Letter to the Editor

Hepatoid adenocarcinoma of the rectal

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We would here like to present a treatment experience of an interesting case of hepatoid adenocarcinoma (HAC), which is a very rare clinical malignancy of the gastrointestinal tract. A 58-year-old male was admitted to our hospital with intermittent hematochezia for 1 month. A computed tomography (CT) of the abdomen revealed the thickened anterior wall and nodules of the middle rectum, the lumen of which was narrowed. Enhanced scans showed the significant enhanced lesion and blurred peripheral fat gap with enlarged local lymph node (*Figure 1A*). The magnetic resonance indicated the thickened mid-rectum involved a length of 47 mm (*Figure 1B*). Under colonoscopy, a proliferative lesion was detected about 4 cm to the anus, invading 2/3 of the lumen. The surface of the tumor was uneven and the mucous membranes was hyperemia and edema (*Figure 1C,1D*). All procedures performed in the case were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Laboratory tests showed elevated level of alpha-fetoprotein (AFP) (1,168.91 ng/mL) and carcinoembryonic antigen (CEA) (5.88 ng/mL), whereas liver function and other tumor-associated antigen were in normal ranges. The results of histological studies were consistent with primary rectal HAC. The patient was then started on palliative XELOX (oxaliplatin, capecitabine) plus cetuximab chemotherapy for 5 months. AFP level was significantly elevated (2,047.46 ng/mL) after that. Then, laparoscopic radical rectal resection and terminal ileostomy were performed.

The pathological study revealed that the tumor was composed of two types of lesions with hepatocellular carcinoma and adenocarcinoma characteristics, with mutual migration between the cells of the two components. In the hepatocytic differentiation zone, differentiated tumor cells were in a trabecular or nest-like arrangement, occasionally along the blood sinuses and blood vessels. The cytoplasm was finely granular or transparent, and periodic acid-Schiff (PAS)-stained vitreous bodies were seen in or between cancer cells (*Figure 2A*). Correlated with the various morphologic cell types and it confirmed the hepatoid nature of the rectal tumor. Hepatocyte, glypican-3, and cytokeratin (CK)8/18 were positive, and AFP was strongly positive in the hepatoid areas (*Figure 2B*).

HAC is a rare tumor and often makes the diagnosis challenging. It is an adenocarcinoma in nature with hepatocellular carcinoma-like structural and cytological features that occurs in extrahepatic organs or tissues. The most common site of HAC is the stomach, and there are less than 20 cases of HAC in the colorectum, accounting for 2% of all (1,2). HAC is more prevalent in middle-aged and elderly men, with a significantly higher incidence in male than in female. The age of onset ranges from 31 to 75 years, with a mean age of 63.5 years (3). HAC is highly aggressive and prone to recurrence and metastasis, with the most common metastatic sites were lymph nodes (57.5%)

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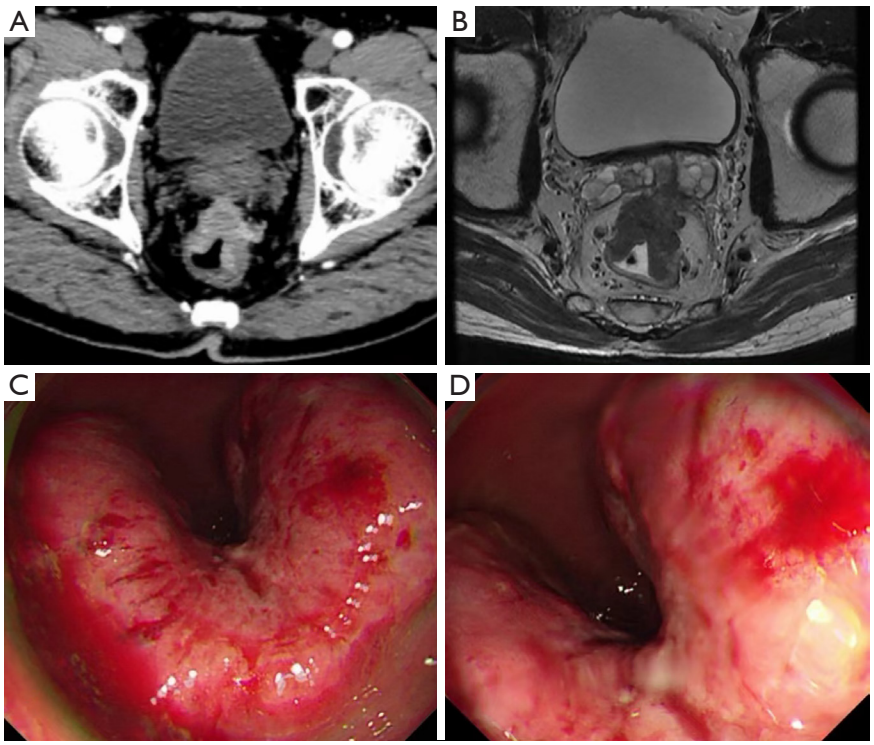

Figure 1 Imaging examination of the patient's lesion site. (A) CT scan and (B) MRI showed the thickened anterior wall and nodules of the middle rectum, the lumen of which was narrowed. (C,D) Colonoscopy showed the surface of the tumor was uneven and the mucous membranes was hyperemia and edema. CT, computed tomography; MRI, magnetic resonance imaging.

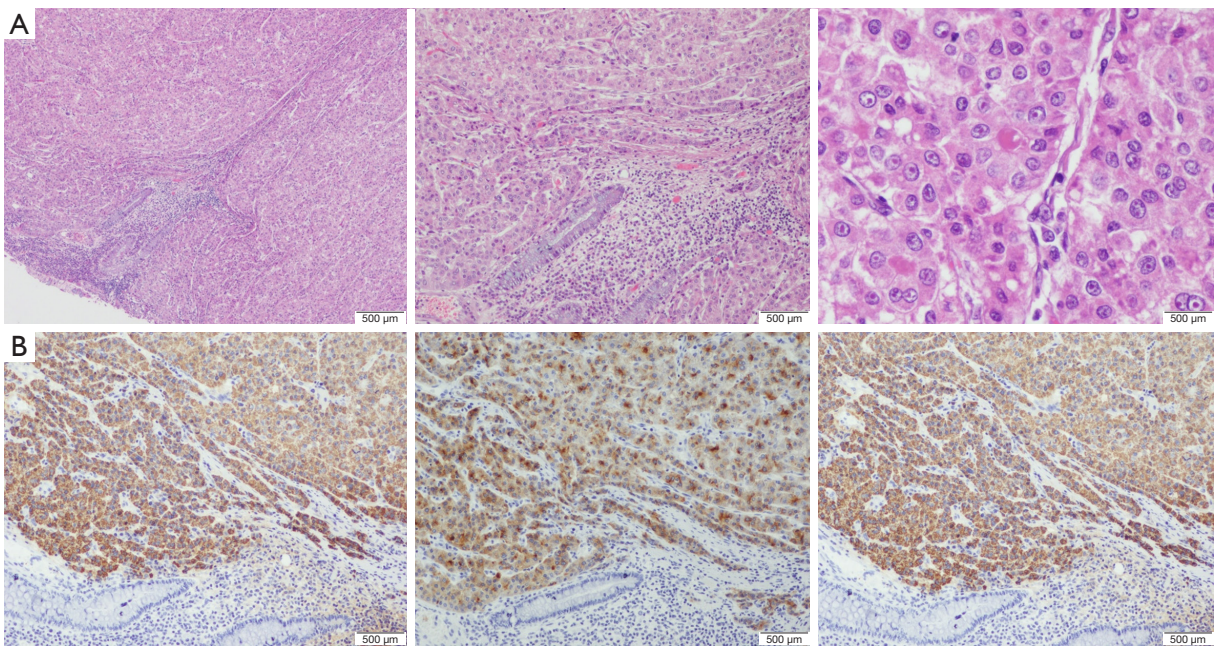

Figure 2 Histopathology of hepatocellular carcinoma and adenocarcinoma differentiation characteristics. (A) Tumor cells were cuboidal with eosinophilic cytoplasm (the left and middle panel: H&E, ×100; the right panel: H&E, ×400). (B) Immunohistochemical reactivity for CK8/18, glypican-3, and hepatocyte (EnVision, ×100). H&E, hematoxylin and eosin; CK, cytokeratin.

and liver (46.3%), followed by the lungs (3.4%). It has been reported that the 1-year survival rate for HAC was 55%, with an overall median survival time of 11 months (4). The clinical manifestations are abdominal pain or discomfort, abdominal distention and black stools, etc. Although the main basis of HAC diagnosis is morphology, serum AFP and related immunomarkers are important in the ancillary diagnosis, differential diagnosis and monitoring of recurrence of tumors. The vast majority of patients with elevated serum AFP is a feature of HAC and is clinically important (2). If the patient is a middle-aged or elderly male with elevated serum AFP or if the pathologic biopsy result is a poorly differentiated adenocarcinoma, the clinicians should be aware of the potential of HAC and reduce misdiagnosis. Inagawa *et al.* (3) reported that the level of AFP was related to the degree of tumor differentiation, and a normal serum AFP indicates a low level of tumor differentiation. Therefore, the level of serum AFP cannot be a necessary condition for the diagnosis of HAC, regardless of whether it produces AFP or not.

HCC and HAC share numerous clinicopathological features like an elevated level of serum AFP, hepatoid morphology and immunoreactivity with AFP and polyclonal CEA (5). Therefore, HAC of the rectum with liver metastasis may closely mimic and be indistinguishable from HCC (6). In generally, most patients with HCC with or without extrahepatic metastases have a history of hepatitis or cirrhosis, and the histopathological pattern is usually without adenocarcinoma component. In contrast, HAC usually has no history of various types of hepatitis or cirrhosis, and its liver metastatic lesions are often multiple nodules, with microscopic findings of tubular or papillary adenocarcinoma components and mucus secretion visible in the adenoid component. In addition, immunohistochemical results can also effectively identify HAC and HCC.

The treatment of colorectal HAC is mainly surgical and postoperative adjuvant chemoradiotherapy, and the AFP level often decreases to the normal range after tumor resection but increases again when the tumor recurs or metastasizes. Therefore, whether AFP level is elevated again can be used as a marker of tumor recurrence and metastasis. The prognosis of HAC is worse than that of common adenocarcinoma, and similar to that of hepatocellular carcinoma. According to the characteristics of HAC, early diagnosis and treatment are the key factors to prolong survival, independent of chemotherapy regimens, which may not be sensitive to HAC. Nagai *et al.* (7) found that patients with HAC with or without AFP expression had a significantly worse prognosis than ordinary adenocarcinoma, with 2/3 of patients dying within 1 year.

In summary, HAC is a rare type of tumor with strong aggressiveness and poor prognosis, prone to vascular and lymphatic infiltration, and even lymph node and liver metastases. Most of the patients are already in the middle and late stages when they are diagnosed and there is no targeted treatment or strategy. Clinicians should improve their understanding of HAC to achieve early diagnosis and early treatment, which may bring more benefits to patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in the case were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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