty liver disease

Alcoholic and nonalcoholic fatty liver diseases have a similar spectrum of hepatic changes that include : fatty liver(steatosis), steatohepatitis, fibrosis and cirrhosis.

Morphology of Alcoholic and nonalcoholic fatty liver disease

1. **Hepatocellular steatosis (liver fatty change)**
   - **Gross** : Large (may reach 4 to 6 kg), yellow, soft and greasy liver
   - **Histopathology:** Lipid droplets accumulate in hepatocytes, first in centrilobular area ranging from small to large droplets that fill and expand the cell displacing the nucleus to the periphery of the cell, as steatosis become more extensive, changes extend to mid zone and finally to periportal zone
2. **Steatohepatitis**
   - More pronounced with alcohol use than nonalcoholic fatty liver disease
   - Usually superimposed on a fatty liver
   - H/P : Ballooning of hepatocytes , neutrophils infiltration and Mallory-Denk bodies

Mallory-Denk bodies (eosinophilic cytoplasmic inclusions in degenerating hepatocytes due to accumulation of intermediate filaments (keratin) in the damaged cells)

*Mallory-Denk bodies are a characteristic but **not specific** feature of alcoholic and nonalcoholic fatty liver disease, since they also present in other conditions e.g. hepatocellular tumors

3. **Fibrosis ,** and finally if the cause persists , cirrhosis develops (usually micronodular cirrhosis)

*** Alcoholic liver disease :** due to excessive ethanol consumption

Pathogenesis of alcoholic hepatocellular steatosis

1. Shunting of normal substrates away from catabolism and toward lipid biosynthesis
2. Impaired secretion of lipoproteins
3. Increased peripheral catabolism of fat

Pathogenesis of alcoholic hepatitis: Uncertain but may be due to direct effect of alcohol and its toxic byproducts (e.g. acetaldehyde) that will damage the cells

Pathogenesis of Fibrosis: Results from collagen deposition by activated stellate cells leading to cirrhosis.

***Nonalcoholic fatty liver disease**

- NAFLD is a common condition in which fatty liver disease develops in individuals who do not drink alcohol
- Strongly associated with insulin resistance and other components of the metabolic syndrome (obesity, insulin resistance (type 2 diabetes), dyslipidemia, hypertension and microalbuminuria), at least 3 features are required for diagnosis

Pathogenesis of NAFLD : obesity and insulin resistance are the key initiating events

Liver cirrhosis

- A diffuse process involving the entire liver in which the normal liver architecture is converted into a number of **nodules of regenerating hepatocytes** separated by anastomosing bands of **fibrous** tissue
- Is the end stage of many chronic liver diseases

Etiology

1. Chronic viral hepatitis (B, C)
2. Immune mediated: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis
3. Alcoholic and nonalcoholic fatty liver disease
4. Inborn errors of metabolism: e.g. hereditary hemochromatosis, Wilson disease
5. Secondary iron over load: due to e.g. multiple transfusions , ineffective erythropoiesis and excessive iron intake
6. Chronic biliary obstruction

7. Drug induced e.g. methotrexate

8. Unknown 10%: (Cryptogenic cirrhosis)

Pathogenesis : Depends on 4 processes:

Hepatocytes death, extracellular matrix deposition, hepatocytes regeneration and vascular reorganization

1. Hepatocytes death (according to the cause)

2. ECM deposition: The main source of excess collagen are the perisinusoidal stellate cells (that lie in the space of Disse) that are activated and converted to myofibroblasts due to the release of certain inflammatory mediators .Activated stellate cells also release mediators (specially TGF-β) that result in further proliferation and collagen synthesis leading to perisinusoidal fibrosis and cirrhosis

3.Vascular injuries:The main vascular lesions are:

- Loss of sinusoidal endothelial cell fenestrations converting thin-walled sinusoids into high pressure vascular channels
- Development of portal vein-hepatic vein and hepatic artery-portal vein shunts that cause abnormal vascular pressures in the liver and portal hypertension.

4. Finally, the damaged liver cells are replaced by nodules of regenerating hepatocytes.

Morphology of cirrhosis

Gross features

☒ **Size :** normal or enlarged at first, shrinks as the disease progresses

☒ **Surface : diffusely nodular**

According to size of the nodules, cirrhosis is classified into (morphological classification):

1. **Micronodular cirrhosis**: in which the nodules are of the same size, the size of the nodules is less than 3 mm in diameter
2. **Macronodular cirrhosis**: in which the nodules are equal or larger than 3mm in diameter
3. **Mixed type cirrhosis**: in which both small and large nodules are present

THANK YOU