Hepatoid adenocarcinoma of the stomach: Nine case reports and treatment outcomes

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Abstract. Hepatoid adenocarcinoma (HAC), an extrahepatic tumor, has notable morphological similarities to hepatocellular carcinoma, which has been reported in gastrointestinal tract organs, including the rectum, gallbladder, lung, ovary and urinary bladder. HAC of the stomach (GHAC) is a rare variant of gastric cancer, characterized by aggressive behavior and extremely poor prognosis. Correct diagnosis depends on clinicopathological and immunohistochemical studies. In the present study, we reported nine cases of GHAC who were treated in the First Affiliated Hospital of Zhejiang University, China, from January 2009 to December 2013. All patients underwent radical gastrectomy; among them, one patient had stage I, one had stage II and seven had stage III. Elevated serum α-fetoprotein was observed in eight cases. Until now, only one patient has succumbed, four patients have liver metastases, one has lung metastasis and four remain disease-free. Relatively longer survival requires accurate diagnosis at an earlier stage and active multimodality treatment, including radical gastrectomy and adjuvant chemotherapy.

Introduction

Hepatoid adenocarcinomas (HACs) have been reported in gastrointestinal tract organs, including the gallbladder (4%), pancreas (4%), uterus (4%), lung (5%) and ovary (10%); however, the stomach (63%) is the most common origin of tumors according to a study of 261 HAC cases (1). This is due to the fact that the gastric system and liver were derived from the primitive foregut of the embryo (2). Bourreille *et al* firstly reported a case of α-fetoprotein-producing gastric carcinoma (AFPPGC) with liver metastasis in 1970 (3), and Ishikura *et al* termed this type of gastric cancer 'hepatoid adenocarcinoma of the stomach (GHAC)' (4). The majority of patients with GHAC demonstrate an elevated serum AFP level; however, 46% of GHAC tissues were negatively stained with AFP (2). GHAC is a rare type of gastric adenocarcinoma, with an incidence of only 0.38-1% among all gastric cancers (5,6). In view of the high incidence of liver metastasis, GHAC has a relatively poorer prognosis than common gastric cancer. It is difficult to distinguish GHAC with liver masses from primary hepatocellular carcinoma (HCC). To present the clinicopathological features, and to evaluate the therapeutic regimen and outcomes for patients with GHAC, we retrospectively analyzed nine cases which were treated in the First Affiliated Hospital of Zhejiang University, China, from January 2009 to December 2013.

Case report

Clinical data. Relevant clinical data are provided in Table I. Eight patients were male and one was female (median age, 63 years; range, 47-72 years). Eight patients had epigastric discomfort that had persisted for a certain time. Case 5 had an elevated serum AFP level that had persisted for two years; ultrasonographic and computed tomography (CT) scans had detected multiple hepatic nodules, so the patient was initially misdiagnosed as having primary HCC. Then hepatic artery digital subtraction angiography and transcatheter arterial chemoembolization (TACE) were performed, followed by a gastric biopsy which revealed gastric carcinoma. The hepatic nodes in this case were confirmed as angioma. Gastroscopy and biopsy revealed that gastric adenocarcinoma was present in all patients. The tumors of six cases were located in the antrum, two in the cardia and one in the corpus. All patients were serologically negative for hepatitis B surface antigen and hepatitis C antibody, and they did not reveal any imaging signs of cirrhosis. Cases 2 and 7 had a history of alcohol abuse, and the others did not. The laboratory investigation revealed that the serum AFP levels of eight patients were notably elevated, with a median level of 916.8 ng/ml (range, 4.4-8455.9 ng/ml; Table I).

Treatment procedures and prognosis. A CT scan revealed that three patients (cases 2, 4 and 6) had multiple retroperitoneal area and perigastric lymph node enlargement, so the three

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Table I. Preoperative clinical features in nine cases of hepatoid adenocarcinoma.

Case	Gender/age	Site/size (cm)	Pre-/postoperative AFP (ng/ml)	Liver/lung metastases	Clinical presentation	Endoscopic Borrmann type
1	M/47	Stomach, gastric body/1.5x1.3	4.4/7.7	No	Epigastric discomfort	II
2	M/63	Antrum/5.0x3.0	916.8/441.9	No	Epigastric tenderness	III
3	F/76	Cardia/7.0x5.0x3.0	448.6/63.0	No	Upper abdominal pain	II
4	M/61	Antrum/6.5x4.0	3633.9/3.3	No	Epigastric discomfort	I
5	M/69	Antrum/3.0x2.5	5333.2/58.2	No	Elevated serum AFP	II
6	M/57	Antrum/3.0x4.0	42.3/5.1	No	Upper abdominal pain	II
7	M/67	Cardia/4.0x3.2	270.0/32.9	No	Epigastric discomfort	II
8	M/58	Antrum/4.5x4.0	8455.9/471.1	No	Upper abdominal pain	II
9	M/72	Antrum/4.0x6.0	1079.3/n.a.	No	Epigastric tenderness	II

AFP, α-fetoprotein; M, male; F, female; n.a., not assessed.

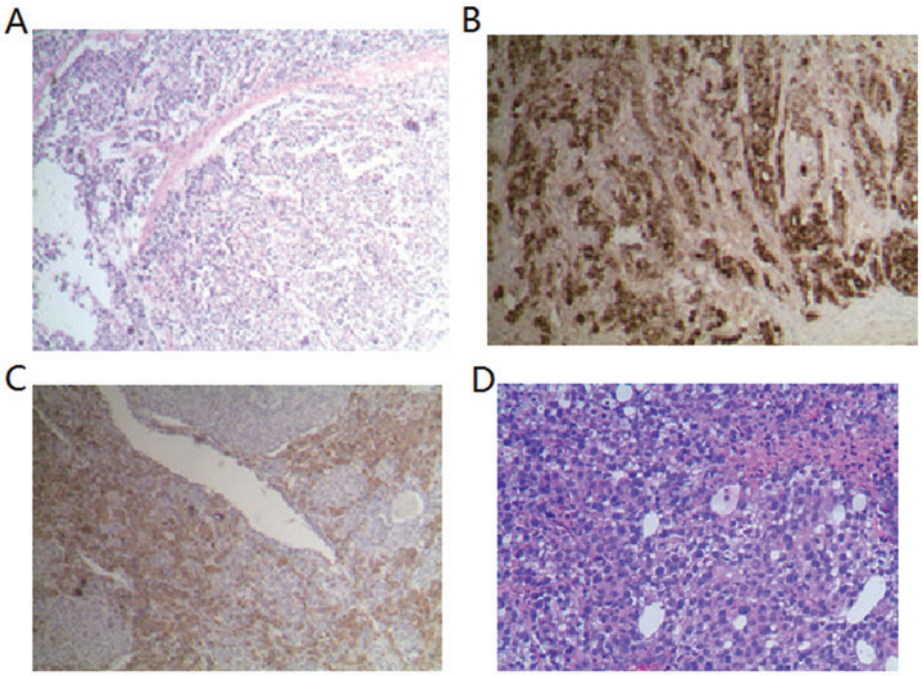

Figure 1. Immunohistochemical features of hepatoid adenocarcinoma of the stomach. (A) Hematoxylin and eosin staining: tumor cells are arranged in a trabecular pattern with eosinophilic cytoplasm and an abundance of blood sinus, with a glandular and hepatoid component (magnification, x100). (B) Immunohistochemical staining: cells are positively stained for α-fetoprotein (magnification, x100). (C) Immunohistochemical staining: cells are positively stained for synaptophysin (magnification, x100). (D) Hematoxylin and eosin staining of liver metastases: liver metastases demonstrated hepatoid differentiation, virtually indistinguishable from hepatocellular carcinoma (magnification, x400).

cases received neo-adjuvant chemotherapy. None of these patients developed liver or lung metastases. Due to the notably elevated serum AFP level, case 5 was misdiagnosed as HCC and received TACE treatment at first admission until gastric endoscopy identified gastric adenocarcinoma. All patients received radical gastrectomy, among whom seven received subtotal gastrectomy, and two (cases 1 and 7) received total gastrectomy. According to the American Joint Committee on Cancer (2010AJCC) pathological tumor-node-metastasis (pTNM) staging classification for carcinoma of the stomach, stages I and II were observed in one patient, respectively, and stage III was observed in seven patients. These patients recovered following surgery without any notable postoperative complications. Seven patients underwent adjuvant postoperative chemotherapy. In case 5, after four cycles of chemotherapy regimen with S-1 and oxaliplatin, the serum AFP increased from 58.2 to 1449.0 ng/ml, and a magnetic resonance imaging scan revealed multiple hepatic metastases 6 months after surgery. Case 9 demonstrated multiple hepatic metastases one month after surgery and succumbed 5 months after surgery. Case 2 demonstrated a partial response following six cycles of chemotherapy with FOLFOX regimen, but was observed to have multiple liver metastases, so the patient was administered TS-1 as chemotherapy as well as liver radiofrequency

Table II. Treatment and prognosis of nine cases of hepatoid adenocarcinoma.

Case	Neo/adjuvant chemotherapy	Surgery/R0+D2	Status	DFS (months)	OS (months)
1	No/SOXx6	Yes	Disease-free	7	7 (censored)
2	(FOLFOXx2)/(FOLFOXx4), TS-1	Yes	Liver metastases	4	7 (censored)
3	No	Yes	Disease-free	6	6 (censored)
4	(SOXx2)/(SOXx4), capecitabine plus paclitaxel	Yes	Liver metastases	18	28 (censored)
5	No/(SOXx4)	Yes	Liver metastases	11	15 (censored)
6	(SOXx2)/(SOXx4)	Yes	Disease-free	32	34 (censored)
7	No/(SOXx6)	Yes	Disease-free	36	36 (censored)
8	No/(SOXx6), paclitaxel plus carboplatin	Yes	Lung metastases	22	43 (censored)
9	No	Yes	Liver metastases	1	5

Censored, survival or lost to follow-up; R0, curative resection; D2, D2 lymphadenectomy; DFS, disease-free survival; OS, overall survival; Neo, neo-adjuvant chemotherapy; FOLFOX, oxaliplatin + folinic + fluorouracil; SOX, oxaliplatin + TS-1.

Table III. Histopathological and immunohistochemical features in nine cases of hepatoid adenocarcinoma.

Case	Histopathlogy/ differentiation	AFP	CK	CgA	SYN	Vascular invasion	pTNM stage/pstage
1	Hepatoid with signet-ring cell carcinoma/P	-	$CK2^+$	n.a.	n.a.	+	pT2N3aM0/IIIA
2	Hepatoid/P	+	$CK2^+$	+	+	+	pT4aN3bM0/IIIC
3	Carcinosarcoma	+	n.a.	n.a.	n.a.	n.a.	pT1bN0M0/IA
4	Hepatoid/P	+	$CK7^+CK19^+CK20^-$	n.a.	n.a.	-	pT4aN2M0/IIIB
5	Hepatoid/P	+	$CK20^+$	+	+	-	pT3N1M0/IIB
6	Hepatoid/M-P	+	$CK20^-$	-	-	+	pT4aN3M0/IIIC
7	Hepatoid with tubular adenocarcinoma/P	+	$CK19^+$	-	-	+	pT4aN3M0/IIIC
8	Hepatoid/M-P	+	$CK7^-CK19^+CK20^+$	-	-	+	pT4aN2M0/IIIB
9	Hepatoid/P	-	$CK14^-CK20^+$	-	-	+	PT4aN2M0/IIIB

AFP, α-fetoprotein; CK, cytokeratin; CgA, chromogranin A; SYN, synaptophysin; pTNM, pathological tumor-node-metastasis; P, poorly differentiated; M, moderately differentiated; n.a., not assessed.

ablation (RFA). Case 4 was observed to have a liver metastasis 18 months after surgery, following four cycles of chemotherapy with a combination of capecitabine plus paclitaxel; this case underwent liver tumor resection. Case 8 had lung metastasis 22 months after surgery and received paclitaxel plus carboplatin as the chemotherapy regimen, demonstrating a partial response. Until present, only one patient has succumbed, four patients have liver metastases, one has lung metastasis and four remain disease-free. Relevant treatment procedures and prognosis data are shown in Table II. Written informed consent was obtained from the patient's family and this study was approved by the ethics committee of First Affiliated Hospital of Zhejiang University, Hangzhou, China.

Pathological and immunohistochemical features. The pathological diagnostic criteria of GHAC was that tumor cells histologically demonstrate features resembling HCC. There was no particular quantity requirement for histological hepatoid differentiation, and patients with focal hepatoid or intermingled with sarcoma were also diagnosed with GHAC. Of the nine GHAC cases, six were confirmed to be HAC with complete hepatocyte-like regions; HAC intermingled with signet-ring cell components was observed in one case, with sarcoma cell components in one case and with tubular adenocarcinoma components in one case, respectively. Most of the patients (8/9) had poorly differentiated tumors. Eight patients had lymph node metastasis. Six had endovascular tumor emboli. Tumor cells were arranged in a trabecular pattern and resembled HCC, with abundant blood sinus. Polygonal cells with eosinophilic cytoplasm and hyperchromatic nucleoli indicated hepatoid differentiation. Immunohistochemistry revealed that the neoplastic cells in hepatoid areas of primary

tumors and metastases demonstrated positivity for AFP, with the exception of cases 1 and 9. Specifically, the tumors in two cases were stained positively for synaptophysin and chromogranin A, which indicated neuroendocrine differentiation. The histopathological and immunohistochemical features of the nine cases are shown in Table III. Immunohistochemical features of hepatoid adenocarcinoma of the stomach are showed in Fig. 1

Discussion

The GHAC cases in our study were characterized histologically by hepatoid differentiation and shared clinical features, including elevated serum AFP, predilection for elderly male patients and location in the antrum, aggressive behavior, and preferential metastases to the lymph nodes and liver, which is similar to the results of previous studies (6-9). GHAC patients usually have an elevated serum AFP level, so it is often misdiagnosed as primary HCC, particularly in GHAC patients with simultaneously occurring liver-occupying lesions. Generally, neighboring cirrhotic lesions are frequently observed in primary HCC, while they seldom occur in GHAC with liver metastases. Although metastatic lesions in the liver demonstrate a histological appearance similar to that of HCC, the clinical background and immunohistochemical examination still aid the differential diagnosis, since HCC often develops from liver cirrhosis to HCC, frequently accompanied by positive HepPar1 (10). The clinicopathological entity of GHAC is a tumor composed of polygonal cells arranged in a solid or trabecular manner that resembles HCC; hence, the pathological diagnostic criteria of GHAC is that tumor cells histologically demonstrate hepatoid features (11,12). Although two tumor cases in our study did not express AFP, the morphology and immunophenotype were consistent with GHAC. Immunohistochemical staining is conducive to distinguishing HCC from GHAC with liver metastases; however, its success has been limited by the lack of a reliable positive marker for hepatocellular differentiation. GHAC is frequently positive for AFP (91%), cytokeratin (CK)18/CK19 (100%), CK20 (25%), pancytokeratin (AE1/AE3) (92.3%) and α1-antitrypsin (91%) (13), and glypican-3 has been reported to be useful in the differential diagnosis between GHAC and HCC (1). In addition to these markers, palate, lung and nasal epithelium carcinoma-associated protein represents a promising marker in distinguishing HAC from HCC, since it is detected in liver metastases of GHAC, but not in HCC (14). However, none of these markers are sensitive or specific enough. The serum AFP level was not associated with the dimension, size, stage or prognosis of GHAC (15); however, patients with AFP-positive gastric cancer have a significantly higher tendency to develop liver metastasis and have a shorter long-term survival than patients with AFP-negative gastric cancers (16), since AFP's ability to suppress lymphocyte DNA synthesis inhibits lymphocyte transformation (17). Koide *et al* reported that AFP-producing gastric cancers have high malignant potential (high proliferative activity, weak apoptosis and rich neovascularization) compared with that of AFP-negative gastric cancers (18). Patients with normal AFP levels may represent a subtype of GHAC, with a more positive biological behavior (19). The measurement of the serum AFP level is also helpful during the follow-up period, as it usually falls sharply following adequate surgical treatment, while persistence of AFP elevation following active multimodality treatment including tumor resection may indicate regional or distant metastasis. Kumashiro *et al* reported that the histogenesis of HAC was strongly associated with the intestinal phenotype, and its hepatoid component was in some way associated with reduced CDX2 expression. High levels of CD10 and low levels of CDX2 expression may be associated with the aggressive biological behavior of GHAC (5).

Although there is no standard therapy protocol for GHAC, the disease's primary treatment modality can be based on that of common gastric adenocarcinoma. The majority of patients (6/9) in our study received first-line postoperative adjuvant chemotherapy. The liver metastases should undergo tumor resection if metastatic tumors are resectable; certain patients gain a survival benefit from this (case 4). Additionally, RFA is a safe and effective alternative for the partly unresectable liver metastases (case 2). TACE with doxorubicin transiently arrests the progression of recurrent liver metastases (20). Systemic chemotherapy demonstrated good effects in our cases.

The poor prognosis is associated with tendency of venous invasion, lymphatic permeation, lymph node metastasis, and synchronous and metachronous metastasis of the liver or other organs. One study reveals that a higher expression of c-Met may be associated with the poor prognosis of AFP-producing gastric cancer (21). Survival is closely associated with the pTNM stage. Baek *et al* reported that the median overall survival of patients with stages I-III and stage IV was 28.0 and 8.2 months, respectively (9). Relatively longer survival requires accurate diagnosis at an earlier stage as well as active multimodality treatment, including radical gastrectomy and adjuvant chemotherapy.

In conclusion, GHAC usually occurs with an elevated serum AFP level, and has unique pathological and immunohistochemical characteristics with notable morphological similarities to primary HCC. GHAC is associated with liver and lymph node metastases, indicating that the prognosis is poorer than with ordinary gastric cancer. It is essential to differentiate metastatic liver lesions of GHAC from primary HCC.

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