Approach to liver biopsies

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Outline

1. Approach to the diagnosis in liver biopsies
2. Patterns of morphological changes seen in the liver – algorithmic approach to diagnosis
3. Answers to biopsies
Approach to liver biopsies
What to do with a liver biopsy

- Don’t be intimidated
- Pattern based diagnostic approach
  - Be systematic
- Clinical context is very important in liver disease assessment
  - Look at the bloods
  - Discuss the case with the referring clinician
- For every biopsy try to answer these questions
  - What is causing the change (diagnosis)
  - How bad is it (activity - grade)
  - How far has it progressed (fibrosis – stage)
Stains for liver biopsies

- **H&E** – for diagnosis – we do 3 slides
- **HVG/Mason trichrome/Sirius red** – to assess fibrosis
- **Reticulin** – to assess architecture, nodularity and for loss of network
- **Perls’ Prussian Blue** – Iron
- **Orcein** – Elastic fibres (old fibrosis), copper-associated protein, HBV inclusions
  - Rhodanine – copper
  - Hepatitis B SAg IHC – HBV
- **PAS±D** – Glycogen, alpha-1-antitrypsin globules, foamy macrophages, basement membrane
How we report our liver biopsies

- Overall architecture
- Fibrosis
- Portal tracts
  - Inflammation
  - Interface hepatitis
  - Bile ducts
  - Vascular structures
- Lobules
  - Inflammation
- Steatosis
- Apoptosis
- Ballooning
- Special stains
- Malignancy
- Overall Grade and Stage
- Comment/Interpretation
Patterns of liver injury
Patterns of liver injury

1. Chronic hepatitis = portal dominant inflammation
2. Acute hepatitis = lobular dominant inflammation
3. Biliary injury = ductular reaction/bile
4. Fatty liver disease = steatosis
5. (Near) invisible
6. Depositions
7. Fibrosis
8. Mass lesion

Each pattern enables more specific diagnoses by assessing additional changes.

A single disease can manifest in different ways/different diseases can manifest in the same way.
Chronic hepatitis/portal inflammation

- Cellular expansion of portal tracts
- Varying degrees of lobular inflammation and hepatocyte damage
- Interface hepatitis

- Most common causes = VAD
  - Hepatotropic viruses
  - Autoimmune hepatitis
  - Drugs
    - Minocycline, isoniazid, nitrofurantoin
    - Statins
Acute hepatitis

• Lobular injury more severe than the portal inflammation
• Characterised by inflammation, hepatocyte necrosis, cholestasis, regenerative changes

• Most common causes
  • Viruses
    • Hepatotropic and non-hepatotropic
  • Drugs
Biliary injury

- Expanded portal tracts with a ductular reaction

- Characterised by portal oedema, fibrosis, bile duct proliferation and inflammation
  - Cholestasis may or may not be present

- Cholate stasis suggest chronic biliary injury

- Most common causes
  - Obstruction of large ducts
  - Chronic biliary obstruction – PBC and PSC
Fatty liver disease

- Accumulation of lipid within the hepatocytes
- It can be macrovesicular or microvesicular
- Characterised by steatosis, hepatocyte damage, inflammation and fibrosis
- Most common causes
  - Alcohol
  - Non-alcoholic steatohepatitis
Invisible/near normal liver

• Absence of major damage with subtle changes evident

• Characterised by subtle changes within the liver

• Most common causes
  • Resolving infection
  • Vascular injury
  • Drugs
Deposition

• Accumulation of material within the liver
• Usually brown, pink or invisible
• Characterised by material within the tissue, may cause other effects

• Most common causes
  • Age related changes - lipofuscin
  • Haemosiderosis/haemochromatosis
  • Wilson’s disease - copper
  • A1 anti-trypsin
  • Amyloid
Fibrosis/cirrhosis

• Collagen deposition that distorts the hepatic architecture; it is the common progression for almost all liver disease
• Another pattern may be present in the background to suggest an aetiology

• Characterised by fibrous deposition

• Most common causes
  • Chronic hepatitis
  • Leads to cirrhosis
Mass lesion

• Presence of a tumour

• Characterised by loss of portal tracts and an infiltrate within the tissue or abnormal hepatocytes

• Most common causes
  • Hepatocellular carcinoma
  • Adenocarcinoma – cholangiocarcinoma and metastasis
Answers to cases
Case 1

54F Liver biopsy for abnormal LFTS, ?stage
AST – 103 U/L (5-30)
ALT – 77 U/L (5-35)
ALP – 37 U/L (30-110)
GGT – 23 U/L (5-35)

Bilirubin – 8 µmol/L (1-20)
Anti-HCV Ab – Positive
Chronic hepatitis C - Late stage 3 fibrosis

• Prototypic condition causing chronic hepatitis pattern

• Rarely seen now
  • Changes to PBS
  • Non-invasive measures of fibrosis
  • New drugs – direct acting antiviral drugs

• I have only seen 2 cases in last 5 years
Microscopic features

• Features of all chronic hepatitis
  • Portal chronic hepatitis
    • Portal inflammation
    • Interface activity/hepatitis
  • Variable lobular injury
    • Apoptotic (acidophil) bodies, spotty necrosis through to bridging/panacinar necrosis
  • Fibrosis

• Features suggestive of HCV as the cause
  • Mild steatosis, lymphoid follicles in portal tract, bile duct injury
Natural history of untreated HCV

• Acute HCV infection

• Chronic infection

• Progression of fibrosis to cirrhosis

• Hepatocellular carcinoma
Grading and Staging chronic hepatitis

• Grade = inflammatory activity
  • Portal
  • Interface
  • Lobular

• Stage = Location and extent of fibrosis

• Common schemes used
  • METAVIR
  • Scheuer
  • Batts and Ludwig
  • Ishak (HAI)
Case 2

64F Liver biopsy for fatigue and pruritis
with abnormal LFTs
AST – 19 U/L (5-30)
ALT – 21 U/L (5-35)
ALP – 800 U/L (30-110)
GGT – 400 U/L (5-35)

Bilirubin – 17 µmol/L (1-20)
AMA – Positive
ANA – Negative
MRCP – Normal
Primary biliary cholangitis (PBC)

• Chronic cholestatic disease characterised by the destruction of small and medium sized interlobular bile ducts with progressive fibrosis

• Clinical presentation

• Autoantibodies
Histological features

• Nonsuppurative cholangitis
  • Bile duct injury
  • Lymphocytes within the epithelium – lymphocytic cholangitis
  • Surrounding granulomatous inflammation – granulomatous cholangitis
  • Florid duct lesion

• Bile duct loss and ductopaenia

• Ductular reaction

• Portal inflammation

• Fibrosis and staging
• Natural history

• Treatment

• PBC-AIH overlap syndrome
Case 3

57F Liver biopsy for fatigue and jaundice with abnormal LFTs

- AST – 751 U/L (5-30)
- ALT – 536 U/L (5-35)
- ALP – 140 U/L (30-110)
- GGT – 30 U/L (5-35)
- Bilirubin – 17 µmol/L (1-20)

AMA – Negative
ANA – Positive 1/160
Compatible with autoimmune hepatitis

• A progressive immune mediated inflammatory liver disease
  • Characteristic clinical, biochemical and histological features
• There are no pathognomonic histological features of AIH
• AIH typically presents with a chronic hepatitis pattern of injury
  • Usually also has moderate interface hepatitis
    • Lobular injury
    • Plasma cells
    • “rosettes and emperipolesis”
• Refined criteria for AIH
  • Histology compatible with AIH
Variant forms

• Giant cell hepatitis
• Centrilobular injury
• Overlap forms – AIH-PBC, AIH-PSC

• Up to 20% are antibody negative
• Repeat biopsy may be performed to assess treatment response and may allow for cessation of immunosuppression
Case 4

65F Fever and jaundice with abnormal LFTs
AST – 889 U/L (5-30)
ALT – 975 U/L (5-35)
ALP – 150 U/L (30-110)
GGT – 96 U/L (5-35)
Acute hepatitis pattern

• Causes
  • Acute viral infection
    • Hepatotropic – Hepatitis A-G
    • Liver features
  • Non-hepatotropic
    • Opportunistic infections – CMV, EBV, parvovirus, adenovirus
    • Icteric viral haemorrhagic fevers – Dengue, Yellow fever Ebola
  • Drug induced hepatitis
    • Nitrofurantoin, isoniazid, disulfiram
    • Herbal remedies
  • Autoimmune hepatitis
Outcome of acute hepatitis

• Outcome often depends on the cause of the injury
• Resolution without sequelae
• Progression to fulminant hepatitis and acute liver failure
• Progression to chronic hepatitis
Case 5

71F Jaundice and right upper quadrant pain ? stone
AST – 14 U/L (5-30)
ALT – 17 U/L (5-35)
ALP – 437 U/L (30-110)
GGT – 340 U/L (5-35)
Bilirubin – 66 µmol/L (1-20)
Ascending (suppurative) cholangitis secondary to large duct obstruction

• Neutrophilic infiltration in and around bile ducts
• Portal tracts show expansion by oedema and a prominent ductular reaction

• Neutrophilic microabscess in bile ducts suggests bacterial inflammation in the liver; cholangitis lenta suggests sepsis
Case 6

75F Recent URTI treated with augmentin
AST – 20 U/L (5-30)
ALT – 15 U/L (5-35)
ALP – 205 U/L (30-110)
GGT – 84 U/L (5-35)
Bilirubin – 201 µmol/L (1-20)

MRCP normal
Perls – not iron
Cholestasis with evidence of duct damage

• Typically seen in DILI

• Causative agents
  • Bland cholestasis – androgens and oestrogens
  • Associated with duct injury that can lead to vanishing bile duct syndrome – Antibiotics – penicillins, amoxycillin-clavulanate acid, rifampicin
LiverTox® provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbs and dietary supplements. LiverTox also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LiverTox website provides a comprehensive resource for physicians and their patients, and for clinical academicians and researchers who specialize in idiosyncratic drug induced hepatotoxicity.
Case 7

36F Central obesity, abnormal LFT
AST – 63 U/L (5-30)
ALT – 91 U/L (5-35)
ALP – 114 U/L (30-110)
GGT – 80 U/L (5-35)
Bilirubin – 8 µmol/L (1-20)
Steatosis with steatohepatitis - NASH

• Microscopic features of steatohepatitis

• Grading and staging

• Prognosis

• Differential diagnosis of NASH/ASH
Microscopic features

• Changes are most prominent in the pericentral areas

• Steatosis
• Lobular inflammation
• Ballooning

• Fibrosis
Other features

- Mallory-Denk bodies
- Glycogenated nuclei
- Apoptotic hepatocytes
- Iron deposition

- Paediatric type NASH is when the steatosis is periportal
  - Seen in some cases of NASH in young people
Grading and Staging

• All grading systems use a combination of steatosis, ballooning and inflammation
  • BRUNT
  • NAS
  • SAF
  • FLIP

• In all cases, determination of the fibrosis stage is the most important feature to report
Features that MAY discriminate ASH and NASH

• Canalicular cholestasis
• Intense neutrophilic inflammation
• Possibly Mallory-Denk bodies
• Fibrous obliteration of hepatic veins

• Advanced fibrosis
Other causes of steatosis/steatohepatitis

- Alcohol
- Other drugs
  - Oestrogen/tamoxifen/raloxifene
  - Other chemotherapy agents – methotrexate, irinotecan
  - Amiodarone
- TPN/Starvation
- Lipid metabolism disorders
- Hepatitis C infection
- Wilson’s disease
Case 8

41M Abnormal LFTs
AST – 54 U/L (5-30)
ALT – 67 U/L (5-35)
ALP – 39 U/L (30-110)
GGT – 12 U/L (5-35)
Bilirubin – 9 µmol/L (1-20)
Perls