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Patterns of liver fibrosis and their clinical significance

Alastair D Burt
Professor of Pathology and Dean of Clinical Medicine
University of Newcastle upon Tyne
Collapse of reticulin framework or dynamic process?  Popper 1960s
Hepatic fibrosis

- Consequence of repair process following chronic liver injury with resultant net accumulation of extracellular matrix proteins with abnormal distribution: dynamic process involves increased production and decreased turnover of matrix

- Effects not only space occupying but influence gene transcription, cellular proliferation etc: via integrins and non-integrin ECM receptors
Hepatic stellate cells: principal effectors in liver fibrogenesis

- Found within the space of Disse
- Pericyte-like with long cytoplasmic processes: contractile
- Principal site of storage of vitamin A (fat-storing cells)
- Origin
  - Mesenchymal
  - Neural crest
  - Bone marrow
  - (Epithelial-mesenchymal transition)
HSC response to injury

Quiescent

Injury

Cytokines

Activated
• Fibrosis may be reversible: animal models and anti-viral trials

• HSC apoptosis important as is changing profile of MMPs/TIMPs
Second layer cells and myofibroblasts

Other possible effectors:

• Bile duct epithelium
• Hepatocytes
• EMT
• Endothelium
• ‘Fibrocytes’
• Other portal tract fibroblasts
Assessment of fibrosis

- Histochemistry
  - Silver impregnation: type III/fibronectin and type I
  - Trichrome stains/Van Gieson
  - Picro Sirius Red
  - Orcein/Victoria Blue

- Immunohistochemistry
  - Collagen subtypes
  - Elastin
  - Activated HSCs (α SMA)

- Quantitative
  - Semi-quantitative scoring
  - Elution of Picro Sirius Red
  - Image analysis
PBC: which stage?
Oh yes it does!!
Sampling variability of liver fibrosis in chronic hepatitis C

- Surgical specimens of livers from patients with HCV
- Image analysis and METAVIR: overall reference value
- Virtual biopsies of increasing length
- 15mm biopsies categorised correctly in 55%; increased to 65% with 25mm
- Concluded that at least 25mm required for accurate semi-quantitative assessment of fibrosis

Bedossa et al, 2003
Surrogate markers of hepatic fibrosis

- Forns score: based on age, GGT, platelets, cholesterol
- FIBROTEST: apoA1, haptoglobin, α2-MG, GGT, bilirubin
- Effective at identifying patients with mild fibrosis
- Large percentage within indeterminate range
- Enhanced by incorporating ECM markers
Patterns of hepatic fibrosis

- **Localised**
  - Abscess
  - Inflammatory pseudotumour
  - Intra and peritumoral
  - Trauma

- **Generalised**
  - Portal tracts/zone 1
  - Hepatic veins/zone 3
  - Perisinusoidal
  - Septal
  - Others………..
Portal tracts/zone 1 and fibrosis

- **Portal tract fibrosis**
  - Increased density and fibrous enlargement of PTs
  - *Biliary diseases; chronic hepatitides; NASH; ?? ALD*
- **Pipe stem fibrosis**
  - *Schistosomiasis*
- **Hepatoportal fibrosis**
  - *Idiopathic non-cirrhotic hypertension*
- **Periportal fibrosis**
  - Fibrous spurs extending from PTs
  - May be associated with interface hepatitis
- **Periductal fibrosis**
  - *Sclerosing cholangitis (primary or secondary)*
- **Periductular fibrosis**
  - Accompanies ductular reaction: *cholestatic diseases and chronic hepatitides*
Hepatoportal sclerosis
Progressive fibrosis in autoimmune biliary disease

- Progressive periportal fibrosis is associated with and may be driven by the so-called ductular reaction.
- Portal-portal fibrous linkage ensues leading to a monolobular form of cirrhosis.
Hepatic veins/zone 3 and fibrosis

- Perivenular fibrosis
  - *Alcoholic liver disease*
  - *NASH*
  - *Veno-occlusive disease*
- Centrilobular fibrosis (distinct)
  - *Alcoholic liver disease* (‘central sclerosing hyaline necrosis’)
  - *NASH*
  - *Ischaemic injury (chronic venous outflow obstruction)*
Ischaemic fibrosis
Pericellular/perisinusoidal fibrosis

- Zone 3 predominance
  - Chicken wire appearance: *alcoholic liver disease/NAFH*
- Diffuse
  - *Diabetes type 1*
  - Similar appearance with *amyloidosis* and *light chain disease*
  - *Congenital syphilis*
Septal fibrosis

- Portal-portal septa
  - Link adjacent portal tracts
  - *Chronic cholestatic diseases* (‘biliary fibrosis’); *chronic hepatitides*
- Central-central septa
  - Scarring stage of confluent necrosis/central-central bridging necrosis
- Portal-central septa
  - Scarring of portal-central bridging necrosis
- Active septa
  - Prominent inflammatory infiltrate and ongoing necrosis
- Passive septa
  - Post-necrotic collapse
NEWCASTLE A: POST TREATMENT BIOPSY
Other fibrosis

- Glisson’s capsule fibrosis

- Granulomas
  - Sarcoidosis
  - Mineral oil granulomas
Other fibrosis

- Developmental abnormalities
  - Congential hepatic fibrosis
  - Mesenchymal hamartoma
Patterns of cirrhosis

- Micronodular
- Macronodular
- Mixed
- Incomplete septal

- *Should we stage cirrhosis?*
  - *Laennec scoring: 4A, B and C*