

Alpha-Fetoprotein-Producing Hepatoid Adenocarcinoma of the Stomach

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Abstract

Hepatoid adenocarcinoma of the stomach (HAS) is a rare type of gastric cancer with unique clinicopathological features. HAS has a poor prognosis because of early liver, lung, and lymph node metastasis. Owing to its rarity and malignant potential, data on its pathophysiology and management are scarce. Herein, we describe a case of alpha-fetoprotein-producing HAS (AFP-HAS) with metastases to the liver, lungs, and spine. The patient presented with a 3-month history of epigastric pain and intractable emesis, initially thought to be gastroparesis given her uncontrolled diabetes mellitus. Contrast-enhanced computerized tomography (CECT) of the abdomen and pelvis revealed thickening of the gastric wall with hepatic metastases. Upper endoscopy revealed a fungating gastric mass, and the histopathology confirmed AFP-HAS. The patient did not tolerate palliative chemotherapy and died 6 months after her gastric cancer diagnosis.

Keywords: Alpha-fetoprotein-producing gastric cancer; Hepatoid adenocarcinoma of the stomach; Abdominal pain; Palliative chemotherapy

Introduction

Hepatoid adenocarcinoma of the stomach (HAS) is a rare and most malignant subtype of gastric cancer [1-6]. It accounts for 0.38-1.6% of all gastric cancers and has a very poor prognosis due to hepatic and early lymph node metastases [1, 2, 7,

8]. The term “hepatoid adenocarcinoma of the stomach” was coined in 1985 to describe a variant of gastric cancer with glandular and hepatoid differentiation [3, 9, 10]. Since then, more case reports have been published in the literature, most of which originated in East Asia [3]. Fewer cases have been reported in Europe and North America [3].

About 80% of patients with HAS have elevated serum alpha-fetoprotein (AFP) levels [9, 11]. AFP is an oncofetal glycoprotein secreted in the gastrointestinal tract, fetal liver, and yolk sac [8]. Elevated serum levels of AFP in adulthood are seen in hepatocellular carcinoma (HCC), yolk sac tumor (YST), and some gastric cancers such as HAS [8]. HAS is the most common AFP-producing gastric cancer, and serum AFP levels tend to correlate with the proportion of hepatoid-like cells in the tumor mass [1]. HAS cases with normal serum AFP levels have the same morphology, immunophenotype, and malignant potential as AFP-producing HAS (AFP-HAS) cases [11]. Herein, we present a case of AFP-HAS in an adult female.

Case Report

A 49-year-old female presented to the emergency room (ER) complaining of nausea, vomiting and abdominal pain for 3 months. Her medical history included gastroesophageal reflux disease (GERD) and diabetes mellitus with retinopathy. The pain was worse in the epigastric area, sharp in nature, constant, and rated 8/10 on a 0 - 10 pain scale. It was associated with early satiety and worsened with food intake. The patient endorsed a 15 pounds weight loss over 3 months and intermittent blood-stained stools. She denied having dysphagia, hematemesis, diarrhea, constipation, fever, dysuria, or gross hematuria. She also denied prior abdominal surgery, alcohol use, or use of non-steroidal anti-inflammatory drugs.

In the ER, the patient appeared in mild distress due to epigastric pain and nausea. She was afebrile and hemodynamically stable. She received symptomatic treatment for nausea, vomiting, and abdominal pain with improvement. On physical examination, her abdomen was soft, obese, and tender in the epigastrium. There was no guarding, rigidity or rebound tenderness. She had decreased sensation of touch in the lower extremities and lower thoracic spinal tenderness. The rest of the physical examination findings were unremarkable. Laboratory values were significant for anemia, thrombocytosis, elevated alkaline phosphatase, hypoalbuminemia, hyperglycemia, elevated AFP,

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Table 1. Patient's Admission Laboratory Values Compared to Normal Ranges

Variables	Admission labs	Normal ranges
Hemoglobin (Hb)	6.8	12.0 - 16.0 g/dL
Alkaline phosphatase	111	34 - 104 U/L
Platelet count	551	140 - 440 × 10 ³ /mm ³
Albumin	3.2	3.5 - 5.7 g/dL
Blood glucose	180	70 - 100 g/dL
AFP	1,252	0.5 - 9 ng/mL
CA 125	82.0	0 - 38 U/mL
CA 19-9	68	0 - 35 U/mL
CEA	126	0 - 3 ng/mL
LDH	144	140 - 271 U/L
<i>Helicobacter pylori</i> stool antigen	Negative	N/A

AFP: alpha-fetoprotein; CA: cancer antigen; CEA: carcinoembryonic antigen; LDH: lactate dehydrogenase.

elevated cancer antigen (CA) 19-9, elevated CA 125, and elevated carcinoembryonic antigen (CEA) levels (Table 1).

Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis showed gastric wall thickening, multiple necrotic lymph nodes in the upper abdomen, and hepatic lesions consistent with metastatic disease (Fig. 1). A bone nuclear scan revealed lesions at the T11 and L1 vertebrae, consistent with osseous metastasis. Upper endoscopy revealed a large, fungating, and ulcerated mass involving almost the entire lesser curvature of the stomach (Fig. 2). Biopsy results of the gastric mass revealed a moderately-to-poorly differentiated hepatoid gastric adenocarcinoma (Fig. 3). Histopathology of the liver lesions revealed tumor cells consistent with metastatic AFP-HAS (Fig. 4). The immunohistochemical staining (IHS) profiles of both the liver and gastric specimens were significant for AFP, caudal-type homeobox 2 (CDX2), and Sal-like protein 4 (SALL4) positivity (Figs. 3, 4).

The patient started palliative chemotherapy consisting of cisplatin 75 mg/m² on day 1 and etoposide 100 mg/m² on days

1 - 3 and completed the first cycle while in the hospital. The patient was not a candidate for adjunctive trastuzumab therapy due to her negative human epidermal growth factor receptor 2 (HER-2) status. The patient experienced severe adverse reactions during consecutive chemotherapy sessions that required multiple hospitalizations. She had febrile neutropenia, intractable nausea and vomiting, acute kidney injury, decreased appetite, poor nutrition, and rapid weight loss, leading to a decline in performance status from Eastern Cooperative Oncology Group (ECOG) 1 to ECOG 3. Ultimately, a decision was made to transition the patient to comfort care with at-home hospice services, and she died 6 months after her diagnosis.

Discussion

Herein, we describe a novel case of AFP-HAS in a female patient with a 3-month history of constant epigastric pain, weight

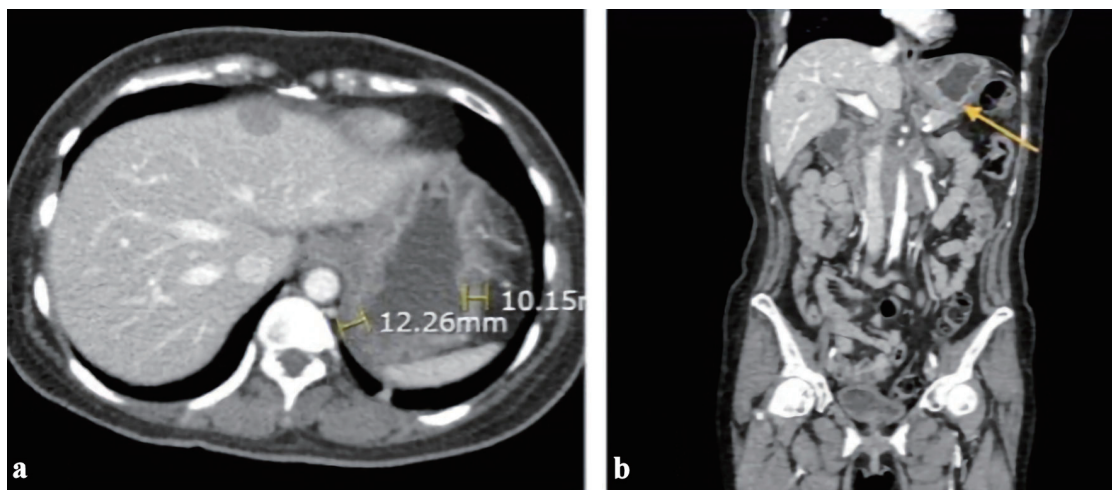


Figure 1. Contrast-enhanced CT scan of the abdomen/pelvis showing abnormal gastric wall thickening with extensive liver metastases. (a) An axial view of the CT scan with yellow lines estimating gastric wall thickness. (b) A coronal view with a yellow arrow showing stomach wall thickening consistent with gastric malignancy. CT: computed tomography.

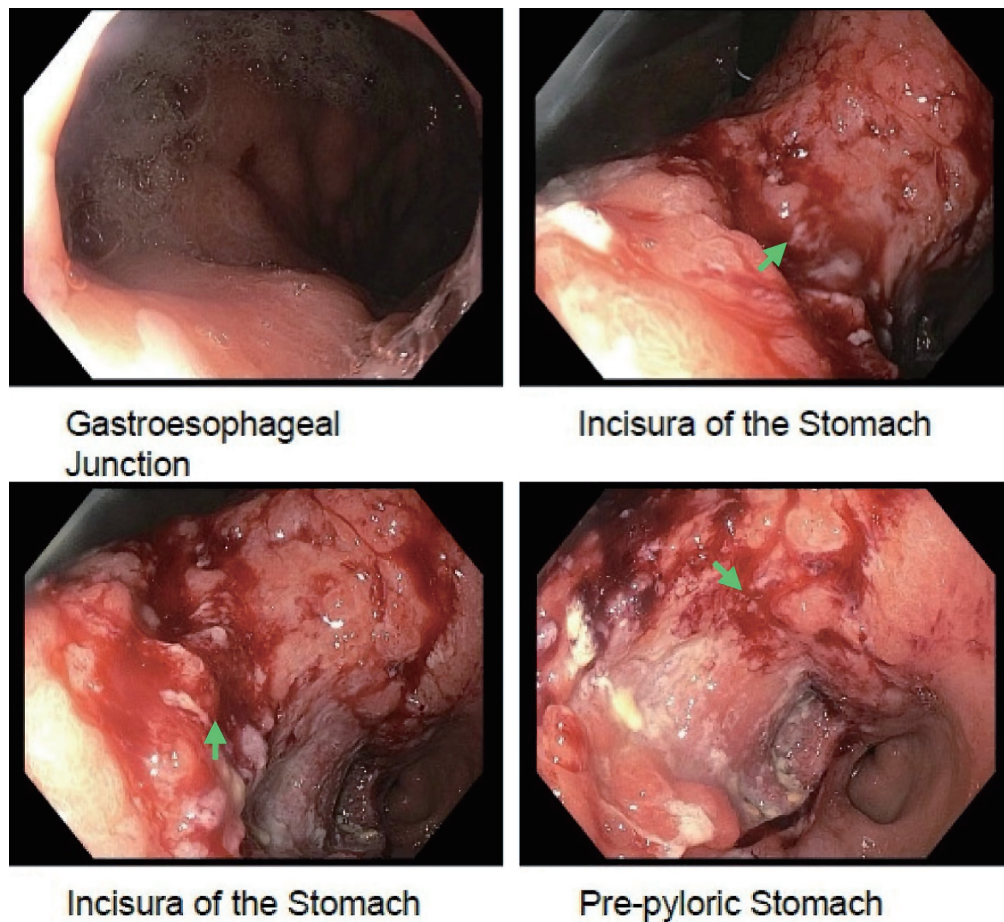


Figure 2. An endoscopy image showing a large, fungating, and ulcerated mass with friability involving almost the entire lesser curvature of the stomach (green arrows).

loss, and occasional hematochezia. Our patient is an outlier owing to her age, gender, and ethnicity. HAS is a rare type of gastric cancer that morphologically mimics HCC [3, 5, 9] and is often associated with elevated AFP levels. It has enteroblastic and hepatocellular differentiation and a poor prognosis due to liver and early lymph node metastasis [9]. HAS cases typically involve older males in Asian countries such as Japan and China [9, 12]. This rarity highlights the need for clinicians to consider HAS in differential diagnoses when encountering gastric tumors with unusual features, even in populations where this condition is exceedingly infrequent.

HAS typically presents with vague symptoms, but epigastric pain and fatigue are the most common [3, 9, 11]. Due to its rarity and ambiguous symptoms, HAS can easily be missed, leading to a delayed diagnosis [9]. Persistent abdominal pain is a common initial symptom in patients with HAS, which often warrants a computed tomography (CT) scan of the abdomen and pelvis. Gastric wall thickening is noted in most cases [5]. The tumor size usually ranges from 1.6 to 14.0 cm, and a heterogeneous texture of the mass correlates with tumor necrosis and hemorrhage [3, 5]. On histology, HAS consists of glandular and hepatocellular carcinoma-like foci [3], which can be confirmed by immunostaining of SALL4 and AFP [1]. Our

patient had gastric wall thickening on imaging, fungating mass on esophagogastroduodenoscopy (EGD), and the IHS profile was positive for both SALL4 and AFP.

HAS is a rare type of gastric cancer that morphologically mimics HCC [1, 5]. HAS is genetically unique and does not fit any of the Cancer Genome Atlas Program (TCGA) primary gastric cancer profiles [1]. As a result, there are no set treatment protocols for this cancer [1]. Since *TP53* is frequently mutated in both HAS and conventional gastric cancer cases, it can help differentiate AFP-HAS from HCC [1, 3]. Both AFP-HAS and YST-like carcinoma of the stomach can present with elevated AFP level; it is therefore important to distinguish between the two clinical entities through histopathological analysis. YST-like carcinoma of the stomach is a rare type of gastric carcinoma that histologically resembles YSTs, featuring patterns like microcystic, reticular, and solid structures, and often showing aggressive behavior with a poor prognosis [13-15]. While both conditions involve elevated AFP levels, they differ in their histology, with the YST-like carcinoma showing distinct YST-like patterns, which are not present in most AFP-producing gastric cancers.

Patients with HAS have a poor prognosis, with a median survival of 6 months [16] and a 5-year survival rate of 9% [5]. In early-stage cancers, surgery is the primary treatment with

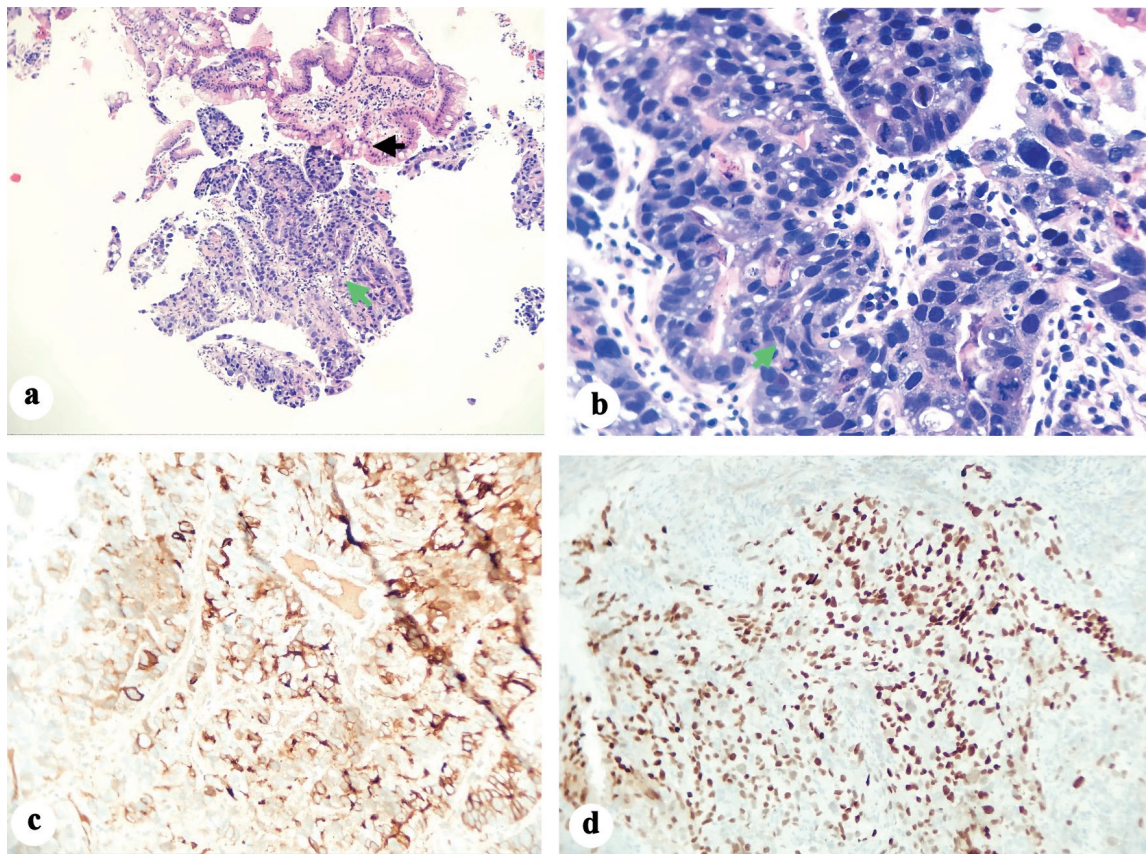


Figure 3. (a) Histological specimen showing mainly sheets of malignant cells (basophilic cells shown by green arrow) with focal glandular formation and prominent desmoplastic stromal response. The non-involved gastric glands (acidophilic staining and shown by black arrow) show focal intestinal metaplasia that is highlighted by PAS staining. (b) A closer look at the tumor showing sheets of malignant cells, pseudoglandular and hepatoid components (green arrow). Immunohistochemical staining was strongly positive for AFP (c) and positive for CDX2 (d). AFP: alpha-fetoprotein; CDX2: caudal-type homeobox 2.

curative intent, but the role of endoscopic resection and neoadjuvant and adjuvant chemotherapy is unclear [3, 11]. Given the rarity of this variant of gastric cancer, almost all evidence is retrospective in the form of case reports [3, 16]. Although infrequent, there are isolated cases of successful and curative endoscopic resection of AFP-producing gastric cancers. Ishikawa et al described a unique case of AFP-producing gastric cancer which was successfully resected via endoscopic submucosal dissection [17]. At the 1-year follow-up, the patient remained disease free. Similarly, Hirasaki et al shared a unique case of AFP-producing early gastric cancer that was managed through a hybrid approach [18]. The patient underwent endoscopic mucosal resection followed by distal gastrectomy with lymph node dissection. Interval tumor marker levels show no evidence of disease recurrence 3 years after intervention.

Due to the paucity of data on this HAS [19], there are no clear National Comprehensive Cancer Network (NCCN) guidelines for the treatment of advanced stages of the disease [11, 19]. Patients with advanced HAS have limited therapeutic options, and palliative chemotherapy is the mainstay of treatment [3, 19]. Cisplatin-based chemotherapy regimens have been used in some cases, resulting in mixed results [11]. Palliative gastrectomy and resection of hepatic metastases have also

been reported in some studies, but data are limited [11]. Our patient did not tolerate cisplatin-based palliative chemotherapy and was transitioned to comfort care after a total of four cycles.

Learning points

AFP-HAS is a unique and malignant type of stomach cancer. With a propensity to metastasize to the liver and lymph nodes, HAS has a very poor prognosis and limited therapeutic interventions. Presently, there are no specific chemotherapy treatment protocols for the advanced stages of this disease. Gastrectomy with adjuvant chemotherapy has been used in most cases with limited efficacy. Since current evidence is only in the form of case reports and case series, more studies are needed to understand this malignancy's clinicopathologic features and identify effective treatments.

Acknowledgments

We are grateful to the patient for allowing us to share this interesting case report with the rest of the medical community.

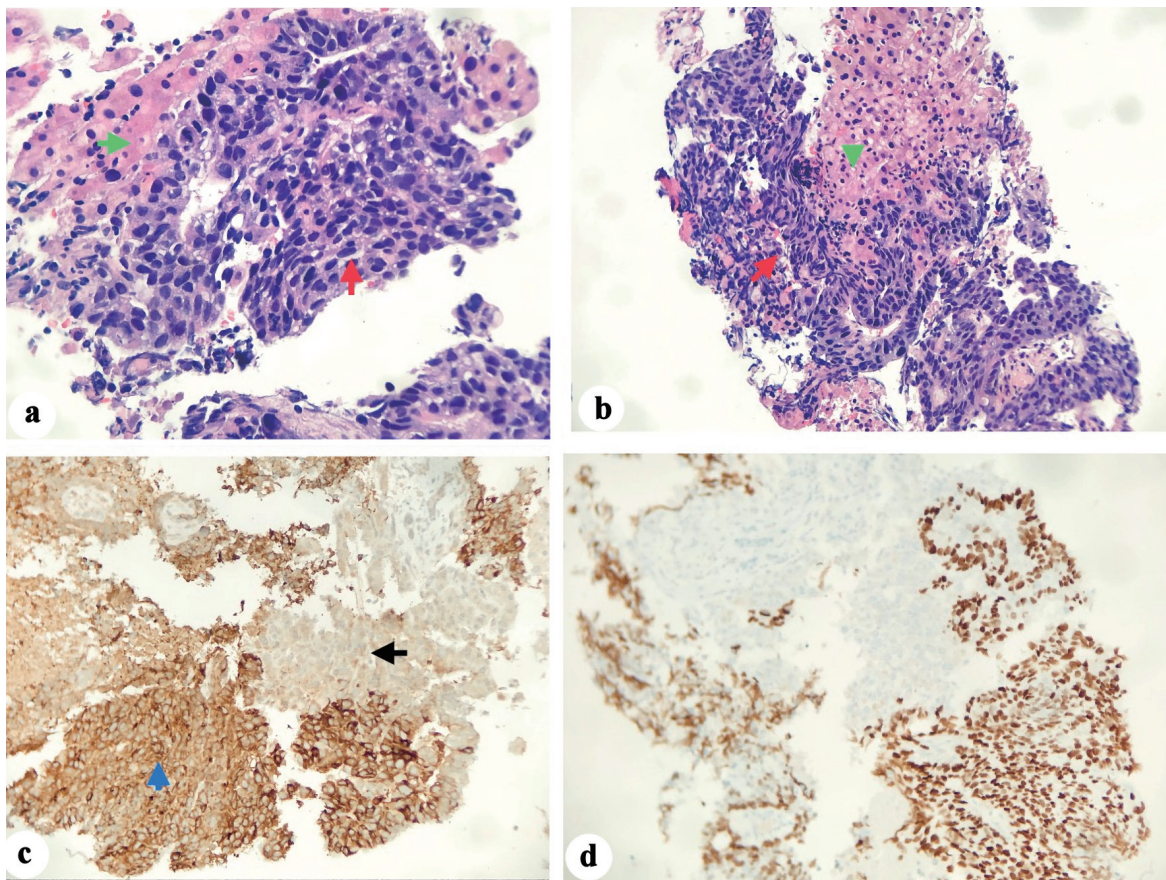


Figure 4. (a, b) The biopsy specimen shows liver parenchyma (green arrows) infiltrated by tumor cells (red arrows) forming nests and rare glands in the background of necrosis. (c) Tumor cells (blue arrow) in the background of normal liver tissue (black arrow). (d) Immunohistochemical staining showed positivity for SALL4 (d), CDX2, and AFP. AFP: alpha-fetoprotein; CDX2: caudal-type homeobox 2; SALL4: Sal-like protein 4.

Financial Disclosure

No funding was obtained for the writing or submission of this case report.

Conflict of Interest

A portion of this case report was presented as a poster at the American College of Gastroenterology Annual Conference, in October 2023, and published as an abstract in the American Journal of Gastroenterology.

Informed Consent

The patient consented to the publication of this case report.

Author Contributions

LB and ME conceptualized the idea for this case report and

crafted an outline. AM, JK, RY, and GM wrote some sections of the case report. AA prepared the pathology slides and helped with the interpretations. YC and WB edited and proofread the final version of this case report.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

HAS: hepatoid adenocarcinoma of the stomach; AFP: alpha-fetoprotein; AFP-HAS: alpha-fetoprotein-producing hepatoid adenocarcinoma of the stomach; ER: emergency room; CA 19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; CECT: contrast-enhanced computed tomography; CDX2: caudal-type homeobox 2; SALL4: Sal-like protein 4; ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma; TCGA: Cancer Genome Atlas Program; NCCN: National Comprehensive Cancer Network

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