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Illuminating and Instructive Clinical Case

Hepatocellular Carcinoma with Gastric Metastasis Mimicking a 4 cm Gastrointestinal Stromal Tumor After a 3-year Disease-free Interval

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive tumor that usually occurs in patients with chronic liver disease and cirrhosis. Surgical resection is an optimal treatment for HCC, but the 5-year recurrence rates are significantly high. The majority of recurrent HCCs occur through intrahepatic metastasis with local tumor progression, and less than 20% of recurrences are extrahepatic metastases. HCC with gastric metastasis is extremely rare, and it is easily misdiagnosed as primary gastric cancer with liver metastasis. An 80-year-old male chronic hepatitis B virus carrier had received lamivudine and entecavir for years and was regularly followed up in the clinic. He had a 3.5 cm solitary HCC with microvascular invasion and received curative surgical resection in 2009. In 2013, he developed a 1.3 cm solitary HCC again and was treated with combination therapy with radiofrequency ablation and pure ethanol injection. Afterwards, he was followed every 3–6 months and was HCC-free. Three years later, in 2016, endoscopy for intermittent epigastralgia showed a solitary 4 cm intraluminal gastric subepithelial tumor without mucosal ulcers or erosions over the gastric fundus. All imaging studies, including computed tomography, favored the diagnosis of gastrointestinal stromal tumor (GIST), but the pathology of the tumor proved to be HCC. The patient did not receive any systemic anticancer therapy but only wedge resection of the stomach and remained tumor- and HCC-free until his latest clinic visit in 2023. The current case is unique and indicates the possibility of HCC with late solitary gastric metastasis mimicking GIST. Complete gastric tumor resection ensured an extremely good outcome for the patient, which is different from the devastating prognosis of most cases of HCC with gastric metastasis.

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Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor that usually occurs in patients with chronic liver disease and cirrhosis. Surgical resection is an optimal treatment for HCC, but the 5-year recurrence rates are significantly high.[1] The majority of recurrent HCC cases occur through intrahepatic metastasis with local tumor progression, and less than 20% of recurrences are extrahepatic metastases.[2] HCC tends to metastasize to extrahepatic organs by direct invasion to surrounding organs, by lymphatic routes to regional lymph nodes and by hematogenous routes to distant organs.[2] Recurrent extrahepatic HCCs usually occur in the lung, bone, heart and regional lymph nodes.[2] HCC with gastric metastasis is extremely rare, and it is easily misdiagnosed as primary gastric cancer with liver metastasis. Here, we report a unique case of HCC with gastric metastasis mimicking a 4 cm gastrointestinal stromal tumor (GIST) after a 3-year HCC-free interval. The patient did not receive any systemic anticancer therapy and remained tumor- and HCC-free after wedge resection of the stomach.

Case report

An 80-year-old man has been followed up at our clinic since 1979, when a liver biopsy showed chronic active hepatitis B virus (HBV) infection. He had received lamivudine and entecavir (ETV) therapies for years. The last antiviral therapy course was terminated in November 2008, which was followed by an alanine aminotransferase (ALT) level that was persistently <2 times the upper limit of normal. During regular surveillance using ultrasonography and alpha-fetoprotein (AFP), a solitary HCC was detected in October 2009. Curative

Keywords: Hepatocellular carcinoma; Hepatitis B virus; Gastric; Gastrointestinal stromal tumor.
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; CT, computed tomography; ETV, entecavir; GIST, gastrointestinal stromal tumor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IHC, immunohistochemical.
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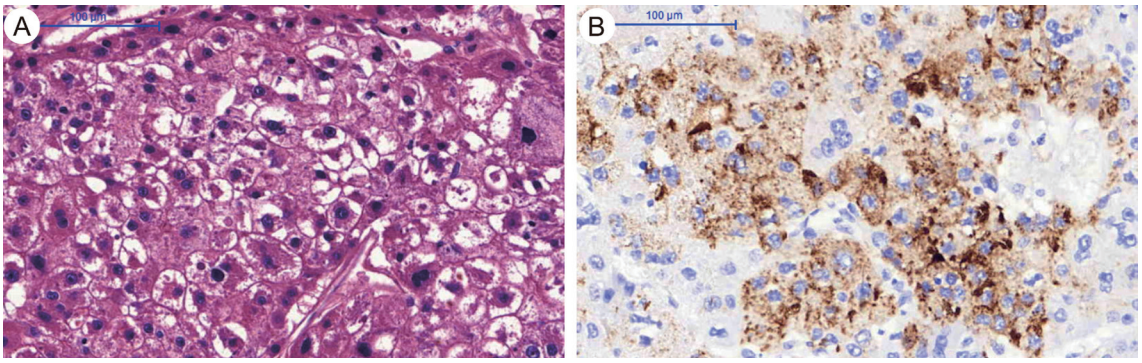

Fig. 1. IHC studies of the liver HCC resected in 2009. (A) Hematoxylin and eosin staining show typical HCC features with large polygonal hyperchromatic tumor cells arranged in broad trabecular patterns. (B) Positive glypican-3 stain (brown) in the tumor cells confirmed the diagnosis of HCC. IHC, immunohistochemical; HCC hepatocellular carcinoma.

surgical resection showed a 3.5 cm HCC with microvascular invasion (Fig. 1). The Ishak score of the non-HCC part of the liver tissue was 0/0/1/2/4, namely, the liver was not cirrhotic. He received ETV again between January 2011 and January 2014 for HBV relapse. During ETV therapy, a 1.3 cm HCC was detected by computed tomography (CT) in February 2013. His serum AFP increased to 8.7 ng/mL and returned to 3.5 ng/mL after combination therapy with radiofrequency ablation (commonly known as RFA) and pure ethanol injection (commonly known as PEI) in February 2013. Afterwards, he was followed every 3–6 months and was HCC-free with persistently normal ALT levels despite virological relapse of HBV in January 2015. In January 2016, endoscopy for intermittent epigastralgia showed a solitary 4 cm intraluminal gastric subepithelial tumor without mucosal ulcers or erosions over the gastric fundus (Fig. 2A). No esophageal or gastric varices were found. Both endoscopic ultrasonography (EUS) (Fig. 2B) and enhanced abdominal CT (Fig. 2C and Supplementary Fig. 1) favored the diagnosis of a solitary gastric GIST without any portal venous tumor thrombi, regional lymph nodes or distant metastasis. Wedge resection of the stomach showed a 4 cm × 4 cm submucosal tumor with intact gastric mucosa, which was an HCC that was well circumscribed by the muscular wall (Fig. 2E, F). The AFP levels both prior to and after gastric resection were within the normal range (<3.5 ng/mL). It was very similar to the original HCC in terms of pathologic findings (Fig. 1A). An additional immunohistochemical (IHC) study with glypican 3[3] and HepPar1[4] staining confirmed the diagnosis of metastatic HCC in the stomach (Fig. 2G and H). The IHC study with the GIST marker c-KIT showed negative findings (Supplementary Fig. 2) and excluded the possibility of mixed tumors of HCC and GIST. The patient did not receive any systemic anticancer therapy, such as sorafenib, because of drug-related toxicity, and because the overall survival using sorafenib is only marginally improved, with a 2.8 month prolongation.[5] Unexpectedly, he remained tumor- and HCC-free up to his latest CT in January 2020 (Fig. 2D) and a clinic visit in April 2023.

Discussion

For solitary gastric GISTs of 2–5 cm without malignant features under EUS, tumor resection is indicated even without tissue proof before surgery. Whether adjuvant therapy is required for GIST depends on the mitotic figures of the resected tissue sample.[6] Therefore, the patient received the operation before tumor biopsy. On the other hand, stomach involvement of HCC is rare and is usually due to direct invasion of HCC via adhesion to the serosal side of the stomach by a large, protruding tumor or through retrograde hematogenous metastasis via the left gastric vein in patients with cirrhosis and portal hypertension.[7] Such metastasis is caused by HCC complicated by tumor thrombi in the portal vein system that are disseminated by hepatofugal portal blood flow to the stomach.[8,9] Thus, HCC with gastric metastasis generally occurs in patients with advanced-stage HCC with a large tumor burden and tumor thrombosis in the portal vein.[2,3] Most patients with HCC with gastric metastasis survive <5 months.[10] Although there was no portal venous tumor thrombi or regional lymph node metastasis, the patient of the current case indeed presented distant metastatic HCC and was supposed to receive adjuvant therapy in addition to tumor resection for systemic tumor control.[11] Ten years ago, sorafenib was the only feasible adjuvant therapy in resected HCC patients and as a frontline systemic treatment in patients with HCC recurrence. However, sorafenib has poor oral bioavailability and is associated with significant drug toxicities, and it only marginally improves the overall survival of patients by 2.8 months.[5] The patient refused to receive sorafenib after an explanation of the risks and benefits. Nevertheless, the current case is unique in that the tumor mimicked a solitary GIST, there was neither a residual viable HCC in the remaining liver nor evidence of liver cirrhosis and portal hypertension, and both his portal and hepatic venous systems were patent. Whether the combined therapy of RFA and PEI induced a transient elevation of portal venous pressure during the procedure and led to the existing tumor emboli inside the hepatofugal portal vein spreading into the left gastric vein or other collateral circulation to elicit gastric metastasis remains uncertain. However, procedure-related tumor emboli, if any, might be tiny since the patient had a 3-year HCC-free lag period from the last emergence of liver HCC in 2013 to HCC with gastric metastasis in 2016. Moreover, the patient remained in good health and HCC-free for over 6 years. The unexpectedly good prognosis of this patient might result from the complete resection of gastric metastatic HCC, of which the well circumscribed muscular wall inhibited local spreading of the tumor; the treatment of prior early-stage liver HCCs with effective local treatments, which diminished intrahepatic or other extrahepatic metastasis; and the use of previous anti-HBV therapy to control HBV infection and associated HCC risks.[12]

In conclusion, the current case is unique and indicates the possibility of HCC with late solitary gastric metastasis mim-

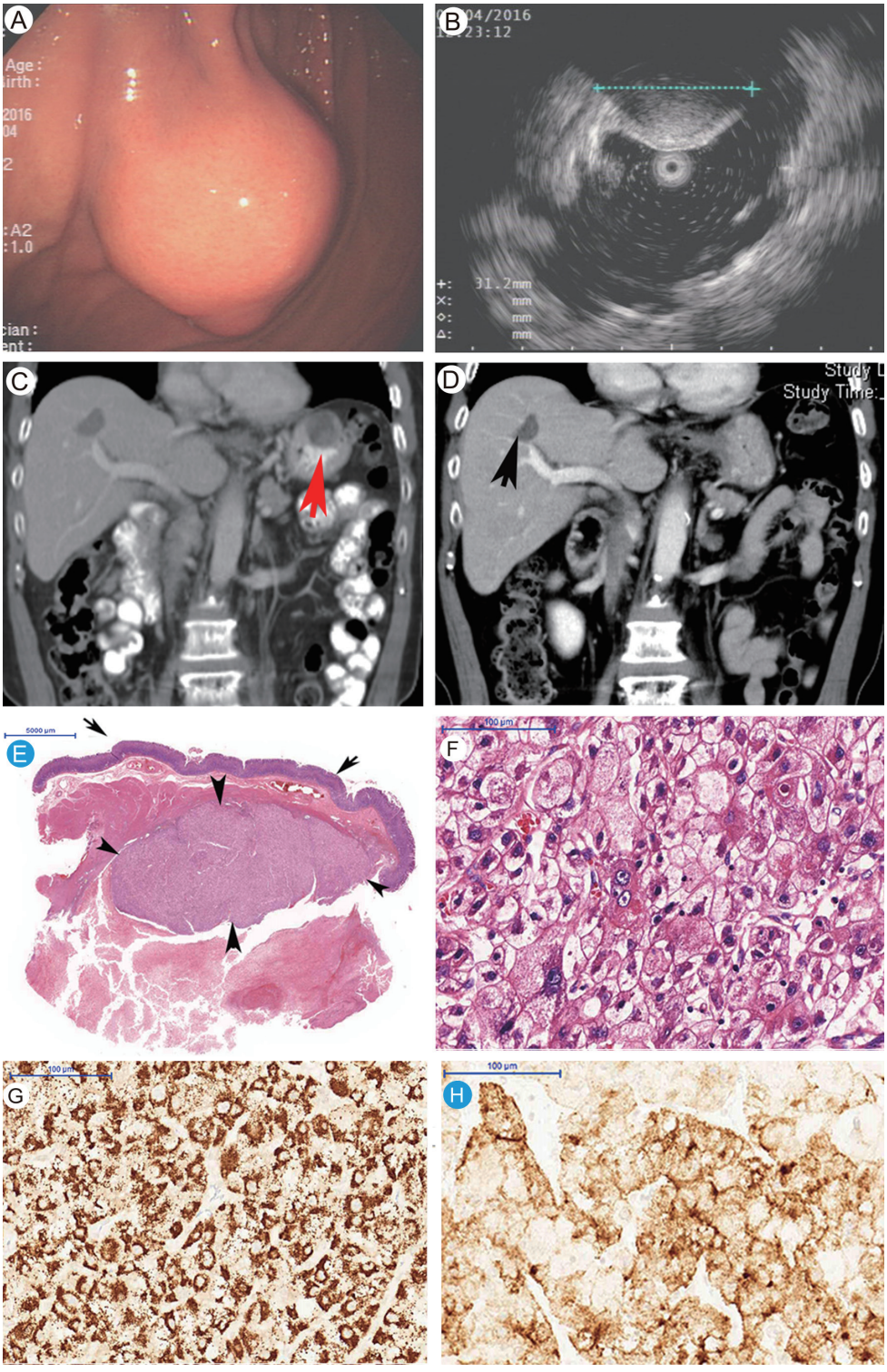

Fig. 2. Endoscopy and staining analyses. (A) A protruding submucosal mass lesion at the gastric fundus with intact mucosa without converged gastric folds. (B) Endoscopic ultrasound shows a well-defined subepithelial homogenous hyperechoic mass lesion arising from the muscularis propria layer favoring GIST. No regional lymph nodes were detected. (C) The venous phase of the contrast-enhanced CT scan showed a hypodense submucosal mass lesion over the gastric fundus (red arrow). (D) A contrast-enhanced CT scan in January 2020 showed a hypodense liver mass lesion near the adjacent right anterior branch portal vein favoring segment 8 HCC after complete RF ablation, with no evidence of recurrent HCC (black arrow). Hematoxylin and eosin staining of the resected gastric tissue shows a muscular wall well-circumscribed tumor (arrowheads). The arrows outline the intact mucosal layer. (F) The tumor cells are large with hyperchromatic nuclei and abundant pale pink cytoplasm arranged in broad trabecular patterns. (G-H) Both HepPar1 (brown) (G) and glypican 3 stains (H) (brown) were positive in the tumor cells. CT, computed tomography; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma.

icking GIST. In particular, complete gastric tumor resection ensured an extremely good outcome for the patient, which is different from the devastating prognosis of most cases of HCC with gastric metastasis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Drafted the article and analyzed the data (WTC), drafted the article and performed the immunohistochemistry (SFKH), drafted the article and critically revised it for intellectual content (MLC, YFL), and read and approved the final version of the article, including the authorship list (all authors).

Consent for publication

The patient's consent for publication had been provided.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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