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

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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.
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 $10 \times 8 \times 8 \text{ cm}$. In addition, the CT scan also showed two necrotic, enlarged lymph nodes in the porta hepatitis, 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 revealed a 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.

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.

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

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.
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 [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 as in 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.

References


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