



Pathology of Liver Fibrosis

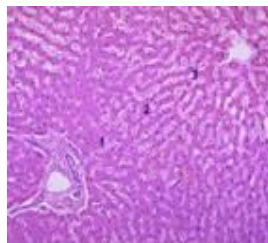


.-Hepatic Fibrosis

- √ Hepatic Fibrosis represents excessive or disordered hepatic ECM -
- √ WHO definition of cirrhosis: diffuse process characterized by fibrosis and -
conversion of the normal liver architecture into structurally abnormal nodules

.-Causes of Cirrhosis

- √ Drugs and toxins (alcohol) -
- √ Infections (HBV, HCV, Sh) -
- √ Autoimmune liver diseases -
- √ Inherited metabolic defect -
- √ Acquired bile duct diseases -
- √ Vascular -
- √ Miscellaneous -
- √ Cryptogenic -



Normal liver

.-Distribution of ECM in normal liver

√Collagens I, III portal tract IV along side hepatocytes -

√Glycoproteins: laminin, fibronectin, entactin, elastin -

√Proteoglycans: heparan sulfate, chondroitin sulfate, hyaluronic acid -

.-ECM degradation

Lysosomal cathepsins -

MMP1: degrading native collagen -

MMP2: do not degrade native collagen regulated by -

proenzyme activation .

inhibition of active enzymes .

gene expression .

TIMP-

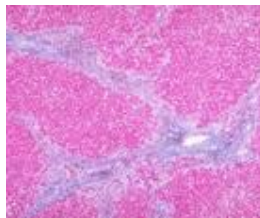
.-Path physiology of liver fibro genesis

√Altered ECM production -

√Altered ECM degradation -

√Microcirculatory changes-

√Regenerating cell population-



.-Molecular mechanisms regulating ECM production

Chronic inflammation: production of cytokines -

TNF α , IL-1, TGF- β , PDGF

By: Kupffer cells, T cells, endothelial cells

Injured endogenous cells produce: -

HGF, TGF- β , PDGF, EGF, FGF

Hepatocytes, bile duct epithelial cells, Kupffer cells, endothelial cells

Phenotypic modulation of stellate cells: lose their retinyl ester stores, transformed -

to my fibroblast like cells (+ve for smooth muscle act in

Phenotypic modulation of hepatic stellate cells -.

Alter collagen gene expression -

Increase fibronectin production -

mediates attachment of collagen & PG to hepatocytes

Stimulates fibroplasia, chemotactic for fibroblast

Modulate cell differentiation & function

Increase osteonectin & entactin production -

Binds & inactivates PDGF

Affects ECM synthesis & degradation

Increase laminin production -

Mitogenic for hepatic stellate cells

.-Microcirculatory changes

sinusoids are transformed into capillaries, increase intraparenchymal vascular resistance

Vascular channels in the septa leads to shunting blood around parenchyma, increase presinusoidal vascular resistance

Bridging fibrosis leads to Porto-venous and arteriovenous shunts, bypassing parenchyma nodules (under perused)

Regenerating cell population-

Cells maintain the potential to multiply during adult life -

Hepatocytes.

Bile duct epithelium.

hepatic progenitor cells.

Liver regeneration occur by 2 mechanisms-

Adult differentiated hepatocytes .

Progenitor cells .

-Staging of Fibrosis

Knodell classification -

No Fibrosis .

Fibrous expansion of PT .

moderate fibrosis .

bridging fibrosis (p-p, p-c links .

Cirrhosis .

-.Schemer classification

No fibrosis -

Fibrous expansion of some portal tracts -

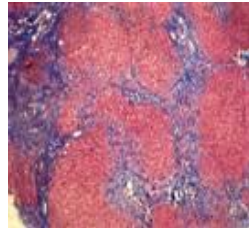
fibrous expansion of most portal tracts with or without portal septa -

fibrous expansion of portal tracts with occasional portal-portal links -

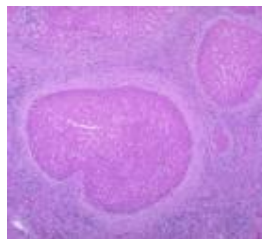
marked bridging with portal-portal and portal-central links-

marked bridging and occasional nodules -

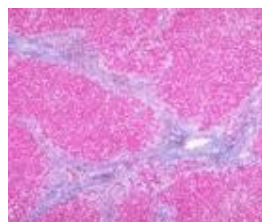
Cirrhosis probable or definite -



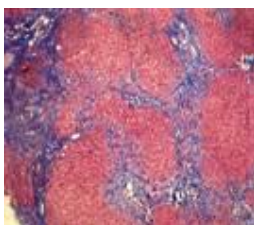
Portal tract expansion by fibrosis

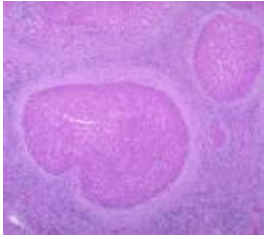


Dense fibrous septa



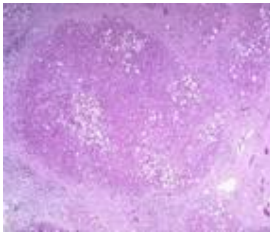
Bridging fibrosis





Marked bridging fibrosis

cirrhosis



Micro nodular cirrhosis of HCV

-.Morphology of Cirrhosis

Micro nodular: uniform, less than 3mm diameter-

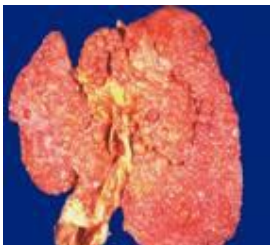
Macro nodular: the majority of the nodules are more than 3mm in diameter -

separated by coarse bands or scar tissue

Mixed -



Micronodular cirrhosis



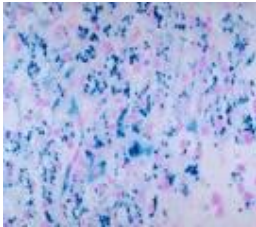
Macronodular cirrhosis

-Iron deposition

32.4% of cirrhotic livers show +ve staining for iron -

Is attributable to redistribution of iron stores from other sites in the body -

Large regenerative nodules that accumulate iron have reported to exhibit hepatocellular foci. hyper plastic



Iron deposition in hepatocytes and Kupffer cells

-Copper deposition

Copper is eliminated from the body principally via biliary secretion -

PBC, SBC & primary sclerosing cholangitis accumulate copper in the per portal hepatocytes

Less than 25% of cirrhotic livers accumulate copper in hepatocytes

Reversal of Liver Fibrosis

Manipulating metalloproteinase gene expression -

Selective apoptosis of stellate cells -

Blocking CD44 binding sites of fibroblasts -

IV administration of d-HGF (decrease mRNA levels of procollagen, decrease TGF- β mRNA)

Complications of Cirrhosis.-

Portal hypertension due to increase intra-hepatic resistance to portal blood flow

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Ascites -

Portosystemic shunts -

Splenomegaly -

Hepatic encephalopathy -

Hepatorenal syndrome

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