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Case Report

Hepatoid adenocarcinoma of colon: a case report and literature review

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Abstract: Hepatoid adenocarcinoma is a peculiar but aggressive type of extrahepatic adenocarcinoma that morphologically resembles hepatocellular carcinoma. To date, only a handful of cases have been described in the colon. Here, such a case is reported and pertinent literature is reviewed. Characteristic features of the tumor include large polygonal cells with marked nuclear atypia, prominent nucleoli and eosinophilic granular or clear cytoplasm arranged in trabeculae and solid nests or sheets. The tumor was immunohistochemically positive for AFP, CDX-2 and hepatocyte paraffin 1.

Keywords: Hepatoid adenocarcinoma, colon, α-fetoprotein

Introduction

Adenocarcinoma with hepatoid features was first described in the stomach by Bourreille et al. [1], which shows a striking morphologic similarity to hepatocellular carcinoma (HCC). In 1985, Ishikura et al. [2] coined the term "hepatoid adenocarcinoma" (HAC) to emphasize the hepatic differentiation. The tumor is associated clinically with an elevated serum level of α-fetoprotein (AFP). Besides the stomach, it has also been reported in gallbladder [3], ovary [4], lung [5], uterus [6], ampulla [7] and bladder [8]. There are so far less than 20 cases of colonic HAC reported in literature. HAC is an aggressive tumor, bearing poor prognosis with propensity of intravascular growth and frequent distant metastasis. Therefore, prompt and accurate diagnosis is important in improving the outcome of patients. This report is of such a case and describes the clinicopathological and immunohistochemical features of the tumor to facilitate accurate diagnosis and to avoid potential pitfalls.

Clinical history and laboratory findings

A 37-year-old male patient was admitted to our hospital for complaint of 3-month abdominal distension and general pain, and 1-month melena in June 2013. The patient had no medical history of inflammatory bowel disease or primary sclerosing cholangitis. Colonoscopy revealed a stenosis at his transverse colon with a 5.5 cm ulcerative mass. No other lesions were found in the upper and lower gastrointestinal (GI) tract. Serum study detected marked elevation of AFP (6263.4 ng/ml), while other laboratory tests, including carcinoembryonic antigen (CEA), CA19-9, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were within normal ranges. No hepatitis B surface antigen was detected. Repeated CT scans detected no liver lesions. No evidence of distant metastasis was found clinically. Abdominal surgical exploration confirmed the mass located to the transverse colon with direct extension into the proximal jejunum and the superior mesenteric vein. The patient underwent radical transverse colectomy.

Pathologic findings

Macroscopically, a 6×5.5 cm ulcerative infiltrating tumor with central necrosis and hemorrhage occupied the full circumference of the transverse colon. The tumor invaded through the colon wall but the rest of the colon was

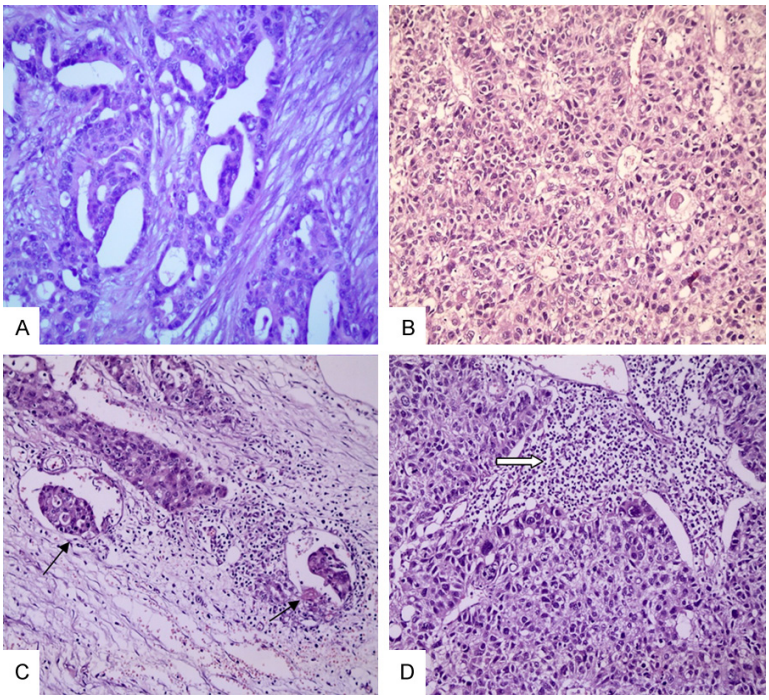

Figure 1. A. Well-differentiated tubular adenocarcinoma. The tumor is located in mucosa (×200). B. Hepatoid adenocarcinoma. The component is composed of large polygonal cells with abundant eosinophilic or clear cytoplasm and arranged in trabecular or solid patterns (×200). C. Tumor thrombi (Thin arrow), composed purely of hepatoid adenocarcinoma cells, were found in the subserosal lymphatic vessels (×200). D. Remarkable lymphocytic (Thick arrow) infiltrates in the stroma of hepatoid adenocarcinoma (×200).

unremarkable. Twenty regional lymph nodes were identified with a maximum diameter of 1.5 cm.

Tissue was fixed in 10% buffered formalin after dissection, sectioned at 4 um, and stained with hematoxylin and eosin. Histologically, the tumor was composed of two distinctive components with transitional morphology in between. The minor component was well-differentiated adenocarcinoma (WDAC) that was primarily located at the periphery of the tumor mass with an intra-mucosal location (**Figure 1A**). No in-situ adenocarcinoma or adenomatous polyps were found in the adjacent colon. The major component of the tumor manifested a hepatoid morphology: large polygonal cells with marked nuclear atypia, prominent nucleoli and eosinophilic granular or clear cytoplasm arranged in trabeculae and solid nests or sheets (**Figure 1B**). Scattered intracytoplasmic hyaline globules were noted within the carcinoma cells, resembling HCC. The second component constituted the invasive front of the tumor that invaded through the muscularispropria into pericolonic fat. Lymphovascular invasion with tumor thrombi consisting of solely hepatoid tumor cells, was identified in the submucosal and subserosal vessels (**Figure 1C**). In addition, remarkable lymphoid infiltrates were found in the tumor stroma (**Figure 1D**). No metastatic carcinoma was identified in any of the 20 regional lymph nodes.

Immunohistochemistry (IHC) was performed by standard procedure at Ventana Automated Immunostainer (A.Z.) for the following antibodies: CK7 (1:120, Invitrogen, USA), CK20 (1:60, Epitomics, USA), CEA (1:180, Leica, USA), AFP (Pre-diluted, Epitomics, USA), NSE (1:270, Gene, USA), CDX-2 (1:130, Gene, USA) and hepatocyte paraffin1 (Pre-diluted, ZETA, USA), CK8/18 (1:100, Invitrogen, USA), CK19 (1:60, Invitrogen, USA). The HAC component was characteristically positive for AFP (**Figure 2A**) and hepatocyte paraffin 1 (**Figure 2B**), while negative for CK20, CEA, CK19 and NSE. The WDAC component showed a reverse immunoprofile. Staining for NSE was focally positive in WDAC. However, both tumor components were positive for CDX-2 (**Figure 2C**) and CK8/18, and negative for CK7. The diagnosis was made by it's classic morphology and immunohistochemical profile. Results of immunohistochemistry were summarized in **Table 1**.

Patient management and clinical follow-up

The patient received post-operative adjuvant chemotherapy with favorable response. No evidence of tumor recurrence or distant metastasis was found during the period of 36 months of post-operative follow-up.

Discussion

HAC most commonly occurs at stomach in GI tract with the hallmark of AFP production. In contrast, it is very rare in colon. To the best of

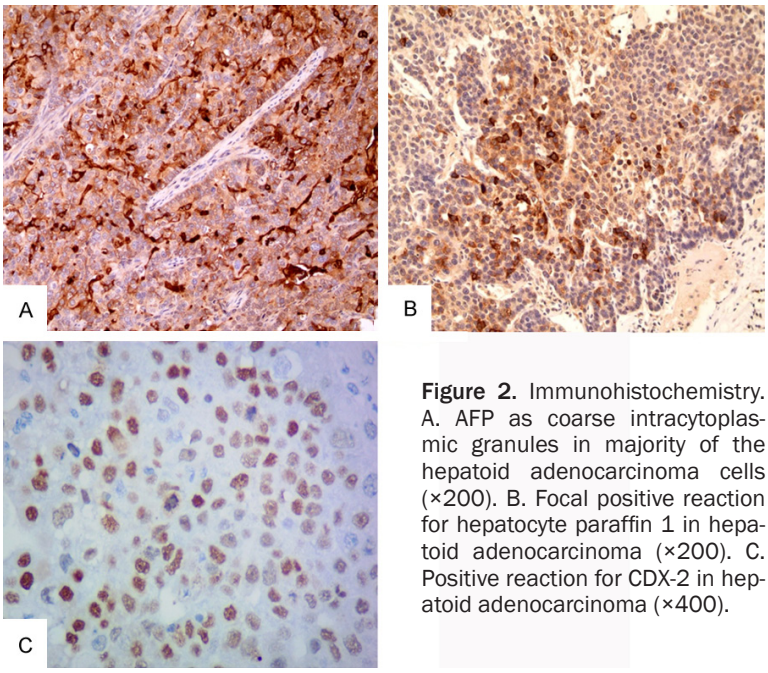

Figure 2. Immunohistochemistry. A. AFP as coarse intracytoplasmic granules in majority of the hepatoid adenocarcinoma cells (×200). B. Focal positive reaction for hepatocyte paraffin 1 in hepatoid adenocarcinoma (×200). C. Positive reaction for CDX-2 in hepatoid adenocarcinoma (×400).

Table 1. Immunohistochemical findings of the tumor

Antibody	Well-differentiated adenocarcinoma	Hepatoid adenocarcinoma
CK7	-	-
CK20	+	-
CDX-2	+	+
CEA	+	-
AFP	-	+
NSE	Focal +	-
Hepatocyte paraffin 1	-	+
CK8/18	+	+
CK19	+	-

our knowledge, less than 20 cases are so far reported in literature [9-27] (**Table 2**), representing only 2% of all HAC cases reported [22]. Patients have ranged from 36 to 75 years with a clear predominance in males. Because of its rarity, accurate diagnosis can be a challenged daily practice. However, if pathologists keep in mind of this entity and recognize the hepatoid morphology, the diagnosis can be achieved. It has to be differentiated from metastatic HCC, as it is much more common. To make matters more complicated, colonic HAC often presents with liver metastasis. The management and prognosis of these two types of malignancy are different. Helpful hints to differentiate are useful. First, HCC clinically arises in fibrotic liver and its risk factors are usually available. It often presents with a single nodule and morphologically manifests a pseudo-adenomatous or sclerosing growth pattern. In contrast, there is usually no liver mass in HAC patients, unless tumors metastasize to liver that intend to present with multiple masses in non-fibrotic liver. Second, HAC often coexists with well-differentiated adenocarcinoma with papillary or tubular features and clear cytoplasm. A transitional morphology of the two components may present, such as in this case. If cells with hepatoid morphology are found in both trabecular and intestinal-like structures, HAC should be considered. Third, immunohistochemistry is also very helpful. Although it shares certain markers with HCC, such as positive for AFP, HepPar1, and negative for CK7 and CK20, colonic HAC expresses CDX-2 while HCC doesn't. Separation from other types of poorly differentiated carcinoma of colon is relatively easier if attention is paid to the specific morphology, distinctive immunoprofile (**Table 1**) and laboratory evidence of elevated AFP.

HAC tends to behave aggressively, and many of colonic HAC may present with liver or lung metastasis at diagnosis [28, 29] (**Table 2**). However, its prognostic factors are not well identified, and there is no standard protocol of treatment for colonic HAC yet. In our case, although the patient presented with locally advanced disease (pT4b), there was no regional lymph node or distant metastases. The patient was disease free for at least 36 months after complete excision of the tumor followed by chemotherapy. It suggested that tumor metastasis may be a major prognostic predictor. Another interesting feature of this case was that the tumor had remarkable stromal infiltrates of lymphocytes and plasma cells. It is known as an important host defense mechanism, representing local immune-barrier against tumor expansion and neoplastic dissemi-

Table 2. Clinical and pathological features of reported colorectal hepatoid adenocarcinomas

Case	Author [Ref. #]	Age/ Gender	Pretherapy AFP level (ng/ml)	Greatest tumor diameter (cm)	Location	Metastasis	Follow up	Outcome
1	Nakajima et al. [9]	50/M	3018	NS	R	Liver, Lung	5 months	DOD
2	Yu et al. [10]	54/M	5126	8	R	Liver	0 month	OD
3	Sato et al. [11]	43/M	7060	4	R	Liver	4 months	DOD
4	Hocking et al. [12]	39/F	7200	3	S/C	Liver	1 month	DOD
5	Kato et al. [13]	75/M	3,070	8.5	C	Liver, Lung	4 months	DOD
6	Taguchi et al. [14]	71/M	220000	5	R	Liver	12 months	DOD
7	Kurihara et al. [15]	67/M	10978	4	T/C	Liver	NS	NS
8	Ishikura et al. [16]	48/F	6,600	4	S/C	Liver	4 months	DOD
9	Lattes et al. [17]	41/M	NS	NS	R	Liver	12 months	NED
10	Yachida et al. [18]	59/M	12873	5.5	T/C	Liver	2 months	DOD
11	Fu et al. [19]	71/M	318	5	T/C	Lymph node	60 months	NED
12	Orditura et al. [20]	71/M	44074.6	10	T/C	None	36 months	DOD
13	Borgonovo et al. [21]	42/M	32000	NS	R	Liver	19 months	DOD
14	Slotta et al. [22]	59/F	NS	7	T/C	Liver	27 months	NED
15	Nakaqawa et al. [23]	73/M	NS	NS	C	Liver	9 months	DOD
16	Chen et al. [24]	36/M	4896	9	T/C	Lymph nodes	4 months	NED
17	Cappetta et al. [25]	75/F	NS	6	C	Lymph nodes	3 months	NED
18	Armaghani [26]	42/F	NS	NS	S/C	Lung	4 months	NED
19	Anzai et al. [27]	41/F	NS	1.5	R	None	12 months	NED
20	Present	37/M	6263.4	6	T/C	None	36 months	NED

AFP = alpha-fetoprotein; NS = not stated; R = rectum; S/C = sigmoid colon; C = cecum; T/C = transverse colon; DOD = died of disease; OD = operative death; NED = no evidence of disease.

nation [30]. Accumulation of more cases is required to demonstrate the frequency of this manifestation and to verify its prognostic significance.

In conclusion, a rare case of colonic HAC is reported here. This case suggests that tumor metastasis may be a key prognostic factor, in contrast to local advancing. Further study is required to fully explore its clinical course and to establish the appropriate management strategies.

Disclosure of conflict of interest

None.

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