

Effect of immune checkpoint inhibitors in patients with gastric hepatoid adenocarcinoma: a case report and literature review

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Abstract

Gastric hepatoid adenocarcinoma (GHAC) is a highly aggressive histological subtype of gastric cancer (GC) with similar tissue morphology to hepatocellular carcinoma. GHAC frequently produces alpha-fetoprotein (AFP) and has a poor prognosis; however, standardized treatment remains elusive. We report a male patient in his early 60s with GHAC who received immunotherapy, and the curative effect was evaluated. He was admitted because of progressive fatigue and dizziness for 2 months. He had experienced spontaneous epigastric pain with muscular defense of the epigastrium and accompanying tenderness 1 year earlier and underwent radical gastrectomy. Immunohistochemistry showed that hepatocyte-specific marker (Hep) was highly-expressed, indicating probable GHAC. Additionally, imaging suggested GC recurrence or gastric stump cancer. Radioimmunoassay indicated an AFP level of $>1210.00 \mu\text{g/L}$, and liver biopsy was performed following abdominal contrast-enhanced computed tomography. Pathology showed a few hepatocytes and proliferative fibrous connective tissue. The patient received three cycles of chemotherapy, with no obvious improvement. The possibility of surgical treatment was excluded,

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and immunotherapy or palliative treatment was selected. He received 11 cycles of a programmed death-1 (PD-1) monoclonal antibody, and the effect of treatment was satisfactory. The mechanism of action of immunotherapy in GHAC warrants further investigation.

Keywords

Immune checkpoint inhibitor, gastric hepatoid adenocarcinoma, gastric cancer, programmed death-1, case report, pathology, gastrectomy, chemotherapy

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Background

Gastric hepatoid adenocarcinoma (GHAC), as a special subtype of gastric cancer (GC), is a rare primary extrahepatic malignant neoplasm.^{1,2} Patients with GHAC have high serum alpha-fetoprotein (AFP) levels, which might be accompanied by the discovery of a hepatic mass.³ The complexity of GHAC makes the differential diagnosis challenging because this cancer might also originate from other gastrointestinal locations, namely the pancreas, ovary, uterus, lungs, and several other organs.^{4,5} However, the scientific literature mainly comprises case reports or very small patient series.^{4,6} GHAC is considered an aggressive type of GC with unique clinicopathological features, and GHAC is prone to lymph node and distant metastasis and has a poor prognosis.^{1,5} Currently, there is no individualized treatment for these types of advanced GC.^{7,8} Thus, challenges remain regarding both the appropriate identification and diagnosis of GHAC and effective treatments to improve the unfavorable prognosis.

Recently, immunotherapy has shown positive effects in the treatment of advanced GC. Multiple studies have suggested the efficacy of programmed death-1 (PD-1) monoclonal antibody in the third-line treatment of GC.^{9,10} A phase III randomized controlled trial (RCT) showed that PD-1 monoclonal antibody therapy combined

with chemotherapy was not superior to chemotherapy in the first-line treatment of advanced GC.¹¹ However, the ATTRACTION-4 and CheckMate 649 trials showed that immune checkpoint inhibitors can be the first-line treatment for advanced metastatic GC. Additionally, the results of another study indicated that PD-1 monoclonal antibody therapy provided a survival advantage over chemotherapy alone.¹² Thus, the curative effect of immune checkpoint inhibitors in patients with GHAC is still unconfirmed. Herein, we described a case of a 63-year-old man with the complaints of progressive fatigue and dizziness and a high serum AFP level who was diagnosed as having GHAC. We were pleasantly surprised that the effect of immune checkpoint inhibitor therapy in this GHAC patient was satisfactory. In this study, we performed a literature review and reported this case to provide a treatment strategy for patients with GHAC.

Case presentation

A man in his early 60s was admitted to the Huaian Hospital of Huaian City with the complaints of progressive fatigue and dizziness for 2 months, beginning in August 2019. The patient was referred to our hospital after his mental state worsened. He had experienced spontaneous epigastric

pain with muscular defense of the epigastrium and accompanying tenderness 1 year earlier, and radical gastrectomy was performed. After the current admission, the results of blood testing indicated a hemoglobin level of 49 g/L, indicating severe anemia. Blood transfusions were administered, and the hemoglobin level recovered. No abnormal findings were found for the other blood counts, biochemical examinations, and coagulation tests. After the patient's condition stabilized, electronic gastroscopy was performed to evaluate gastric mucosal lesions. The results were as follows: postoperative changes of esophageal carcinoma; a protuberant lesion in the gastric body measuring approximately 2 cm × 3 cm, with a slightly rough surface; and an irregular protuberance of the marginal mucosa that bled easily (Figure 1). Therefore, GC recurrence or gastric stump cancer was considered in this patient.

In addition, biopsy results showed poorly differentiated adenocarcinoma, and immunohistochemical staining showed that hepatocyte-specific marker (Hep) (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China) was highly-expressed, which indicated a probable diagnosis of GHAC (Figure 2).

In mid- to late October 2019, the patient was admitted to the Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University for further treatment. Abdominal computed tomography (CT) showed postoperative changes of GC with wall thickening in the remnant stomach. The possibility of remnant GC was considered, and the clinical observations needed to be taken into consideration. In addition, multiple liver masses were found, and the possibility of metastasis was highly suspected. To further clarify the diagnosis and determine the best treatment for

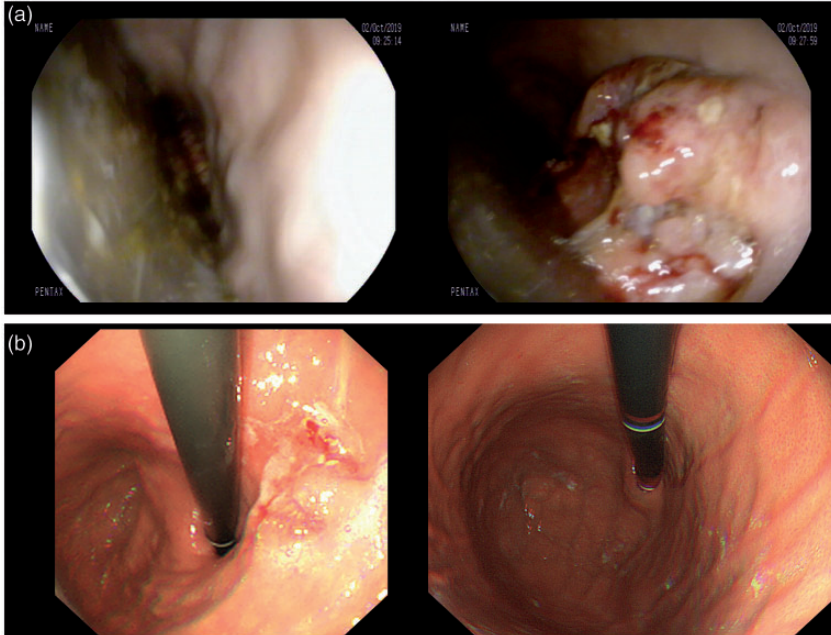


Figure 1. Electronic gastroscopy showing the gastric mucosal lesions before treatment with PD-I/PD-L1 (a); and after treatment with PD-I/PD-L1 (b). PD-I, programmed death-I; PD-L1, programmed death-ligand-I.

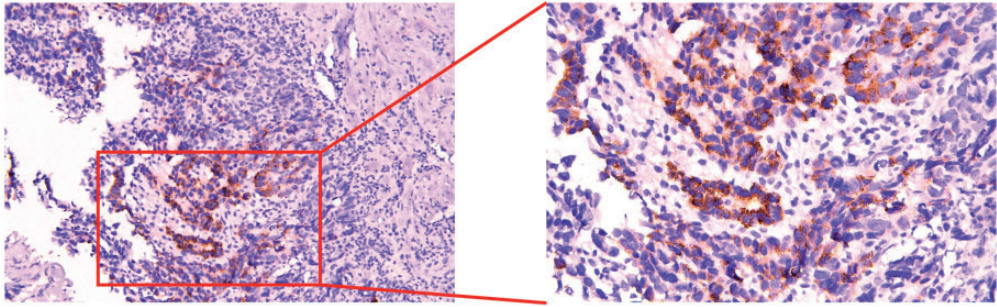


Figure 2. Histopathological findings. Immunohistochemical staining showing that hepatocyte-specific marker (hep) is highly-expressed, and proliferating tumor cells with solid or thick trabecular patterns mimicking hepatocellular carcinoma are seen (left panel, magnification: $\times 10$; right panel [magnification of the box outlined in the left panel] magnification: $\times 40$).

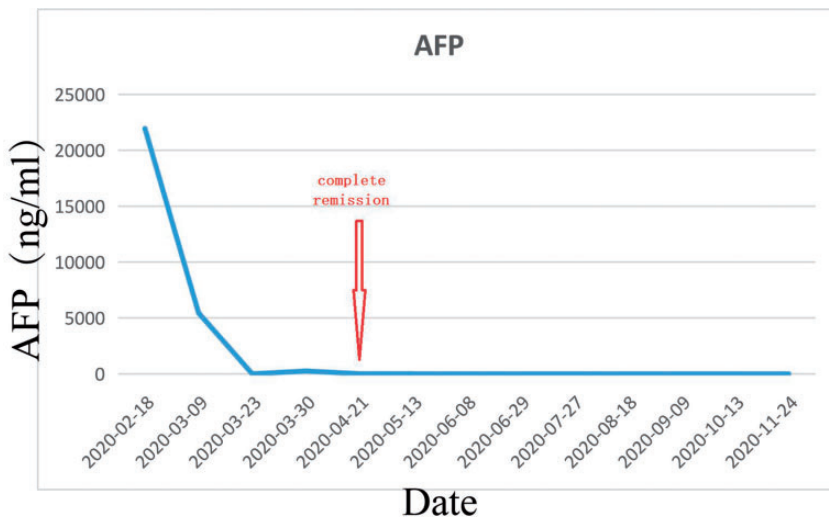


Figure 3. Chart showing the changes in AFP level over time. AFP, alpha-fetoprotein.

GHAC, we performed magnetic resonance imaging (MRI), and the results were consistent with those of the CT imaging. Radioimmunoassay testing showed that the AFP level was $>1210.00 \mu\text{g/L}$. The changes in AFP level over time are shown in Figure 3. To clarify the cause of the AFP elevation, liver biopsy was performed. Pathology showed a few hepatocytes and proliferative fibrous connective tissue. The patient then received one cycle of

oxaliplatin and S-1 palliative (SOX) chemotherapy. During the treatment period, the patient was evaluated at the Department of Oncology of the Cancer Hospital of Fudan University, and the assessment suggested that SOX chemotherapy be evaluated again after two cycles, then the next treatment plan should be decided. Hence, the patient continued SOX chemotherapy for cycle 2 in mid- to late November 2019. After two cycles of chemotherapy, CT

showed that the postoperative changes in GC with wall thickening in the remnant stomach, and the proportion of the remnant stomach, were smaller than those seen in earlier CT imaging. However, a mass occupying the left lobe of the liver and involving the inferior vena cava, which was seen in earlier CT imaging, now measured approximately 5 cm × 3.5 cm, which was larger than before and which was considered metastasis (Figure 4a). The assessment following chemotherapy was that no obvious signs of improvement were found.

After discussion by members of the various medical departments, the possibility of surgical treatment for this patient was excluded, and immunotherapy or palliative treatment was chosen. The patient was then treated with sintilimab (a PD-1 monoclonal antibody; 200 mg/dL) for 11 cycles after consulting the literature and following the

diagnosis and treatment guidelines.¹² The patient developed a fever after the first cycle of treatment; however, this improved after symptomatic treatment. During the third cycle, the patient was re-examined and evaluated before treatment, and his condition was obviously improved. During the fifth cycle, electronic gastroscopy revealed no tumor mass. Additionally, CT found no liver metastases, and the serum AFP level had returned to normal, suggesting complete remission, which was subsequently confirmed. Efficacy was confirmed as stable before the seventh cycle. Subsequent CT showed that the liver tumor lesions and remnant GC lesions were significantly reduced in size after treatment with PD-1 monoclonal antibody (Figure 4b).

The research protocol for this study was approved by the Institutional Review

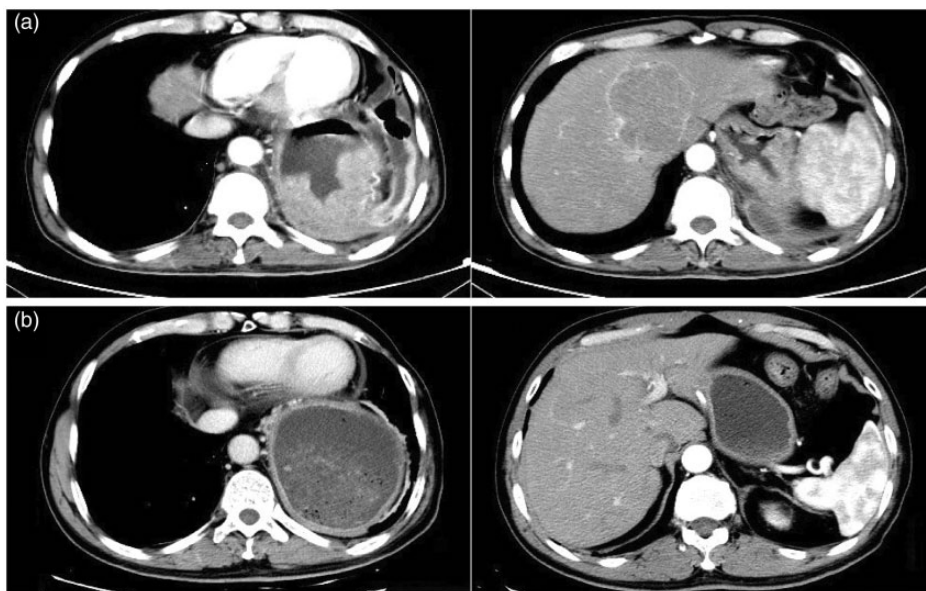


Figure 4. Imaging findings. Abdominal contrast-enhanced computed tomography showing the lateral segment lesions in the liver and gastric stump cancer before treatment with PD-1/PD-L1 (a), and that the liver tumor lesions and remnant gastric cancer lesions were significantly decreased in size after treatment with PD-1/PD-L1 (b).

PD-1, programmed death-1; PD-L1, programmed death-ligand-1.

Board of the Huaian Hospital of Huaian City, Huaian, China (approval number OC20210001, 6 January 2020). The study was performed in accordance with the nationally approved guidelines, and written and verbal informed consent was obtained from the participant and his family for publication. The reporting of this study conforms to the CARE guidelines.¹³

Discussion

GHAC is considered a subtype of GC with hepatic differentiation and morphological similarity to hepatic cells.^{14,15} GHAC occurs relatively more frequently in middle-aged men than the rate in elderly men. GHAC originates in the gastric antrum in 60% of patients, and only 13% of patients are diagnosed with early-stage GHAC.¹⁶ Histopathologically, GHAC resembles hepatocellular carcinoma (HCC) and is a type of extrahepatic carcinoma with a complex histological picture that involves enteroblastic and hepatic differentiation.¹⁷ However, the similarity of GHAC to HCC is evident. Several studies originally described that GHAC was frequently associated with highly differentiated papillary adenocarcinomas. It was thought that GHAC might arise from some cancers through hepatic differentiation; the adenocarcinomatous and hepatoid areas were often intermingled with each other, and an extensive venous involvement by tumor cells was noted.^{18,19} The cells of GHAC grow, proliferate, and invade surrounding tissues with significant accompanying venous infiltration and elevated serum AFP levels.^{3,19}

As a specific tumor biomarker, AFP is an oncofetal protein produced by the fetal liver, gastrointestinal cells, and yolk sac, and AFP is widely used in the diagnosis of yolk cyst tumors, hepatoblastomas, and HCC.^{3,20} Recent studies have shown that AFP is also frequently highly-expressed in

other human tumors, such as those of enteroblastic GC, colorectal cancer, gallbladder cancer, lung cancer, and ovarian cancer, of which GHAC is the most common.^{6,21,22} Clinically, advanced GC patients with liver metastasis or chronic hepatitis B also have elevated serum AFP.²³ The diagnostic basis of GHAC is uncertain, and the diagnosis is often defined as a component of the morphological differentiation of “HCC-like differentiation” in advanced GC.^{17,24} In a word, GHAC represents a special subtype of GC from the perspective of its clinical presentation and pathomorphology; however, the current diagnostic and treatment criteria require further investigation.

The marked clinical features of GHAC are high invasiveness, early metastasis, and rapid progression.^{1,24} The long-term follow-up results from a study by Liu et al. showed a significantly higher incidence of vascular invasion, lymph node metastasis, liver metastasis, and poor overall 5-year survival rates in the AFP-positive group than the respective incidences and rates in the AFP-negative group.²⁵ Another study, by Yang et al., suggested that early and clear differentiation of GHAC from cancerous or noncancerous conditions with AFP elevation and the assessment of high-risk patients by histopathology might improve the clinical prognosis of GHAC.²⁶ In fact, owing to the high degree of malignancy and rapid disease progression of GHAC, most patients have missed the opportunity for surgery at the time of diagnosis.^{1,17,24} Therefore, previous clinical studies of post-operative patients are insufficient to summarize the overall characteristics of patients with GHAC and guide clinical practice. However, there are few reports and a lack of specific treatment guidelines for GHAC patients.

We investigated immunotherapy in GHAC in this study.^{9,10,12} The main purpose of immunotherapy is to regulate the

autoimmune state of patients to directly attack tumor cells.¹² Sintilimab, which is an immune checkpoint inhibitor, can inhibit cellular immunity, and the killing effect of cancer cells can be increased by blocking PD-1/programmed death-ligand-1 (PD-L1). In our case, the patient was treated with the PD-1 monoclonal antibody, sintilimab, for 11 cycles after consulting the literature and following the diagnosis and treatment guidelines.¹² However, because this case report involved a single patient, it was difficult to analyze efficacy-related predictors. In one real-world study, the expression of PD-1/PD-L1 was not balanced between the immunotherapy group and conventional chemotherapy group.²⁷ However, one patient with high expression of PD-1/PD-L1 exhibited hyperprogressive disease, and another patient with PD-1/PD-L1-negative status achieved partial remission.²⁷ These findings showed that the efficacy of combined therapy could not be predicted simply by the expression level of PD-1/PD-L1, which suggests that the therapeutic effect of second-line immunotherapy is not good, and may be closely related to each patient's physical condition and disease load. Whether patients with GHAC respond to immunotherapy may be associated with their specific genetic features. Recent studies suggested that most Cancer Genome Atlas tumors with elevated AFP were categorized as intraepithelial neoplasia subtypes.^{28,29}

Loss of heterozygosity occurs frequently in GC, resulting in chromosomal instability and loss of tumor suppressor genes.^{29,30} The degree of loss of heterozygosity in GHAC is also high, with a median index of allele loss of 72%, which is much higher than the loss level of approximately 50% for other types of GC.³⁰ Some scholars speculated that the silencing of a key gene on chromosome 13q or 18q promoted the development of GHAC, leading to high tumor mutational burden, which could

explain why GHAC patients respond to immunotherapy, from one aspect.³¹ Owing to the lack of pathological tissues, high throughput sequencing was not conducted in this study; therefore, whether key gene silencing is valid still needs further investigation. Symptomatic treatment and close monitoring are indispensable. Furthermore, it is essential to update treatment at any time according to the progression of illness.

Conclusion

As in our case, GHAC is an atypical type of GC, and immunotherapy might be considered a treatment option for GHAC. In addition, diverse treatments for GHAC are indispensable and are administered on the basis of specific symptoms and with continuous monitoring. Further investigation of immunotherapy in GHAC patients is warranted.

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Author contributions

Protocol/project development: KZ and WW;
Molecular biology testing: WC and JY;
Data collection or management: JY and HL;
Data analysis: XZ and KZ;
Manuscript writing/editing: YS and KZ.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed.


Declaration of conflicting interest


The Authors declare that there is no conflict of interest.

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