Reporting Inflammation within the Liver: Also a Matter of Clinical Context

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Etruscan artifact, 2nd-3rd century BC
Morphology alone may be insufficient to make a diagnosis in liver pathology:

- multiple liver disease: similar morphology
- single liver disease: multiple morphologies

- the clinical context is crucial for a correct interpretation of a liver biopsy
- this is particularly true in case of inflammation within the liver: *the hepatic pattern of injury*
Liver biopsy:

- still an essential component in management of most liver diseases:
  
  to confirm clinical diagnosis or to determine the cause
  to predict prognosis and to decide on treatment
  for follow-up

- to make the most out it, the pathologist needs:
  
  good sampling (at least 1.5cm, ideally 2.0cm, 11-15 portal tracts)
  access to special stains and immunohistochemistry
  to be supplied with all relevant clinical and laboratory data
In the normal liver

- occasional lymphocytes and neutrophils in sinusoids
- few lymphocytes, macrophages and mast cells in normal portal tracts

*The number of inflammatory cells in portal tracts increases with age.*
*Their densities vary from one portal tract to another.*
Minor inflammatory changes of little significance

- fat granulomas from mineral oil deposition in perivenular areas and in portal tracts:

- end of a long surgical procedure: “surgical hepatitis”: clusters of neutrophils in sinusoids, around terminal hepatic venules and in portal tracts
Differential diagnosis for the presence of neutrophils:

- alcoholic / non alcoholic steatohepatitis / drugs
Differential diagnosis for the presence of neutrophils:
- cytomegalovirus infection in immunocompromised patients
Differential diagnosis for the presence of neutrophils:

- recent ductular reaction
1. Non specific reactive hepatitis:
= reaction of the liver to a variety of extrahepatic diseases, particularly febrile and affecting the GI tract

Characterized by: prominent Kupffer cells, foci of isolated hepatocytes necrosis, macrophages and inflammatory cells, mild infiltration of some portal tracts by mononuclear cells, no interface hepatitis, some macro/microvesicular steatosis

Differential diagnosis: mild chronic hepatitis and residual stage of acute hepatitis
Minor inflammatory changes of more significance

2. Consequences of vicinity of space-occupying lesion: abcesses, cysts, neoplasms

Characterized by the following triad:
- proliferating distorted bile ductules,
- neutrophils within oedematous portal tracts,
- focal sinusoidal dilatation or congestion
The hepatitic pattern of injury

**Causes:**

- hepatotropic viruses (A, B, C, D, E)
- non hepatotropic viruses (EBV, CMV, Adenovirus, Herpes simplex, Herpes Zoster)
- autoimmune hepatitis (AIH)
- drug-induced liver disease (DILD)
- *Wilson disease*
- *alcohol and non alcoholic steatohepatitis (ASH and NASH)*
- *primary biliary cirrhosis (PBC)*
- *primary sclerosing cholangitis (PSC)*
Approach:

- histology-based first: detailed histological evaluation without any preconceived idea based on the clinical history to avoid any misinterpretation
- obtain the clinical history and laboratory data and check for consistency with the histological evaluation
- give your final pathological diagnosis that takes into account the clinical facts

1. Always to look at the core without any information
2. Never report it without clinical context integration
The hepatitic pattern of injury

Histological patterns of injury: not specific for a disease but help to narrow the scope of differential diagnosis

- Lobular-based
- Portal tract-based
Lobular-based pattern of injury

Characteristics:
- predominant lobular injury
- with or without portal tract changes
- typically predominates in acute hepatitis

From Saxena R, Practical Hepatic Pathology, Elsevier 2011
Portal tract-based pattern of injury

Characteristics:

- expansion of portal tracts by a cellular infiltrate
- varying degrees of lobular inflammation and hepatocyte damage
- main pattern occurring in most chronic liver disease

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<th>Viral hepatitis</th>
<th>Wilson disease</th>
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From Saxena R, Practical Hepatic Pathology, Elsevier 2011
Acute hepatitis

Causes:
- hepatotropic (A > B and C) and non hepatotropic viruses
- autoimmune (AIH) or drug-induced liver disease (DILD): 10-40%
- idiopathic in 15-20%

Liver biopsy not required:
- only performed to verify a diagnosis, in case of unclear or multiple possible causes or if the disease is atypical or prolonged

Predominant lobular pattern of injury:
- necrosis: from spotty to submassive
- diffuse lobular inflammation: activated Kupffer cells, macrophages, lymphocytes
- regeneration with mitotic figures
Chronic hepatitis

Causes:
- hepatotrophic (B, C) and non hepatotrophic viruses
- autoimmune (AIH) or drug-induced liver disease (DILD)
- NASH, ASH, PBC, PSC, Wilson

Liver biopsy important part of the clinical evaluation:
- to verify the diagnosis and exclude other causes, assess grade and stage, guide management, determine prognosis or help for follow-up and special studies

Predominant portal pattern of injury:
- chronic inflammatory cells within the portal tracts with varying degrees of lobular inflammation, hepatocellular injury and fibrosis
Grading and staging of chronic viral hepatitis:
Ishak, Metavir, Scheuer or Batts-Ludwig?

*simple for routine, more complex for clinical trials*

- “It does not matter which system you use”
- “Name the system clearly in your diagnosis and communicate with your clinicians the meaning of the different scorings in that system”
- “In the setting of concomitant diseases (...) grading, and, in particular, staging of changes due to the viral hepatitis may be inappropriate”

*From Theise N, Modern Pathology 2007*
*Liver biopsy assessment in chronic viral hepatitis: a personal, practical approach*
Clinical context: what do we need?

Clinical data:
- sex, age
- past clinical and personal history, transplantation or not
- timing: acute versus chronic (>6 months)
- medications
- imaging findings

Laboratory data:
- viral markers
- autoantibodies: ANA, ASMA, AMA, IgG
- liver enzymes: commonly called “liver function tests” LFTs
  - ALT and AST: hepatitis process: viral, AIH, DILD, NASH, ischemia, metab
  - Serum Alk Ph and γGT: biliary process: PBC, PSC, DILD
Now in the pathologist’s daily life.....
Case 1:
- woman, 43 years old
- no transplantation
- jaundice for 10 days, fever, upper GI symptoms
- under propylthiouracyl (PTU) for 5 months, 100mg/day for hyperthyroidism
- AST 2310 IU/L (<33), ALT 5040 IU/L (<63)
- serum bilirubin: 10.9 mg/dl (0.3-1.2)
- viral markers and autoantibodies negative

Drug-induced acute hepatitis: PTU
0.1 to 1.2% of treated patients
mortality as high as 25%

Benyounes M, WJG 2006
Drug-induced liver disease:

Many different patterns of injury

- if hepatitic pattern: DD is with viral and auto-immune hepatitis and presence of eosinophils, granulomas or cholestasis may help
- if extensive necrosis (toxic): more uniform than viral or auto-immune hepatitis
- definitive diagnosis often impossible
- temporal relationship and exclusion of other causes
- take also into account herbal and “health” products
DILD
Virus (C)
PBC
Obstruction
Case 2:

Male, 61 years old, chronic obstructive pulmonary disease
Bronchitis treated by antibiotherapy: amoxycillin-clavulanic acid
2 weeks after: jaundice and pruritus
US: gallbladder stones
Serum bilirubin: 49.5 mg/dl (72% direct)
ALT: 1.7
AST: 3.1
Alk Ph: 3.1
γGT: 4.2
HAV, HBV, HCV, ANA, AMA, ASMA negative

Drug-induced acute cholestatic hepatitis
related to amoxycillin-clavulanic acid
incidence 1/10000-1/100000
Primary biliary cirrhosis:

A “hepatitic-like” pattern of injury in the early phase
- middle-aged women, elevated Alk Ph ( > 6 months) with AMA + (also in 20% of AIH) and typical duct lesion called “destructive cholangitis” or florid duct lesion; 5% of cases: AMA - ; ANA in 30%
- mononuclear infiltrate in portal tracts, interface hepatitis (but few necrosis) with plasma cells, granulomas often present
- Differential diagnosis:
  - HCV (bile duct injury in 10-25%), AIH (bile duct injury in 20%)
  - true overlap syndromes PBC-AIH: 10%
  - DILD, bile duct obstruction but no bile plugs in PBC
  - sarcoidosis
  - PSC

From Kim E, Kakar S, Ferrell L, 2011 USCAP short course: Common problems in neoplastic and medical liver diseases seen in the consultation practice.
Case 3:
- woman, 65 years old
- nausea, fatigue, abdominal pain, dyspnea
- followed for 2 months because of progressive alteration of LFTs:
  AST 224 IU/L, ALT 263 IU/L, $\gamma$GT 685 (<50)
- methotrexate therapy for 5 years for rheumatoid arthritis, discontinued without improvement one month later:
  AST 1000 IU/L, ALT 990 IU/L, Alk Ph 350 (<94), $\gamma$GT 400 (<50)
  serum bilirubin: 3.7 mg/dl
- viral markers negative
- ANA 1/1280, IgG 2.48 g/dl

Autoimmune hepatitis
Autoimmune hepatitis:

often mixed portal and lobular-based pattern of injury

- simplified criteria for the diagnosis of AIH:
  autoantibodies, IgG, histological evidence of hepatitis (either compatible or typical),
  exclusion of virus (Hennes et al. Hepatology 2008)

-plasma cells prominent in only 1/3 of the cases, also found in viral hepatitis (A > B and C) and in PBC, severe hepatitis, confluent necrosis, bile duct damage in 20% (overlap syndrome with PBC)

-elevated autoantibodies (ANA, ASMA) may also be found in obese patients (ANA in 20-30%, ASMA in 5% and both in 1%)

-major pitfall: DILD: more centrizonal lesions and auto-antibodies rare except for some drugs: Minocycline and Statins

- DD with HCV: bile duct damage, steatosis, lymphoid cell aggregation vs severe lobular necrosis and inflammation, interface hepatitis, broad areas of parenchyme collapse, multinucleated hepatocytes (Bach N et al. Hepatology 1992)
AIH
DILD
Virus (B, C)
PBC
Rejection if LTx
Case 4:

- woman, 20 years old
- no history of liver transplantation
- AST, ALT, γGT and Alk Ph are normal
- no autoantibodies
- HCV + genotype 1b
- HCV RNA: 174571 UI/ml
- Liver biopsy performed for grading and staging before treatment

Chronic hepatitis C, grade 2/4, stage 1/4
Chronic hepatitis C:

a portal-based pattern of injury
- most biopsies performed for grading and staging
- aggressive variants in immunocompromised patients
- milder than HBV (ground-glass hepatocytes and anisocaryosis)
- lymphoid aggregates, reactive changes in bile duct and lymphocytic infiltration, fatty changes

differential diagnosis:
- in LTx: rejection
- + steatosis: associated NASH (at least in 5%) or steatosis related to HCV (genotype 3, < 10%)
Conclusions

Liver biopsy is still an important part of the clinical work-up in patients with liver disease.

Inflammation is often present within the liver and has multiple causes with overlapping morphological features.

A histology-based approach first is the more objective but will only achieve relevance after integration with the clinical scenario.

The optimal interpretation of a liver disease — hence a valid clinical management of each patient — is only achieved by clinicians and pathologists working together.
Thank you very much for your attention.