Case Report
Pure multiple hepatoid adenocarcinoma of the stomach: a rare case report

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Abstract: Hepatoid adenocarcinoma (HAC) is a rare but important type of extrahepatic adenocarcinoma with highly aggressive behavior and a poor prognosis. The stomach is one of the organs in which HAC has been most commonly identified; however, multiple HACs in the stomach have not been previously reported. Here, we report the first case of multiple HACs in the stomach. A 46-year-old male with abdominal pain was found to have seven small to large ulcers scattered in the antrum and anterior wall of stomach. A gastric biopsy indicated poorly differentiated adenocarcinoma. The patient underwent 2 cycles of chemotherapy with oxaliplatin (130 mg; day 1) and capecitabine (2 mg, twice daily; days 1-14). One week after chemotherapy, alpha fetoprotein (AFP) serum levels were found to be markedly elevated (417.52 ng/ml). An expanded gastrectomy was then performed and seven 0.8-2.8 cm ulcerated tumors infiltrating into the gastric wall were found scattered on the antrum and anterior wall of the stomach. Histopathological analysis revealed that all of the tumors were comprised of cells with hepatoid-like features. Furthermore, the tumor cells demonstrated immunostaining positive for AFP, and Hepatocyte paraffin 1 (Hep Par 1). The diagnosis of pure multiple HACs producing AFP in the stomach was established. After the operation, the serum AFP level was significantly decreased (12.87 ng/ml). The patient received chemotherapy post-operatively, and has now survived 3 months without progression.

Keywords: Stomach, hepatoid adenocarcinoma, alpha-fetoprotein, gastric

Clinical summary
A 46-year-old male presented to our hospital with a 30-day history of increasing dull stomachaches. The upper gastrointestinal endoscopies performed revealed several ulcers scattered in the antrum and anterior wall of the stomach. A biopsy confirmed poorly-differentiated adenocarcinoma and the patient then received 2 cycles of chemotherapy with oxaliplatin (130 mg; day 1) and capecitabine (2 mg, twice daily; days 1-14). One week after chemotherapy, alpha fetoprotein (AFP) serum levels were found to be markedly elevated (417.52 ng/ml). An expanded gastrectomy was then performed and seven 0.8-2.8 cm ulcerated tumors infiltrating into the gastric wall were found scattered on the antrum and anterior wall of the stomach (Figure 1A).

Microscopically, each ulcer had several well-defined nodules (Figure 2A). All seven tumors comprised large polygonal cells with abundant eosinophilic cytoplasm, forming trabeculae, sheet-like, and artificial gland-like patterns and some even had a sinusoidal vascularity. Nuclei tended to be centrally placed (Figure 2B-E). All features were similar to those found in hepatocarcinoma. A total of 9 of 25 lymph nodes were involved by metastases. Neoplastic cells were focally positive for AFP and Hepatocyte paraffin 1 (Hep Par 1), but were negative for CD56, synaptophysin and chromogranin (Figure 3A-C). Interestingly, cytokeratin 7 (CK7) was positive in the remaining normal gastric mucosa but negative in the tumor cells, including those with artificial gland-like architecture (Figure 3D, 3E). The proliferation index, as measured with a Ki67/MIB-1 immunostain, was approximately 30% (Figure 3F). Consequently, a diagnosis of pure multiple hepatoid adenocarcinomas (HACs) producing AFP was established. After the operation, the serum AFP level was significantly decreased (12.87 ng/ml) and the patient...
Multiple hepatoid adenocarcinoma of the stomach

was referred to the oncology department to receive chemotherapy. To date, the patient has survived for 3 months without any symptom of progression.

Discussion

Gastric cancer is a common malignancy, but HAC represents only 0.19-0.22% of gastric cancers [1, 2]. The median age at diagnosis is 65.5 years, with a slight male predominance [2]. Lymph node metastases are common (70%) [1] as well as distant metastases (50%) [2], with the liver as the most common site (90%) [2]. A total of 15.8% of the patients with gastric HAC present with liver metastasis at the time of diagnosis [1]. In fact, when liver metastasis is the primary manifestation of gastric HAC, it is difficult to differentiate the primary site. The clinicopathologic features of HAC are not yet entirely clear. Almost all articles about HAC in the English medical literature described only one mass in a patient [3, 4], except one paper that reported a diffuse nodular tumor in the peritoneum [5]. Here, we reported a case of a middle-aged man with multiple masses in the stomach. To our knowledge, this is the first report of multiple HACs of the stomach.

Gastric HAC frequently contains moderately or well-differentiated adenocarcinoma including tubular adenocarcinoma. Kishimoto et al. [6] suggested that HAC develops from tubular adenocarcinoma, and Suzuki et al. suggested that hepatoid components may differ from the tubular component. Akiyama et al. [8] reported that gastric HAC and adenocarcinomatous components are of monoclonal origin. In the present case, gastric HAC was of the histologically pure type with no true glandular component, and CK7 was positive in normal gastric mucosa but negative for in the artificial gland-like areas, suggesting that HAC did not develop from tubular components.

Serum AFP levels are elevated in 88% of HAC patients [2], such as in this case, but the high AFP level is not necessary for a diagnosis of HAC. HAC is histopathologically diagnosed by the tumor with hepatocellular carcinoma-like features, with or without AFP immunostaining. In the present case, although almost all the tumor cells had hepatoid-like features, only some cells were positive for AFP. Hepatoid-like carcinoma cells, with large eosinophilic and clear cytoplasm, infiltrated with a trabecular or sheet-like pattern. HAC is different from the AFP-producing adenocarcinomas of the stomach, which demonstrate AFP immunostaining but lack hepatoid-like morphology. Gastric HAC also should be distinguished from solid-type gastric adenocarcinoma because of their different biological behavior. There is a higher incidence of vascular invasion and distant metastasis in HAC than in solid-type poorly differentiated adenocarcinomas [9]. The median survival time is 7.2-12 months, and the 5-year survival rate 20%, which are worse than those of solid-type gastric adenocarcinoma [1, 2]. However, it is difficult to detect HAC solely based on findings from hematoxylin and eosin staining, especially in small biopsy specimens, such as our present case. Xie et al. [1] reported that the misdiagnosis rate of HAC was 30.8% (8/26). When the microscopic features are suggestive of a poorly or undifferentiated adenocarcinoma, pathologists should pay attention to this rare subgroup to improve identification. The high AFP level in the blood and the positive immunohistochemical staining for AFP, Hep Par 1, α-1-antitrypsin, and α-1-antichymotrypsin may be crucial for the final diagnosis of hepatoid adenocarcinoma of the stomach. Because of the poor prognosis for this type of tumor, correct and early-stage diagnosis of HAC is essential, and long-term follow-up is required.

In conclusion, HAC is a rare subgroup of gastric carcinoma with a poor prognosis. Multiple HACs and the histologically pure type (lacking glandular components) are quite rare in gastric HACs.
HAC is considered to be differentiated from the tubular adenocarcinoma. Correct and early-stage diagnosis of HAC is essential, and long-term follow-up is required.

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**Disclosure of conflict of interest**

None.
Multiple hepatoid adenocarcinoma of the stomach

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References


Figure 3. Neoplastic cells focally positive for AFP (A), and Hep Par 1 (B), but negative for chromogranin (C). Interestingly, CK7 was positive in the remaining normal gastric mucosa but negative in tumor cells, including those with artificial glandular patterns (D, E). Ki67 immunostaining was approximately 30% (F).
Multiple hepatoid adenocarcinoma of the stomach


