Hepatocellular Carcinoma: Pathogenesis, Epidemiology, and Diagnosis

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Conflicts of interest

• None
Objectives

• Practical

• Focus: diagnostic approach to well differentiated hepatocellular tumor

HCA vs HCC
HCC vs HAA

HCA vs HCC: not always so easy

“All too often the diagnosis of an adenoma from a biopsy specimen has been followed sooner or later by proof at surgical operation or at autopsy that the tumor was in reality a liver cell carcinoma”

Edmondson, AFIP fascicle, 1958
Illustrative case

• 53 year old woman
• Single 6 cm liver mass in liver
• Serum AFP levels are normal
• No history of chronic liver disease
• Radiology differential: hepatic adenoma versus hepatocellular carcinoma versus less likely FNH
• Undergoes resection
Not FNH

? HCC or HA
Approach to Diagnosis

What other tools are available?
Approach to Diagnosis

Immunohistochemistry
Approach to Diagnosis

Fork in the road: choice of two different pathways:

Based on H&E findings, which of the following is true:

A. The tissue is all liver, but I’m not sure if it is cancer.
B. The tissue has definite cancer, but I’m not sure if its HCC or cholangiocarcinoma or metastatic.
Approach to Diagnosis

Benign liver Tumor

Versus

Well diff HCC

HCC

Versus

CholangioCA, metastases
Approach to Diagnosis

Benign liver Tumor
Versus
Well diff HCC
Helpful stains when the biopsy shows a well differentiated hepatocellular tumor:

- *Reticulin stain*
- Ki-67
- Glypican 3
- CD34

- Consider others depending on the results of these morphology; eg Glutamine synthetase for FNH
Our case

- Our case
  - Convincing reticulin loss
  - Glypican 3 positive, focal
  - Mild but definite increase in Ki-67

- Final Diagnosis:

  Hepatocellular carcinoma
Most important points on most important stains
Diagnostic Approach

- Reticulin stain
- Ki-67
- Glypican 3
- CD34
Key points for Reticulin

• Reticulin is diminished in HCC
• Particularly helpful in benign vs malignant
• Look for loss of reticulin
  – “plate thickening in HCC”
  – “All cells touching reticulin in benign liver”
  – In most cases, reticulin is not entirely lost
  – Focal minimal loss doesn’t count
Key points for Reticulin

• Key dates
  – **1977** (PMID: 197780)—Retic loss in HCC
  – **1986** (PMID: 2430547)—Retic loss to distinguish HCC from benign liver tumors
  – **Since then:** Confirmed by decades of experience from centers across the world in all liver diseases
Key points for Reticulin

• World wide experience
  – >99% of clinically aggressive HCCs have reticulin loss
  – ~100% of clinically benign tumors have normal reticulin
Key points for Reticulin

But, how do you know retic loss is meaningful in EVERY very well differentiated hepatocellular tumor that has it?

Might some of these still be benign?
Key points for Reticulin

Usually in the context of resected specimens

– “Well differentiated tumors are cured by surgery, so you have no way of really knowing if it’s a HCC or HA, even if it has retic loss”

– True that--these are cured by resection, but at this point reticulin loss is a strong guide for classification of well differentiated tumors
Interpretation of Retic
Hepatic adenoma
Near total loss
Patchy, mild loss
Interpretation of Retic

5 pitfalls to avoid
Pitfall 1
Make sure stain quality is good
Pitfall 2. Morphology important for interpreting retic

Focal plate thickening
Not HCC
Reticulin: pitfall

Pitfall 3
Non-neoplastic liver can have patchy reticulin loss due to fat

(Am J Surg Pathol. 2012 May;36(5):710-5.)
Pitfall 4
Rare HCC with no Retic loss
Pitfall 5
Other abnormal Patterns
Not HCC
Key points for Glypican 3

Glypican 3

• Cytoplasmic staining
• Staining diffuse or patchy
• 50% of well diff HCC negative
• Cross check with H&E
  – Lipofuscin also can stain
Lipofuscin

Glypican 3
Key points for Ki-67

KI-67:

• **Compare to background liver!**
  – Clearly increased above background suggests HCC

• **No absolute cut off**
  – Almost all adenomas are less than 3%
  – HCCs can range from less than 2% to greater than 20%
Ki-67

Check morphology
Key points for CD34

• HCC: strong and diffuse staining
• Adenoma or FNH: patchy and irregular staining (but 30% of adenomas can be diffuse!)
Other stains / tests for HCA vs HCC

5 important points
Immunostains

Point 1. Stains for subtyping hepatic adenomas

– Do not distinguish adenoma from HCC

– Only use these stains after you have made the diagnosis of hepatic adenoma
Immunostains

• Stains for subtyping hepatic adenomas
  – LFABP:
  – CRP:
  – SAA:
  – beta catenin nuclear staining:
  – glutamine synthetase staining:
Immunostains

• Stains for subtyping hepatic adenomas
  – LFABP: 25% of HCC
  – CRP: 50% of HCC
  – SAA: 17% of HCC
  – beta catenin nuclear staining: 30% of HCC
  – glutamine synthetase staining: 50% of HCC
Immunostains

**Point 2. Stromal invasion**

- Helpful in resection specimens
- On biopsy—not so much
  - Only rarely seen on biopsies with definite HCC
    - Many definite HCCs do not have it
  - Never seen a case where it helped in distinction of adenoma vs HCC
Stromal invasion

Supplement With CK7
Cirrhotic vs non-cirrhotic liver

Point 3: Differential depends on the background liver

- Cirrhotic
- Non-cirrhotic
Differential Diagnosis

Noncirrhotic liver
Missed the tumor?
MRN (after massive necrosis)
FNH
hepatic adenoma
HCC
Differential Diagnosis

**Cirrhotic liver**
Missed the tumor?
Maccoregenerative nodule
Dysplastic nodule
HCC
Cirrhotic vs non-cirrhotic liver

**Point 3a: Cirrhosis:**
- Natural history of “adenoma-like nodules” unknown
Immunostains

Point 4. Glutamine synthetase, heat shock protein 70, glypican 3

- Used in cirrhotic livers for HCC versus a high grade dysplastic nodule
  - GS and GP3 staining are most helpful
- My experience with HSP70—high background, hard to interpret
Immunostains

Point 5. Potential molecular tests

– TERT promoter mutations
  • Might be specific, unlikely to be sensitive
  • Not validated for clinical care

– Chromosomal gains
  • Promising, not yet been fully explored
  • Not validated for clinical care
Approach to Diagnosis

Benign liver Tumor

Versus

Well diff HCC
Basik Approach to Diagnosis

HCC
Versus
CholangioCA, metastases
Immunohistochemical stains for hepatocellular carcinoma
Big 3 stains

HepPar1 vs Glypican 3 vs Arginase 1
Stains for hepatocellular differentiation

Stain 1

Stain 2

Who is the champion?
Stains for hepatocellular differentiation

Stain 1

Stain 2
Basik Approach

Well Diff

HepPar1
Arginase
Glypican 3

Mod Diff

HepPar1
Arginase
Glypican 3

Poor Diff

Arginase
Glypican 3
HepPar

UnDiff

Arginase
Glypican 3
HepPar

-----Reticulin-----
Rarely these stains are also needed for well differentiated tumors
HCC mimics

- Neuroendocrine tumor
- Renal oncocytic tumor
- Paraganglioma

Not pictured: Epithelioid AML
Arginase negative HCC
Summary
Summary

1. Comprehensive review of methods for distinguishing benign from malignant hepatocellular proliferations

2. Use H&E to determine what stains are needed
   - Panel A: Benign, but unsure of adenoma vs FNH
   - Panel B: Malignant, but unsure if HCC or metastatic disease
3. Use the stains in conjunction with the morphology; never in isolation
   – Retic
   – Glypican 3
   – Ki-67
The End