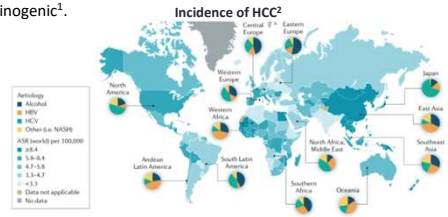
A Rare Presentation of Primary Hepatocellular Carcinoma in Alabama

Cassidy Clark[1], OMSII, Rishika Pandey[1], OMSII, Jackie Jiang[1], OMSI, David Stephen[1], DO, Brandon Johnson[2], MD
[1]Edward Via College of Osteopathic Medicine – Auburn Campus, [2]East Alabama Medical Center, Opelika, AL

INTRODUCTION

Primary Hepatocellular Carcinoma (HCC) is most frequently associated with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) with the latter being the most common risk factor in the United States[1]. Geographical epidemiology is typically associated with areas of high incidence of HBV, such as Sub-Saharan Africa and Eastern Asia, due to perinatal transmission[1]. Other risk factors include Aflatoxin exposure, obesity, diabetes, and non-alcoholic fatty liver disease. While alcohol is synergistic with HCV and HBV through the development of cirrhosis, it is not considered to be directly carcinogenic[1].

Incidence of HCC[2]



CASE PRESENTATION

A 69 year old African American male presented to the Emergency Department with complaints of chest discomfort, shortness of breath, and abdominal pain. His past medical history is pertinent for cirrhosis. Social history is pertinent for heavy alcohol consumption and tobacco use. The patient reported no current medications or allergies. Physical exam revealed ascites and scleral icterus.

Abdominal Ultrasound illustrated changes of cirrhosis with moderate ascites. Portal vein is patent. Questionable thrombus in the Inferior Vena Cava (IVC). Cholelithiasis with increasing diffuse gallbladder wall thickening without a Murphy sign or biliary dilation.

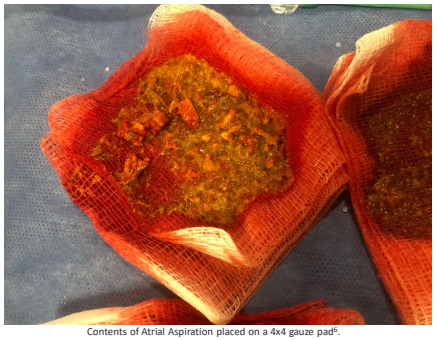
Table 1

Bloodwork			Urine analysis		
BUN	38	(7-25)	U Protein	30	(negative -)
Creatinine	2.2	(0.7-1.4)	U Blood	Trace	(negative -)
Bilirubin total	5.1	(0.3-1.0)	U Urobilinogen	4	(negative -)
Alk Phos Total	515	(38-126)	U Leuk Esterase	Large	(negative -)
AST	126	(13-39)	Granular casts	2	(<= 0)
ALT	65	(7-52)	RBC	9	(<=2)
BNP	122	(0-100)	WBC	67	(<=5)
Troponin	0.19	(<0.05)			
D-Dimer	7,592	(0-243)			

Initial lab work at presentation

ADMISSION & WORKUP

Cardiology performed a TEE which revealed a large thrombus filling most of the Right Atrium. Severe tricuspid regurgitation and pulmonary hypertension. The right ventricle was dilated with evidence of strain. Interventional cardiology performed an Inferior vena cava angiography and thrombectomy which found no significant thrombus, but aspirated a significant amount of loosely adherent brown tissue from the right atrium.



Contents of Atrial Aspiration placed on a 4x4 gauze pad[6].

PATHOLOGY REPORT

Grossly, there are multiple tan to green tissue fragments with a spongy papillary appearance measuring 4.0 cm in aggregate. Histology staining revealed a tumor that was CK7-, CK20-, GATA3-, and PAX8-. The final diagnosis was High-grade papillary adenocarcinoma of uncertain origin.

Figure 1[3]

CK7+/CK20−	CK7+/CK20+	CK7−/CK20+	CK7−/CK20−
Breast carcinoma Lung adenocarcinoma Endometrial adenocarcinoma Endocervical adenocarcinoma Ovarian (serous) carcinoma Cholangiocarcinoma Small cell lung carcinoma Mesothelioma Thyroid carcinoma Salivary gland tumours Kidney (papillary) Urothelial carcinoma (subset) Pancreatic adenocarcinoma Gastric adenocarcinoma	Urothelial carcinoma Pancreatic adenocarcinoma Ovarian mucinous carcinoma Bladder adenocarcinoma Gastric adenocarcinoma Cholangiocarcinoma	Colorectal adenocarcinoma Merkel cell carcinoma Gastric adenocarcinoma	Prostate adenocarcinoma Renal (clear cells) Hepatocellular carcinoma Adrenocortical carcinoma Non-seminoma germ cell tumours Mesothelioma Small cell lung carcinoma Gastric adenocarcinoma

Main primary origins of carcinomas of unknown origin based on staining of CK7 and CK20.

Figure 2[3]

Primary Site	IHC Profile
Prostate [58,59,60,61,62]	PSA+, NKX3.1+/−, PSAP+, P504S+, ERG+/−
Colon (medullary) [29,35,36]	SATB2+, CDH17+, TFF3+/−, Calretinin+/−, CDX2−/+
Renal [21,63]	CD10+, PAX8+, Vimentin+, pVHL+, RCCMa+, Inhibin−, TTF1−, CEA−
Liver [64]	HepPar1+, CD10+, pCEA+, mCEA−, AFP+, Glypican-3+, Arginase-1+, CK19−
Adrenal (cortical) [4,7,10]	Melan A+, Calretinin+, Inhibin A+, Synaptophysin+, Chromograni−, CEA−
Germ cell tumours [4,7,10]	CD117+, OCT4+, CD30+, Glypican-3+, PLAP+, SALL4+, NANOG+

Immunohistochemistry staining patterns in the differential diagnosis of tumors of unknown origin expressing CK7-/CK20-

ONCOLOGY

Oncology ordered an MRI of the abdomen based on prior elevated alpha-fetoprotein (AFP), abnormal liver function tests, and suspected HCC. Imaging revealed a markedly atrophic and nodular liver with a 12 cm, partially exophytic, mass in the right lobe with invasion of the IVC extending into the IVC-right atrial junction. Additionally, there were scattered nodules in the left lobe as well as in the right lobe near the porta hepatis. Bilateral adrenal masses were also noted.

Table 2

Lab	Value
AFP	>19,000
HIV-1/HIV-2 Antibody	Nonreactive
Hep A/B/C Ab	Nonreactive

DISCUSSION

There is a relatively low incidence of primary HCC in the United States[1]. While this patient did have a history of cirrhosis due to heavy alcohol use, he was born and raised in Alabama and denied occupations associated with aflatoxins such as factories or mills. With the original presentation bringing concern for a Pulmonary Embolus and thrombectomy illustrating a loosely adherent mass in the right atrium, an embolized mass of cancerous origin was investigated. Pathology report of CK7- and CK20- narrowed the differential to prostate, renal, hepatocellular, or lung cancer[3]. Renal cell carcinoma was initially favored due to visualization of a possible clot in the renal vein during venogram and decreasing kidney function; however, PAX8 was negative and thus ruled out renal carcinoma. AFP, while also elevated in patients with liver cirrhosis, is elevated to a much higher extent in HCC and correlates with a poor prognosis[4]. Abdominal MRI in conjunction with AFP led to the diagnosis of primary HCC. The presentation of this case is unique in that a primary tumor was multinodular in origin which is more characteristic of metastatic cancer as well as a lack of the most common risk factors for HCC. Although HCC is very aggressive, its spread to the heart is very unusual and has been reported in only a handful of case studies that list this incidence at less than 3%[5].

REFERENCES

1. Mittal, S., & El-Serag, H. B. (2013). Epidemiology of hepatocellular carcinoma: consider the population. *Journal of clinical gastroenterology*, *47 Suppl*(0), S2–S6. https://doi.org/10.1097/MCG.0b013e3182872f29
2. Llovet, J.M., Kelley, R.K., Villanueva, A. *et al.* Hepatocellular carcinoma. *Nat Rev Dis Primers* **7**, 6 (2021). https://doi.org/10.1038/s41572-020-00240-3
3. Selves, J., Long-Mira, E., Mathieu, M. C., Rochaix, P., & Ilié, M. (2018). Immunohistochemistry for Diagnosis of Metastatic Carcinomas of Unknown Primary Site. *Cancers*, *10*(4), 108. https://doi.org/10.3390/cancers10040108
4. Mehinovic, L., Islamagic, E., Husic-Selimovic, A., Kurtovic-Kozaric, A., Vukobrat-Bijedic, Z., & Suljevic, D. (2018). Evaluation of Diagnostic Efficiency of Alpha-Fetoprotein in Patients with Liver Cirrhosis and Hepatocellular Carcinoma: Single-Center Experience. *Open access Macedonian journal of medical sciences*, *6*(9), 1668–1673. https://doi.org/10.3889/oamjms.2018.344
5. Dedeilias, P., Nenekidis, I., Koukis, I. *et al.* Acute heart failure caused by a giant hepatocellular metastatic tumor of the right atrium. *J Cardiothorac Surg* **6**, 102 (2011). https://doi.org/10.1186/1749-8090-6-102
6. Photo curtesy of Dr. Holmes.