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CASE REPORT

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A case of rectal hepatoid adenocarcinoma in a patient with inflammatory bowel disease: case report and review of literature

Hari K Krishnan Nair[1*], Archana Agarwal[2], David Ricklan[3] and Olga Kozyreva[2]

[1]Department of Medicine, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA
[2]Department of Pathology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA
[3]Department of Medical Oncology, Dana-Farber Cancer Institute at St. Elizabeth's Medical Center, Boston, MA, USA

Abstract

Hepatoid adenocarcinoma is a rare extrahepatic malignancy with histological features and biochemical profile similar to hepatocellular carcinoma. A 38-year-old male with a 10-year history of ulcerative colitis on treatment was found to have a large rectal mass with locoregional lymphadenopathy and distant spread to peri-portal nodes, hepatic parenchyma, and portal vein. Based on elevated serum AFP levels and immunohistochemical staining of rectal tissue, he was diagnosed with metastatic hepatoid adenocarcinoma and was treated with ten cycles of palliative folinic acid, fluorouracil and oxaliplatin (FOLFOX). Following an excellent response to FOLFOX, he was treated with curative intent with 5-fluorouracil (5-FU)-based neoadjuvant chemoradiation followed by proctocolectomy for local cancer control and ulcerative colitis treatment. This was followed by stereotactic body radiation therapy (SBRT) to the liver. The patient had no evidence of relapse three months after his last day of SBRT.

This is the first report of comprehensive genomic testing in a patient with hepatoid adenocarcinoma. Genomic testing revealed a TP53 mutation with wild-type K-RAS. The tumor also revealed low (5-10%) expression of programmed death-ligand 1 (PD-L1) and stable microsatellite instability. Though the patient had metastatic disease, he was treated with curative intent with excellent response. This case highlights the fact that aggressive management might lead to good response in this highly aggressive malignancy.

Keywords: *hepatoid adenocarcinoma, afp, inflammatory bowel disease, ulcerative colitis, rectal, genomic profiling*

Introduction

Hepatoid adenocarcinoma (HAC) is a rare aggressive extrahepatic malignant neoplasm that mimics hepatocellular carcinoma by histopathology and immunohistochemistry [1]. Most tumors produce alpha-fetoprotein (AFP) [2]. It was first described by Bourreille et al. in the stomach [3] and the term was coined by Ishikura [4]. Cases of HAC have been reported in many gastrointestinal organs such as esophagus, pancreas, gallbladder, large intestine, extrahepatic bile duct, as well as other organs such as the urinary bladder, kidney, peritoneum, and lung [5]. This is an aggressive malignancy that presents itself at advanced stages and has overall poor prognosis [6,7]. Only 5 cases of hepatoid adenocarcinoma of the colon or rectum in association with inflammatory bowel disease have been described in the literature to our knowledge [5,6,8,9]. In this report we describe a patient with stage IV hepatoid adenocarcinoma in the setting of longstanding ulcerative colitis. He underwent comprehensive genomic profiling revealing a TP53 mutation. This is the first report of genomic profiling in hepatoid adenocarcinoma. He received treatment with curative intent with complete response. We also review the literature regarding all cases of colon and rectal adenocarcinoma in the setting of ulcerative colitis.

Case report

AA 38-year-old male with a 12-year history of ulcerative colitis, on treatment with sulfasalazine and budesonide, presented with rectal bleeding for two months and severe tenesmus for two days. He underwent a colonoscopy which showed a friable, necrotic and ulcerated rectal mucosa oozing blood, from the anus up to 20 cm proximally (Figure 1). A full colonoscopy could not be done because of the risk of perforation.

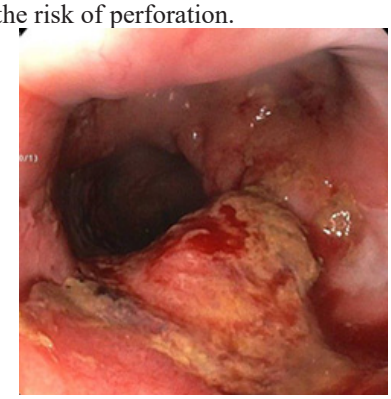

Figure 1. *Colonoscopy showing friable, necrotic, and ulcerated rectal mucosa oozing blood.*

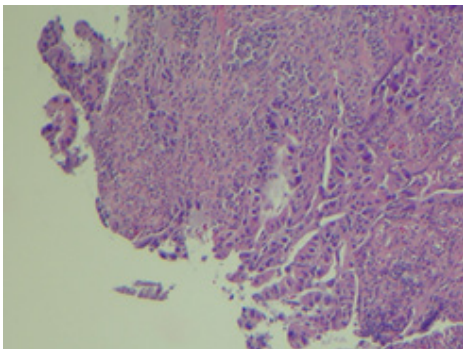

Figure 2. *Histopathology of rectal mucosa showing poorly differentiated tumor with extensive necrosis.*

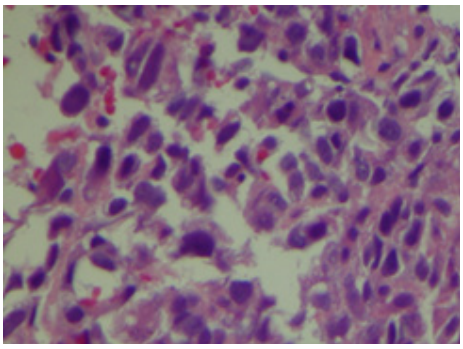

Figure 3. *Histopathology of liver tissue demonstrating pleomorphic giant cells.*

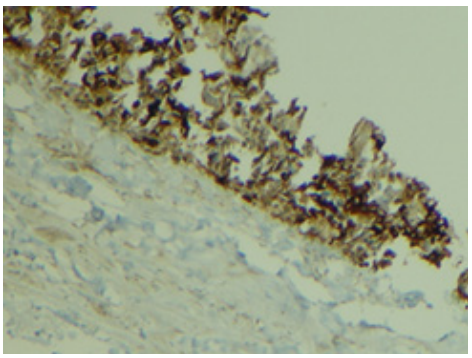

Figure 4. *Immunohistochemical staining of liver tissue demonstrating AFP positivity.*

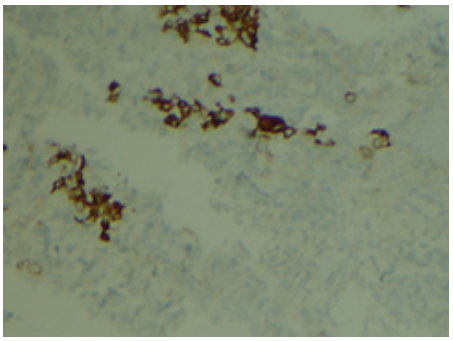

Figure 5. *Immunohistochemistry of the liver tissue demonstrating CK-20 positivity.*

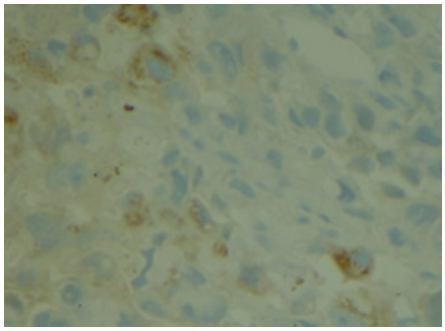

Figure 6. *Immunohistochemistry of the liver tissue demonstrating Hep par-1 focal positivity.*

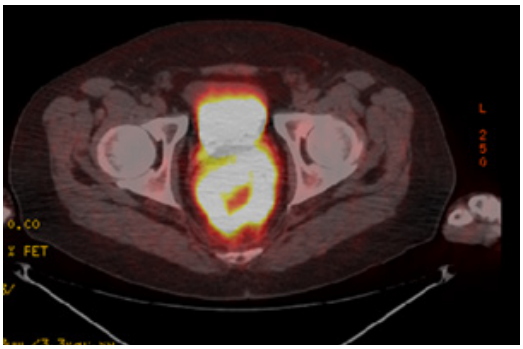

Figure 7. *Abdominal PET demonstrating hyper metabolic liver mass.*

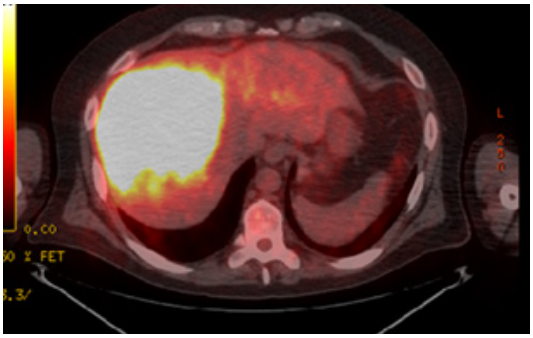

Figure 8. *Pelvic PET demonstrating hyper metabolic liver mass.*

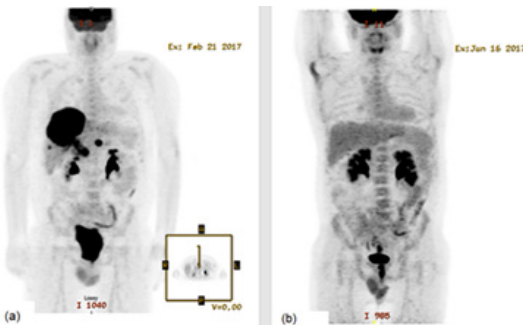

Figure 9. *Whole body PET at (a) the initiation of therapy, demonstrating increased uptake in the liver and rectum, and (b) 4 months into chemotherapy, demonstrating significant interval decrease in uptake in the liver and rectum.*

Age (years) and sex	Type of IBD and duration if available	Location of the primary tumor	Site of metastasis, if any	Treatment	Prognosis	Reference
41, male	Ulcerative colitis for 15 years	Rectum and perirectal lymph nodes	Liver (3 hepatic nodules 6 months later)	Surgical resection of the primary and hepatic lesions	No signs of recurrence 1 year later	[8]
50, female	Ulcerative colitis for 15 years	Distal rectum	NA	Surgical resection	NA	[12]
36, male	Ulcerative colitis for 12 years	Proximal transverse colon	Multiple abdominal lymph nodes (16 months after primary tumor was diagnosed)	Surgical resection and FOLFOX + bevacuzimab	No signs of recurrence 6 months later	[9]
42, male	Ulcerative colitis for 10 years	Distal rectum	Liver	Surgical resection of primary and hepatic lesions followed by chemoembolization	Died from liver failure 19 months from initial diagnosis	[6]
38, male	Ulcerative colitis for 10 years	Rectum and perirectal lymph nodes	Liver and perihepatic lymph nodes	FOLFOX, chemoradiation and surgical resection	No signs of recurrence 5 months later	This patient

Table 1. *Review of the 4 cases of rectal and colon HAC in the setting of ulcerative colitis described in the literature. HAC: Hepatoid adenocarcinoma; IBD: Inflammatory bowel disease; FOLFOX: Folinic acid, 5-fluorouracil, oxaliplatin.*

He was admitted to the hospital and underwent a computerized tomography (CT) scan of the abdomen and pelvis to visualize the extent of the ischemic colitis. It showed a mass in the recto-sigmoid region measuring 11 cm with multiple enlarged perirectal lymph nodes. Incidentally, a large hypodense heterogeneously-enhancing mass in the right hepatic lobe (segment VIII) was identified that measured 10 × 8 × 8 cm. In addition, the CT scan also showed two necrotic, enlarged lymph nodes in the porta hepatis, and associated portal vein thrombosis. These lesions were confirmed by magnetic resonance imaging (MRI) of the abdomen and pelvis and four-phase liver CT. His serum alkaline phosphatase (AFP) was elevated to 15,592 ng/mL (reference range <8 ng/mL). A testicular ultrasound was done that ruled out non-seminomatous germ cell testicular cancer as the cause of his elevated serum AFP. Biopsies of both the rectal and liver mass were performed. The tissue obtained from the rectal biopsy was consistent with a poorly-differentiated tumor with extensive necrosis, and there was insufficient viable tumor for accurate morphological assessment (Figure 2). A CT-guided liver biopsy was done, with the histopathology showing pleomorphic giant cells (Figure 3), and was sent for immunohistochemical (IHC) staining, that returned focally positive for CK 20 and CDX-2, positive for AFP and PD-L1, and negative for CK 7 and Hep par-1 (Figures 4-6). The patient was found to have a microsatellite stable tumor which ruled out a colorectal cancer associated with Lynch syndrome or with a sporadic microsatellite unstable carcinoma. The tumor was positive for the programmed death-ligand 1 (PD-L1) with a low expression of the PD-L1 ligand (5-10%). His peripheral blood was sent for genomic testing which tested tumor DNA circulating in the peripheral blood. It revealed a TP53 E171fs*10 genomic alteration. His tumor was K-RAS wild-type.

He also underwent a staging CT scan of the chest that ruled out metastatic lesions in the chest. A positron emission tomography (PET) scan confirmed the previous findings and showed a hypermetabolic liver mass with portal vein thrombosis (Figure 7) and a large rectal mass with local and regional lymphadenopathy as well as distant spread to peri-portal nodes, liver parenchyma and portal vein (Figure 8). He was therefore staged as having metastatic rectal cancer stage IV. He was then started on palliative FOLFOX (folinic acid, 5-fluorouracil [5-FU], oxaliplatin). Bevacizumab, an anti-vascular endothelial growth factor drug used in metastatic colorectal cancer, was not given because of the risk of colonic perforation. He completed ten cycles of FOLFOX for tumor reduction, followed by a combination of 5-FU and radiation. Cetuximab, an anti-epidermal growth factor receptor drug used for K-RAS wild-type mutation, was initiated, however he developed an erythematous rash over his trunk and upper extremities, warranting discontinuation of the drug. Multiple interval imaging studies demonstrated serial decrease in the size and uptake of the liver mass, rectal mass, and perirectal and peri-portal lymphadenopathy (Figure 9).

Subsequently, he developed an ulcerative colitis flare that was successfully controlled with infliximab therapy and intravenous steroids. However, he had yet another flare that did not respond to steroids, warranting proctocolectomy with end-ileostomy and abdominoperineal resection. Pathological examination of the colonic tissue revealed diffuse moderate-to-severe chronic active colitis with ulceration and inflammatory polyps consistent with chronic ulcerative colitis, high grade dysplasia involving the descending colon, negative lymph nodes, and absence of perineural invasion. Anorectal tissue yielded small focus of residual low-grade invasive adenocarcinoma with no lymphovascular or perineural invasion. The margins and lymph nodes were negative for malignancy. With treatment, his serum AFP levels fell from a peak of 34,884 ng/mL to 7.0 ng/mL over a period of around 4 months (Figure 10). Subsequently, he was started on liver stereotactic body radiation therapy (SBRT) for his hepatic metastases and completed a full course of 5 fractions of 5000 cGy radiation with good response.

Discussion and conclusion

The pathogenesis of hepatoid adenocarcinoma is very poorly understood. When the tumor was first discovered in the stomach, hepatoid differentiation was thought to have occurred because of the common origin of the stomach and the liver from the foregut [6,10]. However, this does not explain the different locations of the tumor such as the colon, rectum, lung, urinary bladder and pancreas. There is no genetic basis for the origin of cancers in inflammatory bowel disease and it is thought to occur in the presence of chronic inflammation [6,8,9,11,12]. The evidence of hepatoid differentiation in the context of inflammation has been seen in Barrett's esophagus and hepatocellular carcinoma in chronic hepatitis B or C infection [6]. Hepatoid adenocarcinoma of the colon and rectum in the setting of ulcerative colitis has been described in four previous cases. Table 1 summarizes the findings in these cases as well in as our case.

4 out of 5 cases were seen in young males less than 50 years of age. All the five cases had ulcerative colitis for 10-15 years. The tumor was located in the rectum in 4 out of 5 cases, and in the transverse colon in 1 case. AFP was reported to be elevated in all the cases. Serum AFP levels can be an indicator of unsuspected HAC, in the absence of a hepatic lesion. Metastasis was present in 4 out of 5 cases. The most common site of metastasis was the intraabdominal lymph nodes in 4 cases and the liver in 3 cases. The subjects were treated with surgery and organ-specific chemotherapy. Prognosis is difficult to determine from the reported cases.

In conclusion, this case report describes a very rare colon cancer associated with ulcerative colitis. Most of these cases described in the literature were treated with surgical resection and organ-specific chemotherapy. We describe the first case of comprehensive genomic profiling revealing a TP53 mutation. We were unable to find any other targetable mutation. Hepatoid adenocarcinoma is associated with a very poor prognosis despite an aggressive and multimodal strategy for treatment. The pathogenesis of this rare malignancy is poorly understood and no data about effective chemotherapy is available. Future studies are needed to understand the pathogenesis of this rare malignancy and to identify effective chemotherapy, immunotherapy and targeted agents.

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Correspondence: Hari K. Krishnan Nair, Department of Medicine, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA, USA, Tel: +1 617-415-6184; E-mail: hari.k.krishnan@gmail.com

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