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Original Article

AFP-negative mixed hepatoid adenocarcinoma of the colon: a case report with review of literature

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Abstract: Aim: To investigate the clinicopathologic profile of hepatoid adenocarcinoma (HAC) of the colon and to improve the diagnostic and treatment level. Materials and methods: The clinical observations and histopathologic and immunohistochemical features of HAC were analyzed. Results: HAC is usually composed of well-differentiated common adenocarcinoma and hepatoid differentiation. The tumor cells in hepatoid differentiation area are arranged in trabecular or solid shape, with large polygonal tumor cells, and abundant cytoplasm. Immunohistochemical markers showed the HAC cells were positive for Glypican-3, HepPar1, CK19, and carcinoembryonic antigen (CEA), while alpha-fetoprotein (AFP) was negative. Conclusion: HAC is a rare malignant tumor of the colon. Its diagnosis depends on histopathology and immunohistochemical staining. Surgical resection should be the treatment of choice if possible.

Keywords: Colon, hepatoid carcinoma, immunohistochemistry, diagnosis

Introduction

Hepatoid adenocarcinoma (HAC) is a rare subtype of extrahepatic adenocarcinoma that is characterized by its histopathologic and immunohistochemical similarities to hepatocellular carcinoma. The first case report of HAC of the stomach was introduced in 1986 by Ishikura H et al. [1]. Since then, HAC has been reported increasingly. HAC usually occurs in the stomach. Other sites of origin include ovary [2], lung [3], mediastinum [4], pancreas [5] et al. Few articles about HAC of the colon reported in the English literature [6, 7], especially about AFP-negative cases. Therefore, an erroneous diagnosis is easily made. In order to facilitate the diagnosis and understanding of this rare cancer, we describe a case of AFP-negative HAC of the colon, with clinicopathologic profile. In addition, we review the literature on HAC.

Materials and methods

A case diagnosed as HAC of of the colon that was AFP-negative was obtained from Department of Pathology, Tianjin Nankai Hospital. The detailed clinical data were gathered from hospital records.

Affinity-purified mouse monoclonal antibodies for CDX-2, Villin, CK19, CK20, CEA, Hep Par-1 antibody, Glypican-3, AFP, MSH2, MSH6, PMS2, and MLH1 were purchased from Beijing Zhongshan Golden Bridge Biotechnology Co. LTD. EliVisionTMplus Polyr HRP (Mouse/Rabbit) IHC kit (KIT-9901) were purchased from MAIXIN-BIO.

Pathologic materials were fixed in 10% buffered formalin and routinely processed for light microscopy. 4-μm-thick sections were cut from the tissue blocks and stained with hematoxylin and eosin (H&E). The avidin-biotin-peroxidase complex (ABC) method was used for immunohistochemical staining studies. In order to evaluate the specificity of the antibodies, serial sections were incubated with PBS displacing the primary antibody as negative controls, and known positive tissues were used as the positive controls.

Results

Clinical data

A 61-year-old man presented to our hospital with lower gastrointestinal (GI) bleeding and right-sided abdominal pain. Abdominal contrast-

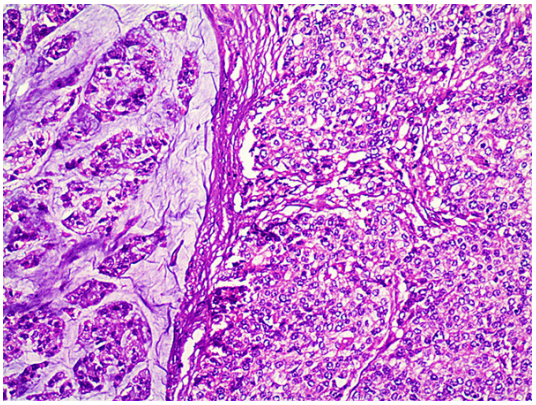

Figure 1. The tumor was composed of a mixture of two areas, including hepatoid-like areas (right) and adenocarcinomatous areas (left). HE ×200.

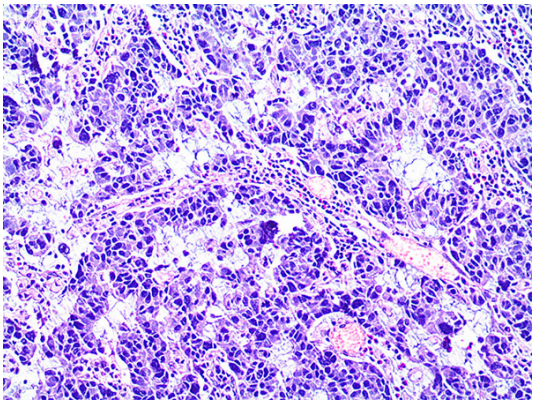

Figure 2. Hepatoid-like area is composed of cords of polygonal cells with abundant, eosinophilic cytoplasm and centrally located nuclei. HE ×200.

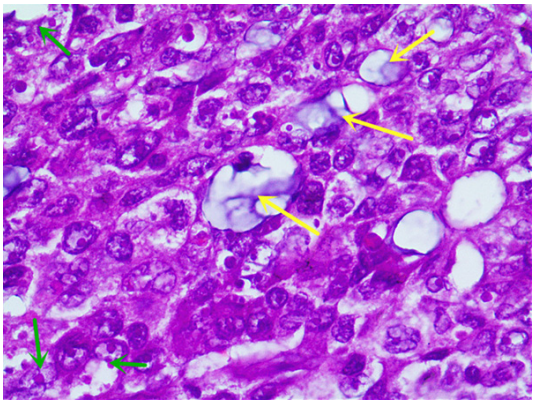

Figure 3. Some hyaline globules (green arrows) and small mucus lakes (yellow arrows) appeared in the cytoplasm of some tumor cells. HE ×400.

enhanced computed tomography (CT) showed that the local intestinal wall of transverse colon was thickened and the lumen was narrow, and no cirrhotic change was observed in the liver. Colonoscopy found a large ulcerative mass in the transverse colon near the spleen. Laboratory examination showed no elevated level of serum AFP, and CEA (8.36 ng/mL) was slightly higher than normal. Serum markers for hepatitis B and C were also negative. The mass in the transverse colon near the spleen was found and removed surgically. The neoplasm measured 15×10×3 cm. The mass was excised and sectioned for histologic examination. Several enlarged lymph nodes (maximum diameter, 20 mm) were identified along the mesentery. Microscopic examination revealed the tumor was composed of a mixture of two areas, including a hepatoid-like area and adenocarcinomatous area, which were often intermingled with each other (**Figure 1**). The tumor infiltrated the whole layer of the intestinal wall and broke through the serous membrane to reach the fatty tissue of the intestine. Adenoid differentiation is mainly characterized by mucinous adenocarcinoma. The arrangement of tumor cells in hepatoid-like area had a similar morphology to hepatocellular carcinoma (HCC), which had clear, eosinophilic, abundant cytoplasm, round nuclei in a trabecular pattern, and obvious nucleoli with high mitotic activity (**Figure 2**). Hyaline globules and small mucus lakes appeared in the cytoplasm of some tumor cells (**Figure 3**). Lymph node metastasis of cancer cells was observed. Immunohistochemical analysis showed that the HAC cells were positive for Glypican-3, CK19, CDX-2, CK20, Villin, CEA, MSH2, MSH6, PMS2, MLH1, while negative for AFP and Hep Par-1 antibody. (**Figures 4**-**6**). Thus, the tumor was considered to be AFP-negative mixed HAC of the colon with lymph node metastasis. The patient received radiotherapy after the operation for 3 months, and died of this disease 7 months after diagnosis. SP ×200.

Criteria

Tumor cells are positive for Glypican-3, Hep Par-1 antibody, CEA, and CK19, while negative for AFP.

Discussion

HAC is considered an aggressive subtype of adenocarcinoma with a detrimental prognosis [8]. The colon is an uncommon site for HAC. Most of colorectal HAC cases were reported

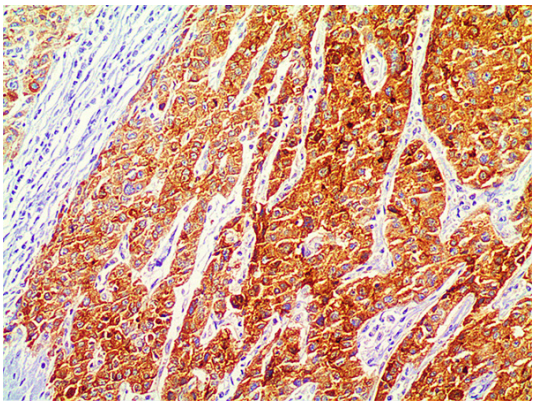

Figure 4. Tumor cells stained positive for Glypican-3. SP ×200.

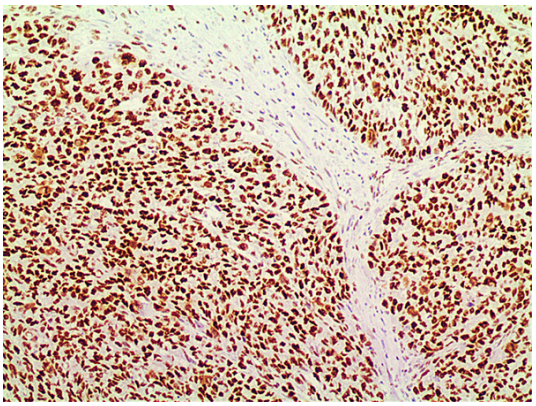

Figure 5. Tumor cells stained positive for CDX-2. SP ×100.

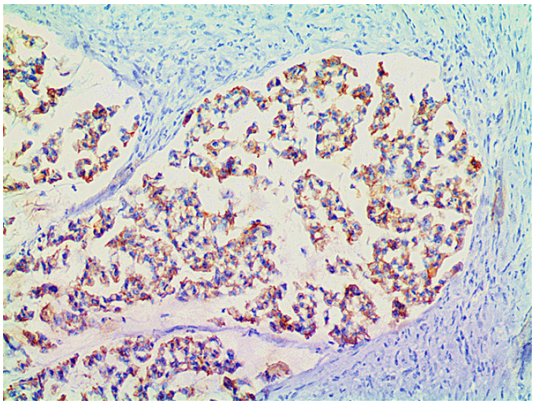

Figure 6. Mucinous adenocarcinoma area stained positive for CEA.

associated with inflammatory bowel disease (IBD) [9], which indicated there was some causal link between HAC and IBD, while our case had no history of IBD [10].

Through review of the literature, we find that the concept of HAC has changed from its discovery to present. In 1986, Ishikura et al. introduced the concept of HAC after they conducted an investigation of AFP-producing gastric HAC cases with morphological features mimicking HCC. However, there was a proportion of HAC which did not express AFP [11]. Currently, the diagnosis of HAC is based on the histological characteristics, irrespective of its capacity to produce AFP [12]. In our case, AFP in serum and immunohistochemistry appeared negative, but pathologically similar tissue morphology to HCC meant we were able to diagnose the tumor as a HAC.

HAC has characteristic features remarkably similar to HCC. HAC is composed of a mixture of two areas, including hepatoid-like areas and adenocarcinomatous areas, which are often intermingled with each other. The hepatoid-like area is composed of cords of polygonal cells with abundant, eosinophilic cytoplasm and centrally located nuclei. Some hyaline globules and small mucin lakes appear in the cytoplasm of tumor cells. Most adenocarcinomatous areas are frequently associated with highly differentiated papillary adenocarcinomas. However, such a mucinous adenocarcinoma was not detected in the present cases. The majority of HAC cases present with lymph node metastases. Routine immunohistochemical staining, such as Hep Par-1 antibody, AFP and Glypican-3, are useful but not specific for differential diagnosis. Our cases are consistent with these findings.

In differential diagnosis, primary HCC should be excluded especially when HAC metastasizes to the liver. In primary HCC, neighboring cirrhotic lesions can be seen, and tumor cells are positive for Hep Par-1 antibody, which is a sensitive and specific immunohistochemical marker for hepatocyte differentiation, while in metastatic HAC, Hep Par-1 antibody is often negative, neighboring cirrhotic lesions are uncommon, and small mucus lakes appeare in the cytoplasm of some tumor cells, which help with identification. It is necessary to know whether the patient received any treatment for liver tumors, or had alcohol abuse, or infection with hepatitis virus.

Surgical resection is an effective clinical treatment for HAC. The survival rate of surgical resection for non-metastatic cases is significant-

ly higher than non-operative therapy. Serum AFP has long been used for the screening and diagnosis of HAC [13], but as for our case, which has no elevated level of serum AFP or positive AFP by immunohistochemical staining, AFP remained meaningless. The prognosis of HAC is extremely poor, mainly resulting from its strong tendency for vascular permeation and early distant metastases. Most HAC patients died within one year.

However, further reports of similar cases will be needed in order to clarify the clinical characteristics and the prognosis of this rare malignant tumor.

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Disclosure of conflict of interest

None.

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