A LIVER TUMOR WITH AN IDENTITY CRISIS

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CASE HISTORY
- Elderly female
- ETOH user, but not known to have cirrhosis
- Abdominal fullness
- LFT normal
- 4-5 lesions in the liver with 5.7cm dominant nodule
- PET CT otherwise normal
- Biopsy obtained

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Thomas Starzl, MD. Died on March 3, 2017
Differential Diagnosis, take 1

- Obviously malignant
- Obviously carcinoma
- Not obviously primary or secondary
- IHC markers of common sites of metastasis negative
  - TTF1
  - CDX2
  - PAX8
  - GATA3
- Main considerations:
  - HCC
  - Intrahepatic cholangiocarcinoma (ChCa)
  - Metastatic pancreatobiliary adenocarcinoma

Histological features of HCC and ChCa

Features that favor HCC
- Cells quite pink
- Somewhat trabecular
- No definite gland formation
- No definite mucin production

Features that favor ChCa
- Extensively fibrotic tumor stroma
- Wouldn’t swear that there are no glands
- No bile identified
Conclusion

- Scirrhous variant of hepatocellular carcinoma
- Rare
- Cords and nests of neoplastic cells in dense fibrous stroma (Matsuura 2005)
- Cells have hepatoid morphology
- Must NOT have mucin production
- Mucin is a feature of adenocarcinoma, not HCC
- Seems to have similar clinical features and prognosis as traditional HCC
- Distinction from traditional HCC probably not relevant for clinical care (as of today)
- Distinction from ChCa and metastatic disease critical

Ancillary testing

- General theme-expresses markers of hepatic and biliary differentiation
- Need some HCC marker; would not make dx without at least 1 convincing marker
- Must not produce mucin (should be proven)
- Newer markers such as albumin ISH and bile salt export pump not yet investigated
  - In my experience, these have both been positive in 2 of 2 cases

Differential Diagnosis, deeper dive

- Combined HCC-ChCa
  - Should have biphasic morphology
  - Populations should stain distinctively
- Combined hepatocellular-cholangiocarcinoma with stem cell features, intermediate cell type
  - According to WHO 2010, the cells are “small, oval-shaped, with hyperchromatic nuclei and scant cytoplasm”
  - Scirrhous HCC cells look like HCC
  - Scirrhous HCC does not express much C-KIT or CD56 (Krings 2013)
- Fibrolamellar HCC
  - Very different patient population (kids, young adults), no cirrhosis
  - Recent discovery of a chimeric kinase due to a deletion on Ch.19 resulting in DNAJB1-PRKACA transcript (Honeyman 2014)
  - Detectable by PCR, FISH, and mRNA ISH (Graham 2015)

Immunohistochemistry

- GPC3 and ARG combined for 100% sensitivity

Newer markers in liver tumors

- Bile Salt Export Pump
  - Present exclusively in hepatocytes at the bile canaliculus
  - Main driver of bile salt efflux from hepatocyte
  - Genetic lack of BSEP causes PFIC2
Low grade HCC, BSEP

High grade HCC

High grade HCC, BSEP

Conclusions regarding BSEP

- Seems to be most specific marker for HCC
- Due to lack of expression in other cell types/carcinomas, do not need canalicular pattern to consider positive
- Though usually canalicular
- Sensitivity is good overall, but drops with worsening differentiation
- Need to optimize in your lab
- Useful as part of a panel

Conclusions regarding albumin ISH

- Excellent sensitivity for HCC
- Probably good sensitivity for intrahepatic ChCa
- Kit, other factors
- This multispecificity means cannot help differentiate HCC from ChCa
- Cannot discriminate BDA vs. ChCa
- Evolving understanding of pitfalls

In-situ hybridization for albumin

- Targets mRNA for albumin
- Commercially available kit which runs on automated platform
- Positive
  - HCC, excellent sensitivity (92 of 93 HCC) (Shahid 2015)
  - Intrahepatic cholangiocarcinoma
  - Highly sensitive (Ferrone 2016)
  - Less highly sensitive (Avadhani, USCAP 2017, #1657), (Lehrke, USCAP 2017, #1680)
  - Bile duct adenomas (May 2016)
  - Hepatoblastoma, fibrolamellar HCC (Koehne de Gonzalez USCAP 2016, #1667)
- Negative
  - Most other cancers (including PDAC, Distal CBD, Klatskin) (Ferrone 2016)
- Pitfalls
  - Pancreatic acinar carcinoma (Askan 2016)
  - Occasional adca of diverse sites (Lehrke, USCAP 2017, #1680)

Albumin ISH in ChCa

Additional studies on BSEP

BSEP was diluted to 1:200 vs. 1:100 and incubation was 15m compared to 32m

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Approach to PD liver tumors

- Careful H&E assessment, consideration of clinical hx
- Keep the basics in mind (mucin, bile)
- Keep the pitfalls in mind
- Let the amount of tumor determine your work-up
- No silver bullets
- Cost of ancillary testing in pathology is a rounding error in cancer care
- Need to build a base of experience with these tests
- If limited tumor, get 20 serial blanks with occasional H&E (Bl 10&20)

References