When is immunohistochemistry useful in adult medical liver disease?

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Plan

• examples

• 51 UK pathologists
  • -50 bx 20%
  • -100 bx 27%
  • -200 bx 27%
  • >200 bx 26%
paraffin sections: added value

- immunohistochemistry
  - antigen retrieval
  - enhanced detection
    - polymer (e.g. Envision dextrane chain)
- *in situ* hybridisation
  - oligonucleotide probes
  - peptide nucleic acid probes

- patch size - “clonality”
  - X-chromosome methylation (HUMARA)

- proteomics
  - comparative mass spectrometry

- expression microarrays
  - Exon chips
Local Ab repertoire

- adequate
- marginal
- inadequate
immunohistochemistry

- **Anatomy**
  - *decorate*: arterioles, bile ducts, ductules, “capillarisation”, stellate cells, lymphatics, matrix

- **Foreign proteins**
  - *extrinsic*: infections
  - *intrinsic*: metastasis, inflammation, amyloid, Ab

- **Altered expression**
  - *homeostasis*: cell cycle, stress response, apoptosis
  - *disorganised*: storage disorder, Mallory
  - *illicit*: neoplasia
Anatomy

podoplanin
ductopenia
ihc utility to diagnose ductopenia

N/A never unusual 5-30% 30-60% 60-90% >90%
Bile duct staining

- would like
- don't need
- EMA
- CD56
- AE1
- CK19
- CK7

0 10 20 30 40 50
Bile ducts: CK7, CK19

- also
  - canal of Hering cholangiocytes, “progenitors”
  - bile ductules

- in disease
  - ductular reaction radiating from coH
  - intermediate cells (6-40μ) (CK7) (adj to ductules)
  - cholate stasis in periportal hepatocytes (CK7)
  - cholestasis in chronic PBC (CK7) [Yabushita K, 2001]
Paracetamol overdose
Paracetamol overdose
Allograft fibrosing cholestatic hepatitis C
PBC cirrhosis: CK7
Infections

- Hepatitis B
- CMV
- EBV
  - Hepatitis D
  - Hepatitis C
  - Hepatitis A
  - Others
Utility of iHC to diagnose/Mx infections

- HBV
- HCV
- CMV
- EBV
- other infections

Legend:
- HBV
- HCV
- CMV
- EBV
- other infections
Hepatitis B

• nucleocapsid core protein (cAg)
  – viral replication
  – nuclear (+/- cytoplasmic)

• envelope surface protein (sAg)
  – cytoplasmic (+/- [sub]membranous)
  – “ground glass” cells
    • ΔΔ glycogen, cyanamidine, “induction”
not helpful  |  sometimes  |  usually  |  would like  |  eh?

HBVsAg  |  HBVcAg
Hepatitis D ihc

- European genotype I
  - acute (replicating, HBV cAg suppression)
  - chronic (less replication & HBV suppression)
  - late

- ihc: nuclear positivity
  - sanded nuclei (HDAg)
  - weak/no cytoplasmic staining
  - useful to rapidly diagnose acute coinfection
CMV

• usually viral inclusions evident
• ihc to early Ag
Acute adult EBV hepatitis

- EBV early RNA (EBER)
  - [SuhN, AJSPath, Sept 2007]
    - 8 patients: acute fever, J, lymphocytosis,
    - sinusoidal “beading”, portal mixed & variable interface/lobular hepatitis, venulitis, bile duct injury
    - very sparse EBER +ve lymphocytes (7/8)
    - LMP ihc negative (8/8)
Systemic IgG₄ disease

- corticosteroid-sensitive multisystem nodular fibroinflammatory disease

- tissue infiltration with IgG₄ plasma cells
  - typically raised serum IgG₄
  - pancreatitis, cholecystitis, cholangitis, Mikulicz’s disease, interstitial nephritis, pneumonitis, retroperitoneal fibrosis, gastric ulcer, “PBC-like” inflammation, inflammatory pseudotumour, fevers
  - bispecific, IL-4/T_{H2}
Systemic IgG$_4$ disease

- wide spectrum
- discrete, intense, mass-forming/segmental
- obliterative phlebitis
- eosinophilia/plasma cells
- sclerosis
- bottom heavy-mural infiltrate (gb, cbd)
Systemic IgG₄ disease

• liver biopsy involvement: sensitive
  – large duct obstruction
  – plasma cell-rich portal inflammation +/-interface
  – lobular hepatitis
  – perivenular cholestasis
  – periportal fibrosis

  ihc: >1/hpf or >20% [UmemuraT2007]

• consider if…“Sjogrens”, sialadenitis, cancer-negative Whipples, wheeze, dry eyes/mouth, interstitial nephritis…
Amyloid, MIDD

• acquired
  – AA
  – AL (lambda 3x kappa)

• hereditary
  – neuropathic
  – non-neuropathic
    • fibrinogen α chain, lysozyme, apolipoprotein A1

• MIDD (light+/heavy chain)
\(\alpha_1\)-antitrypsin deficiency

- Z mutant vs normal protein
- \textit{ihc} more sensitive than PAS/D
  - missed 0 vs 5/33 adults \cite{CalleaF1986}
- \textit{globules >3u}
  - specific but 47\% of Z allele \cite{ClausenPP1984}
- in cirrhosis with globules
  - 10\% - but variety of phenotypes, some normal \cite{IezzoniJC1997}
- \textit{a1antichymotrypsin deficiency}
  - smaller, weaker PAS/D+, \textit{ihc} available \cite{ThomasRM2000}
- \textit{ΔΔ} stressed liver, congestion-associated, fibrinogen storage disease
PiMZ stressed liver (ALD)

PiZZ
Cam5.2 Ubiquitin

Mallory bodies
utility of specific ihc

not helpful | sometimes | usually | would like | eh?

Mallory body | a1AT
**ihc importance in medical liver diseases**

- **AIH**
- **overlap**
- **steatohepatitis**
- **a1AT deficiency**

Categories: never, unusual, 5-30%, 30-60%, 60-90%, >90%
Requesting IHC in malignancy

- never
- unusual
- 5-30%
- 30-60%
- 60-90%
- >90%

- Medical
- Metastasis
- HCC
- Cholangio

HCC

CRC
Requesting IHC in hepatocellular lesions

- N/A
- never
- unusual
- 5-30%
- 30-60%
- 60-90%
- >90%

HCC vs Dysplasia
HCC vs Adenoma
Adenoma vs FNH

Images:
- Adenoma
- FNH
- FNH
Hepatocellular differentiation in malignancy

also CD13 (RockenC2005)
CD10: canalicular staining
ihc in liver dysplasia/HCC

![Bar graph showing CD34, Glypican-3, and Proliferation in liver dysplasia/HCC. The graph indicates that Glypican-3 is usually helpful, and Proliferation is sometimes helpful. CD34 is not helpful and eh? is usually helpful.](image-url)
• oncofoetal protein marking early HCC
• 70-90% HCC, esp in cirrhosis
• 10-50% HG dysplasia
• 0-3% LG dysplasia
• membranous, canalicular, cytoplasmic
CD34 marking HCC in cirrhosis
“capillarised” vessels in HCC, dysplasia

- CD34, CD31, BNH9
- 40% DN
- 85% HCC
Adenoma typing & ihc

- Bioulac-Sage P: Hepatology, 2007

- **HNF1α inactivation**: absent L-FABP
- **β-catenin activation**: glutamine synthetase/β-catenin
- **Inflammatory/telangiectatic**: SAA↑↑, β-catenin N

- β-catenin mutated adenomas ? higher risk to be borderline or have HCC
cirrhotic nodule in PBC