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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Hepatoid Adenocarcinoma of the Rectum With Liver Metastasis in a Patient With Ulcerative Colitis

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ABSTRACT

Hepatoid adenocarcinoma (HA) is a rare malignant tumor of extrahepatic origin that morphologically and immunophenotypically resembles hepatocellular carcinoma. We report a case of rectal HA with hepatic metastasis arising in a 38-year-old male with a history of ulcerative colitis. Despite elevated alpha-fetoprotein, contrast enhancement of the hepatic mass was not consistent with hepatocellular carcinoma. Immunohistochemistry revealed the diagnosis, and the patient was started on palliative chemotherapy. Colorectal HA should be considered when evaluating malignant lesions in the setting of inflammatory bowel disease and can be distinguished from other tumors based on alpha-fetoprotein, imaging, and immunostaining.

INTRODUCTION

Hepatoid adenocarcinoma (HA) is a rare extrahepatic malignancy characterized by elevated alpha-fetoprotein (AFP) levels and tumor cells histologically resembling hepatocellular carcinoma (HCC). Tumors consist of atypical polygonal cells around glandular and sinusoidal structures with immunohistochemical profiles similar to HCC.[1] Most reported cases arise in the stomach, though HA of the small and large intestines, lung, ovary, uterus, bladder, pancreas, and gallbladder have been described.[2] HA is often metastatic at diagnosis and carries a poor prognosis. Most cases arising in the small intestine and colon have been described in patients with inflammatory bowel disease (IBD), who are at an increased risk of developing adenocarcinoma of the gastrointestinal tract.

CASE REPORT

A 38-year-old white man with a 13-year history of ulcerative colitis (UC) presented to an outside facility with 3 months of diarrhea, mild abdominal pain, and 4.5 kg weight loss. The patient was previously in remission on oral budesonide and mesalamine but had chosen to come off therapy for 3 months. Colonoscopy revealed severe diffusely ulcerated and necrotic-appearing rectosigmoid mucosa without a distinguishable mass, triggering a concern for ischemic colitis. No biopsies were performed during the initial colonoscopy. At our facility, abdominal computed tomography (CT) performed for the initially suspected ischemia showed a large, $8.1 \times 9.4 \times 6.6$ cm hepatic mass, with normal surrounding parenchyma, a portal vein thrombus, and rectosigmoid thickening with locoregional lymphadenopathy. Liver protocol magnetic resonance imaging did not have the characteristic contrast washout seen in HCC (Figure 1). However, AFP (15,523 ng/mL) and carcinoembryonic antigen (CEA) (20.3 ng/mL) were elevated. Contrast enhancement pattern seen on quadruple phase CT was also not consistent with HCC. Scrotal ultrasound, ordered to rule out a primary testicular malignancy, was negative. However, human chorionic gonadotropin was elevated (28 U/L), increasing the concern about an extragonadal yolk sac tumor.

The patient underwent flexible sigmoidoscopy with rectal biopsies and liver core biopsy (Figure 2). The rectal biopsies revealed carcinoma with large eosinophilic cells and trabecular morphology resembling liver tissue (Figure 3). The liver mass biopsy exhibited morphologic and cytologic findings congruent with the rectal carcinoma (Figure 4). Immunohistochemistry displayed positive

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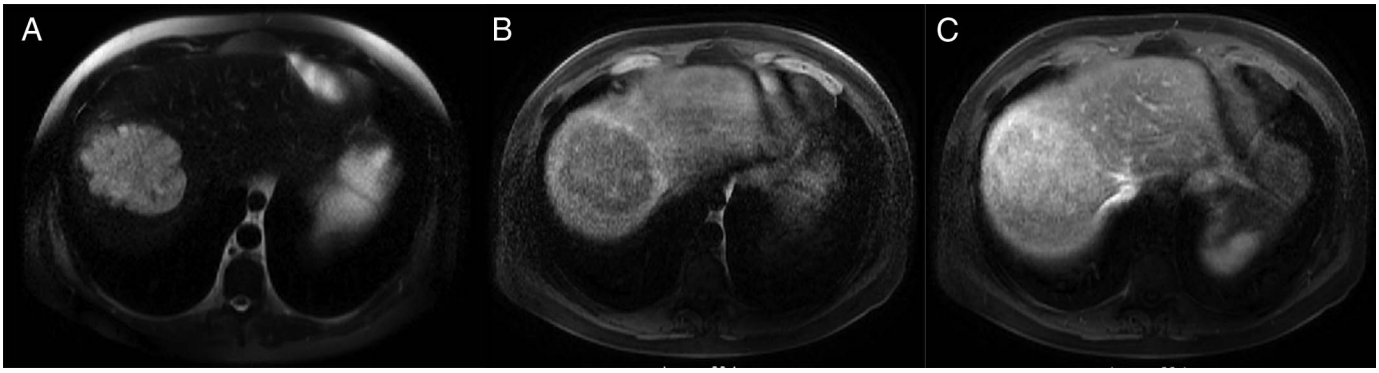

Figure 1. Magnetic resonance imaging of the liver. (A) Axial fat saturated fast spin echo T2 weighted image demonstrates a large heterogeneous soft tissue mass in segment 8 of the right hepatic lobe with high signal intensity. (B) Corresponding lesion during liver acceleration volume acquisition (LAVA) pre-contrast sequence. (C) Axial delayed phase LAVA image shows an isointense mass without washout appearance.

staining for pankeratin, cdx-2, polyclonal CEA, monoclonal CEA, AFP, glypican-3, sal-like protein 4 (SALL-4), and focal positivity for CK20 and was negative for CK7, HepPar-1, Vimentin, CD31, and CD34. Clinical features, histologic morphology, and immunophenotype were consistent with primary rectal HA with hepatic metastasis, and the patient was started on palliative FOLFOX (oxaliplatin, leucovorin, 5-fluorouracil) plus cetuximab chemotherapy.

Two months later, a repeat abdominal CT was taken, which demonstrated a reduction in size of the primary rectal mass, liver mass, and local lymph nodes. AFP was significantly improved (2.8 ng/mL) compared to pre-chemotherapy level (34,884 ng/mL). After 6 of 10 planned cycles of chemotherapy, colonoscopy was repeated for evaluation of abdominal pain and rectal bleeding which showed a well-demarcated partially circumferential polypoid mass with surrounding mild to moderately ulcerated mucosa extending from the rectum to the mid-transverse colon. The previously observed necrotic features of the rectal mucosa had resolved. Neoadjuvant chemoradiation therapy was started but was limited by colitis flare, 1 month into the treatment. The patient was placed on oral prednisone 40 mg and later azathioprine 75 mg with only partial response. Colectomy was recommended when the patient was later admitted for severe UC flare. Inpatient flexible sigmoidoscopy was notable for severe colitis with no discernible mass. The patient was reluctant to have surgery, so infliximab (Remicade) 5 mg/kg was initiated. Nearly 10 months after his initial presentation, and following failed infliximab induction, the patient agreed to undergo proctocolectomy with abdominoperineal resection and end ileostomy.

DISCUSSION

We describe the case of metastatic rectal HA arising in a patient with ulcerative colitis. The diagnostic workup proved to be challenging, as markedly elevated AFP implicated HCC, but contrast enhanced imaging was not compatible with the diagnosis.

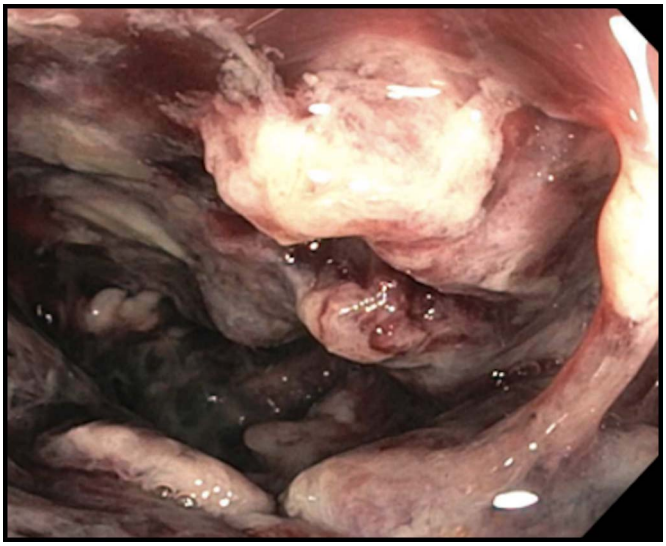

Figure 2. Necrotic appearing rectal mucosa during flexible sigmoidoscopy.

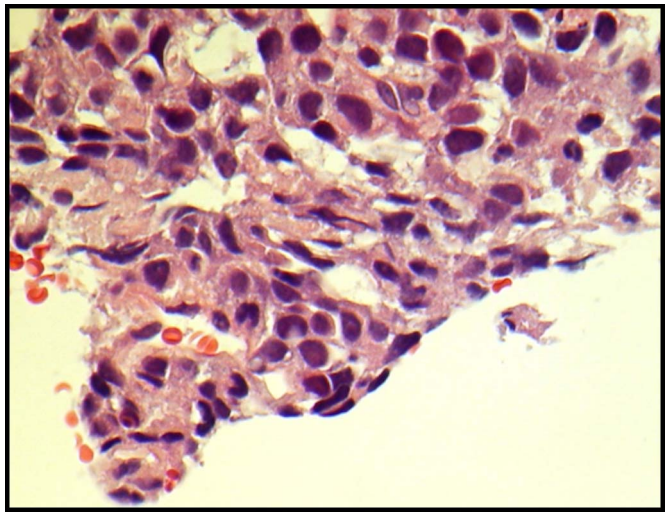

Figure 3. Rectal biopsy reveals large eosinophilic cells with a trabecular morphology resembling normal liver tissue.

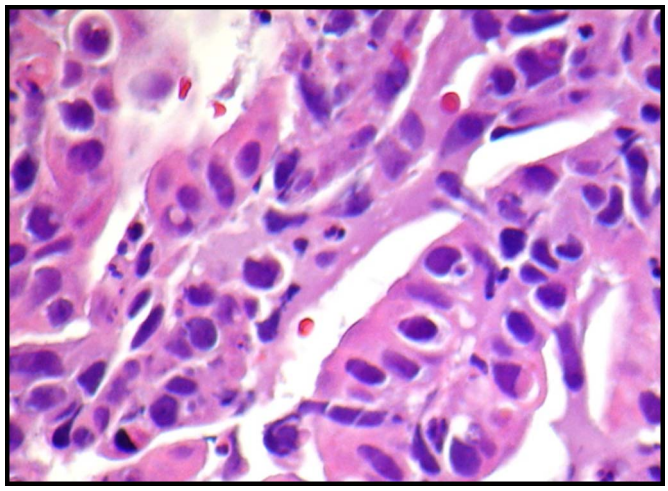

Figure 4. Liver mass biopsy exhibits congruent morphologic and cytologic findings to the rectal biopsy.

Definitive diagnosis of rectal HA with liver metastasis was only made after rectal biopsies, aided by immunohistochemistry-matched liver mass pathology.

HA was first described by Bourreille in 1970 and later named by Ishikura.[3,4] Approximately 84% of HA originates in the stomach, which is potentially attributable to the common embryologic origin of the stomach and liver from the foregut.[5] Colonic or rectal HA represents only 2% of all reported cases. The majority of intestinal HA cases have been described in IBD patients.[6–10] Chronic inflammation has been proposed to have a role in this possible association, however no causality has been established to date. Imaging features of HA liver metastasis can resemble those of HCC. However, a recent case series revealed that less than two-thirds of HA demonstrates HCC-like contrast enhancement, noting considerable variability in enhancement pattern.[11] Inconsistent contrast enhancement, as was seen in our patient, is unlike HCC, where the diagnosis can often be made radiographically due to its characteristic early arterial enhancement and venous washout. Serum AFP is elevated in the majority of HA cases.[5] Typical immunohistochemical profile of HA includes AFP, glypican-3, SALL-4, arginase-1, CK18, CK19, and CK20. Hep-Par1, a specific marker for HCC, is often expressed in HA.[1,5,12] SALL-4 expression is helpful in distinguishing HA from HCC as it is typically absent in normal liver tissue and HCC (Table 1).[13] The staining profile of HA can be similar to yolk sac tumors. However, polyclonal CEA can help differentiate the 2 neoplasms, as it is positive in 100% of reported HA cases and only 23% of yolk sac tumors, per Immunoquery search.[12]

Treating HA involves primary tumor resection with adjuvant chemotherapy. In the cases of colorectal HA, adjuvant chemotherapy with FOLFOX or FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) regimens, with and without cetuximab or bevacizumab, have been described. No standard chemotherapy regimen has been established for HA.[1,2,14] Palliative chemotherapy is indicated for metastatic disease. Colonic HA tends to metastasize early and carries a poor prognosis, with a median survival of 8 months.[3] Our patient had a good response to chemotherapy with significant reduction in tumor burden.

HA is an uncommon aggressive neoplasm with unique features that create diagnostic challenges as highlighted in our case. Its similarity to HCC can lead to misidentification, but immunohistochemistry profiling can aid in establishing the correct diagnosis. A more in-depth understanding of the biology and natural history of HA will be critical to improving diagnostic tests and therapeutic targets. The diagnosis of colonic HA

Table 1. Immunohistochemical profiles by cancer type

Immunohistochemical stain	Hepatoid adenocarcinoma	Hepatocellular carcinoma	Colon adenocarcinoma
AFP	83% (64)	31% (871)	8% (48)
CEA-M	60% (5)	21% (398)	88% (891)
CEA-P	100% (8)	70% (725)	91% (205)
Glypican-3	56% (45)	70% (1,412)	3% (155)
CK 18	92% (13)	83% (181)	92% (66)
CK 19	95% (19)	10% (831)	93% (121)
CK20	42% (19)	8% (450)	86% (2,781)
Hep-Par1	63% (64)	82% (1,391)	7% (441)
CDX-2	0% (0)	0% (110)	88% (2,796)
SALL-4	47% (45)	9% (401)	3% (305)
Chromogranin A	0% (0)	52% (21)	74% (821)
EMA	0% (0)	11% (341)	49% (284)

(%), Percent positive staining reported in ImmunoQuery; (n), total reported cases in ImmunoQuery; AFP, alpha-fetoprotein; CDX-2, caudal type homeobox 2; CEA-M, monoclonal carcinoembryonic antigen; CEA-P, polyclonal carcinoembryonic antigen; CK, cytokeratin; EMA, epithelial membrane antigen; Hep-Par1, hepatocyte paraffin 1; SALL-4, sal-like protein 4.

should be considered in IBD patients with metastatic hepatic lesions characterized by high AFP and atypical dynamic contrast enhancement pattern.

DISCLOSURES

Author contributions: AN Levy, R. Ackerman, and MW Winter wrote and edited the manuscript. O. Yilmaz prepared the pathology figure and wrote the manuscript. C. Jouhourian and M. Tandon wrote the manuscript. AN Levy is the article guarantor.

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