Hepatoid Adenocarcinoma of the Duodenum: An Unusual Location

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Key Words

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Abstract

Hepatoid adenocarcinoma (HAC) is a rare extrahepatic tumor distinguished by having both hepatoid and adenomatous features, which can make the diagnosis challenging. Although it mostly originates in the stomach, several other sites of origin have been reported. We report a case of HAC originating in the duodenum, a very unusual location. We also discuss an approach to the diagnosis of HAC using morphological and immunohistochemical features, and explore possible therapeutic options.

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Introduction

Hepatoid adenocarcinoma (HAC) is a very rare malignant tumor of extrahepatic origin which is characterized by having foci with both features of hepatocellular differentiation and adenomatous differentiation. It is most commonly seen in the stomach, comprising about 84% of the total number of cases. However, cases of HAC originating in the ovary, colon, lung, uterus, pancreas, and gallbladder, among other sites, have also been reported. To the best of our knowledge, only 3 cases of HAC involving the small intestine have been reported in the English literature [1, 2], all of which were associated with inflammatory bowel disease – a known risk factor for gastrointestinal tract malignancy. Many of the reported cases of colonic HAC were also associated with inflammatory bowel disease [3]. The exact pathogenic mechanism for inflammatory bowel disease-associated gastrointestinal malignancy is un-

known but is thought to arise from chronic inflammation leading to dysplasia, and subsequently to adenocarcinoma [1]. We report a very interesting case of HAC of the duodenum in a patient without underlying inflammatory bowel disease, and review the literature.

Case Report

The patient was a 65-year-old African-American man with a history of hypertension, diabetes, coronary artery disease, and ischemic cardiomyopathy (ejection fraction 30–35%) who presented to the emergency department with moderate-to-severe mid-abdominal pain, nausea, vomiting, and constipation for 4–5 days. He had demonstrated a decreased appetite and an about 70- to 80-pound weight loss in the preceding 2 months. His medical history was also significant for atrial fibrillation, left ventricular thrombus, and cerebral aneurysm with prior intraventricular hemorrhage. He had a 40-pack-year smoking history, a history of chronic alcoholism for over 40 years, and prior cocaine and marijuana use. He denied any family history of cancer. His physical examination was notable for abdominal distention and mild epigastric tenderness, but his abdomen was soft and he had normoactive bowel sounds. He had no hepatosplenomegaly and his examination was otherwise unremarkable.

His workup included laboratory tests, which showed normal serum amylase and lipase levels. Liver function tests revealed alkaline phosphatase at 172 U/l (normal = 30–165), alanine transaminase at 12 U/l (normal = 0–55), aspartate transaminase at 49 U/l (normal = 0–50), bilirubin at 1.3 mg/dl (normal = 0.2–1.2), and albumin at 2.8 g/dl (normal = 3.2–5.5). His other serum chemistries were normal. Serum tumor markers were obtained, which showed carcinoembryonic antigen (CEA) at 10,400 ng/ml (normal = <2.5 for nonsmokers, <5 for smokers), cancer antigen 125 at 358 U/ml (normal <35), and α -fetoprotein (AFP) at 4,970 ng/ml (normal = <6.1). A contrast-enhanced computed tomography (CT) of the abdomen and pelvis showed a markedly dilated, debris-filled stomach with no contrast beyond the gastric antrum, and a mass-like density in the gastric antrum or proximal duodenum measuring approximately 4 cm in diameter (fig. 1a). Multiple hypodense hepatic lesions (the largest being 6 cm in the right hepatic lobe) were also seen, which was consistent with metastatic disease (fig. 1b).

The patient subsequently underwent upper endoscopy, which showed distal esophageal varices and undigested food in the stomach. A circumferential, friable mass at the duodenal bulb was noted, obliterating 80% of the lumen and preventing scope advancement beyond the second portion of duodenum (fig. 2). Biopsies were obtained. He underwent colonoscopy as well, which was essentially normal. The gastric antrum biopsy showed mild chronic inactive gastritis, and the pyloric antral biopsy showed mild chronic active gastritis with foveolar hyperplasia; a Giemsa stain was negative for *Helicobacter pylori*. A biopsy of his duodenal mucosa showed mild chronic active inflammation of the lamina propria with no significant villus blunting. The biopsy of the visualized duodenal mass, however, showed a moderately differentiated adenocarcinoma with glandular formation, which was confirmed by mucin-positive staining. There were also areas with trabecular and nested patterns seen (fig. 3a). A comprehensive immunostain panel showed that the tumor cells were negative for Hep Par 1 and glypican-3, essentially ruling out hepatocellular carcinoma. The tumor cells were positive for CEA, AFP, CK18, CK19, and CDX-2, but were negative for CK7, CK20, and synaptophysin (fig. 3b, c).

The patient also underwent a CT-guided biopsy of his liver lesions, which showed invasive, moderately differentiated adenocarcinoma with striking morphological and immunohistochemical similarity to the duodenal bulb mass biopsy, suggesting that the duodenal

bulb was the most likely primary origin. Given the pathological and laboratory findings of adenocarcinoma of the duodenum with AFP-positive tumor staining and elevated serum AFP levels in the absence of hepatocellular carcinoma, he was diagnosed with stage IV HAC of the duodenum.

His course subsequently was notable for pyloric stent placement to help relieve his gastric outlet obstruction. He unfortunately continued to have nausea and bilious vomiting despite stent placement, and required total parenteral nutrition. Chemotherapy was deferred due to his poor performance status (ECOG PS 4), and he was managed supportively. His hospital course was further complicated by septic shock due to *Escherichia coli* bacteremia and fungemia, acute hypoxic hypercapnic respiratory failure requiring mechanical ventilation, and loculated empyema. Unfortunately, he died from multiorgan failure within 1 month of his diagnosis.

Discussion

First described by Bourreille and colleagues in 1970 and termed by Ishikura and colleagues in 1985, HAC is a rare extrahepatic neoplasm, so named because it embodies both foci of adenomatous and of hepatocellular differentiation. Interestingly, it morphologically and functionally resembles hepatocellular carcinoma, which can make the diagnosis challenging [4]. HAC occurs more often in males, with a male-to-female ratio of 2.3:1 [3]. The median age at occurrence is 63 ± 12.8 years (range 21–100) [3]. The most common site of origin of HAC is the stomach, comprising about 84% of all HAC cases [5]. However, HAC accounts for only 0.19% of gastric cancers, a testament to its rarity [6]. Other common primary sites include the female genitourinary tract, lung, and colorectal and urinary tracts. HAC of the small intestine is extremely rare, with only 3 cases reported in the English literature to the best of our knowledge, all of which were associated with inflammatory bowel disease [1, 2]. A case of periampullary HAC with duodenal invasion was reported but was thought to originate in the pancreas [7]. A few cases of HAC of the small intestine have also been reported in the Japanese and Chinese literature [8–10]. To the best of our knowledge, ours is the first case of HAC of the duodenum in the English literature that is unrelated to inflammatory bowel disease.

The diagnosis of HAC is made by morphology and immunohistochemistry. Pathological examination of the affected tissue reveals polygonal tumor cells arranged in both trabecular and glandular structures [3]. The biochemical profile may show elevated serum AFP levels, which is often the trigger for ruling out HAC, especially in the absence of underlying liver cirrhosis. Elevated serum AFP is, however, only seen in 84.8% of HAC cases, and thus, although considered characteristic of HAC, it is not a universal marker [1, 3]. Major immunohistochemical markers in cases of HAC include AFP, CEA, glypican-3, CK18, and CK19 [5]. Hep Par 1 staining is usually negative in HAC, but it may occasionally show focus-positive staining [6]. Hep Par 1 and glypican-3 are markers of hepatoid differentiation that are used in diagnosing hepatocellular carcinoma, with high sensitivity and specificity. They may, however, stain positive in cases of HAC given the hepatoid component. In our case, negative staining for Hep Par 1 and glypican-3 essentially ruled out hepatocellular carcinoma. CDX-2, on the other hand, is a highly sensitive and specific marker of adenocarcinomas of intestinal origin and typically shows no expression in hepatocellular carcinoma. CDX-2 expression in our case was corroborated by endoscopic findings, confirming the duodenum as the primary site of the tumor. The diagnosis of HAC of the duodenum was made given the morphological

appearance of features of both hepatoid and adenomatous differentiation and by positive staining for AFP, CEA, CK18, CK19, and CDX-2.

HAC is an aggressive tumor and has a poor prognosis, with median overall survival estimated at 11 months [1]. Patients frequently present with metastases, with lymph nodes and the liver being the most common sites of metastasis [5]. With regard to treatment, there is no standardized approach, since due to the rarity of HAC no randomized clinical trials are possible. According to the published case reports and series, the favored approach is to treat gastrointestinal HAC similarly to colorectal adenocarcinoma: with surgical resection if possible, followed by adjuvant chemotherapy with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) regimens, with or without bevacizumab [1, 3, 5]. The prognosis remains poor despite chemotherapy, especially in cases with nodal involvement. The poor response to chemotherapy is thought to be because HAC cells lack thymidine phosphorylase – which is essential for fluorouracil activation – but express an abundance of dihydropyrimidine dehydrogenase, which is responsible for the degradation of fluorouracil [6]. In our case, we were unable to offer our patient either surgery or chemotherapy because of his metastatic disease and his poor performance status (ECOG PS 4). He was given best supportive care and then transitioned to hospice.

Conclusion

Much remains unknown about the pathogenesis of HAC. It is a rare, aggressive extrahepatic tumor with adenomatous and hepatocellular features that carries a very poor prognosis. Mostly found in the stomach, we believe this to be the first case of HAC of the duodenum in the absence of inflammatory bowel disease that has been reported in the English literature. Given its rarity, continued identification and reporting of these cases are essential to increase our knowledge about it and potentially guide standardized management.

Statement of Ethics

Informed consent was obtained from the patient's family for publishing this case and any accompanying images.

Disclosure Statement

The authors state no conflict of interests and have received no payment in the preparation of this paper or in conducting the study.

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Fig. 1. CT of the abdomen and pelvis with contrast showing a mass-like density (arrows) in the gastric antrum or proximal duodenum measuring approximately 4 cm (anterior to posterior) (a) and multiple areas of decreased attenuation (arrows) in the liver which represent metastasis (b).

Fig. 2. Upper endoscopy showing a circumferential, friable mass obliterating 80% of the lumen at the duodenal bulb preventing advancement of the scope to the second part of the duodenum.

Fig. 3. **a** HE stain ($\times 400$) showing invasive adenocarcinoma with gland formation and occasional mucin production. Areas with trabecular and nested patterns are also visualized, as well as tumor cells with moderate-to-abundant eosinophilic cytoplasm (hepatoid). **b** Tumor cells with diffuse, strong staining for monoclonal CEA. **c** Tumor cells with diffuse, strong staining for AFP.