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【 CASE REPORT 】

Hemorrhagic Gastric Metastasis from Hepatocellular Carcinoma Successfully Treated Using Coil Embolization of the Left Gastric Artery

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Abstract:

A 62-year-old man initially underwent transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma (HCC). One year after the initial treatment, he developed anemia. Upper gastrointestinal endoscopy revealed irregularly elevated tumors in the lower anterior gastric body, which were diagnosed to be metastasis from HCC. Left gastric artery coil embolization was performed to prevent sustained bleeding, and his anemia partially improved. In addition to direct invasion, hematogenous metastasis to the stomach from HCC is possible and therefore should be considered during treatment. Transcatheter arterial embolization for gastric metastasis is an effective treatment method which achieves a good degree of hemostasis in patients without any surgical indications.

Key words: glypican-3, hepatocellular carcinoma, metastasis, hemostasis, transcatheter arterial embolization

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Introduction

Extrahepatic metastasis of hepatocellular carcinoma (HCC) occurs in around 30%-50% of all HCC cases. The most common metastatic sites are the lungs, lymph nodes, and bone (1-6); however, gastric metastasis from HCC is extremely rare. Gastric metastasis usually occurs by the direct invasion of a contiguous neoplasm, and metastasis via hematogenous spread is uncommon (7). We herein report a possible pathway for retrograde hematogenous metastasis of HCC to the stomach.

Case Report

A 62-year-old male was admitted to hospital for the evaluation and treatment of an abdominal mass in the right hypochondrium. The patient's medical records showed no items of note or a history of smoking. The patient has drunk from 500 to 1,000 ml of beer daily for 40 years. There were no apparent abnormalities with the upper gastrointestinal endoscopy findings. Contrast-enhanced computed tomography (CT) showed a 17 cm liver tumor located in the right hepatic lobe, depicted as a slightly hypovascular lesion in the arterial phase, showing gradual enhancement on the portal venous phase, and a hypervasular peripheral capsule (Fig. 1-A). A 6 cm liver tumor with an identical enhancing pattern was found to be located in the left lobe (S3), as well as swelling of the periportal lymph node. The serum alpha fetoprotein (AFP) levels were 56,388 ng/mL, the AFP-L3 fraction was 35.8%, des-gamma-carboxy prothrombin was 347 mAU/mL, and the Child-Pugh score was 6 (grade A). HCC was suspected because of a background of alcoholic liver injury, and a percutaneous liver tumor biopsy was performed as the imaging results were not typical. Different sizes of prominent, round, polymorphic atypical cells were

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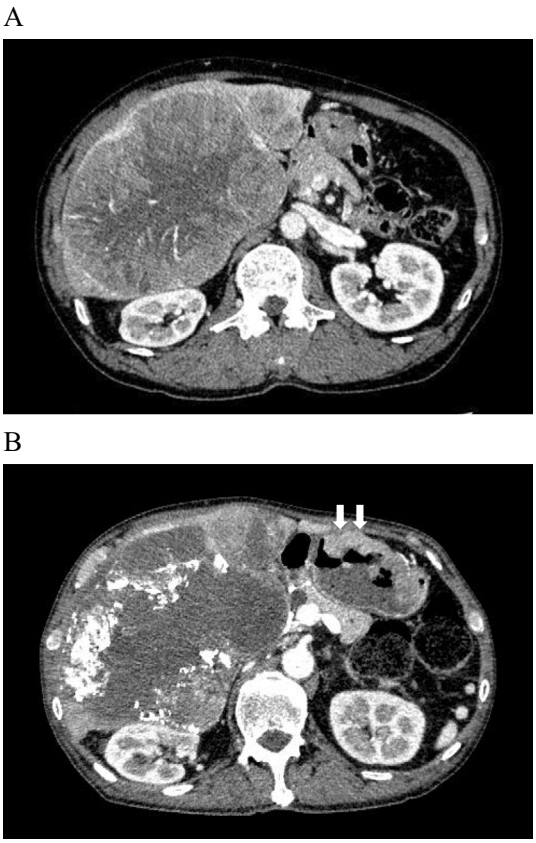

Figure 1. **(A) Contrast-enhanced CT revealed a 17 cm liver tumor located in the right hepatic lobe, depicted as a slightly hypovascular lesion in the arterial phase, showing gradual enhancement on the portal venous phase, and a hypervasular peripheral capsule. (B) CT at the time of diagnosis of gastric metastasis (arrows) showed no evidence of direct infiltration into the stomach from HCC and lymph node metastases.**

observed growing in sheets, while necrotic changes were evident, however, lumen formation was unclear. Immunostaining was positive for glypican-3, focal positive for AFP, and negative for Cytokeratin (CK) 7 and CK 20 (Fig. 2-A). Based on these results, we diagnosed moderate-to-poorly differentiated HCC. The patient was initially treated with transcatheter arterial chemoembolization (TACE) using drug-eluting beads (HepaSphere 50-100 μm), which was repeated every 2 months. One year after the initial treatment, serum hemoglobin levels were 6.3 g/dL, which was a reduction from a baseline value of 9.4 g/dL. Upper gastrointestinal endoscopy revealed the presence of 45-mm large irregular elevated tumors with partial ulceration at the anterior wall of the lower body of the stomach (Fig. 3). There was no active bleeding identified during observation, but there was a hemorrhagic lesion in which blood smears were observed when coming in contact with water. A biopsy of the gastric tumor showed histological findings similar to those of the liver tumor. An immunohistochemical examination of the tumor revealed it to be positive for glypican-3 and focal positive for AFP and was thus diagnosed to be gastric metastasis of HCC (Fig. 2-B). In addition, direct infiltration into the stomach from HCC and lymph node metastasis was shown to be negative on imaging (Fig. 1-B), thus suggesting hematogenous gastric metastasis. Tumor emboli in the portal vein were confirmed from CT performed at the time of diagnosis of gastric metastasis, so it was inferred that the tumor had spread to the stomach via a retrograde portal vein mechanism. The left gastric artery was treated with transcatheter arterial embolization (TAE) with metallic coils to prevent sustained bleeding (Fig. 4), and the anemia partially improved. No adverse events, such as decreased hepatic reserve or decreased renal function were observed in association with TAE. However, the liver failure caused by HCC gradually worsened, and the patient died 5 months after the diagnosis of gastric metastasis from primary HCC.

Discussion

HCC commonly spreads via multicentric carcinogenesis or intrahepatic metastases arising from a primary HCC (8). The most frequent metastatic sites have previously been reported to be the lungs (53.8%), bones (38.5%), lymph nodes (33.8%), and adrenal glands (16.9%) (3), and only 2.65% have been reported to metastasize to the stomach (9). Gastric metastasis in patients with HCC may occur via hematogenous spread (10) or direct invasion. In a study of the reported cases of hematogenous gastric metastasis of HCC, a male sex was more common, and 71% of patients had portal vein tumor thrombus (11, 12). The macroscopic classifications of HCC were nodular in 70% of cases, massive in 20%, and diffuse in 10% (11, 12). In line with previous reports of high levels of AFP observed in many cases, our case also showed abnormally high levels. Although the location of gastric metastasis is not consistent, Borrmann type 2 is considered the most common macroscopic type (13). Hematogenous metastasis of HCC to the stomach is believed to lead to the growth of hematogenously infiltrated tumor cells in the gastric submucosa, rupture of the muscularis mucosae, and the development of submucosal tumors (11). Moreover, as the tumor progresses, central necrosis is thought to cause depressive changes. The macroscopic appearance of the tumor may vary depending on the time of observation (11). In this case, it was identified as a Borrmann type III irregular ulcerative lesion, and it was thought that the original shape of the submucosal tumor had changed due to the tumor collapsing by the time we observed it. The type of metastasis in this case showed no direct infiltration of HCC to the stomach, no peritoneal metastasis, and no clear metastasis to other organs, so it was thought to be hematogenous metastasis. There are two possible routes of hematogenous metastasis to the stomach: the portal-systemic circulation and the retrograde portal vein. It is thought that the presence of tumor thrombi in the portal vein leads to planktonic cancer cells in the portal vein draining retrogradely into the gastric venous system and then becoming implanted into the intramural vein of the stomach (14, 15). In the present case, the tumor thrombus in the

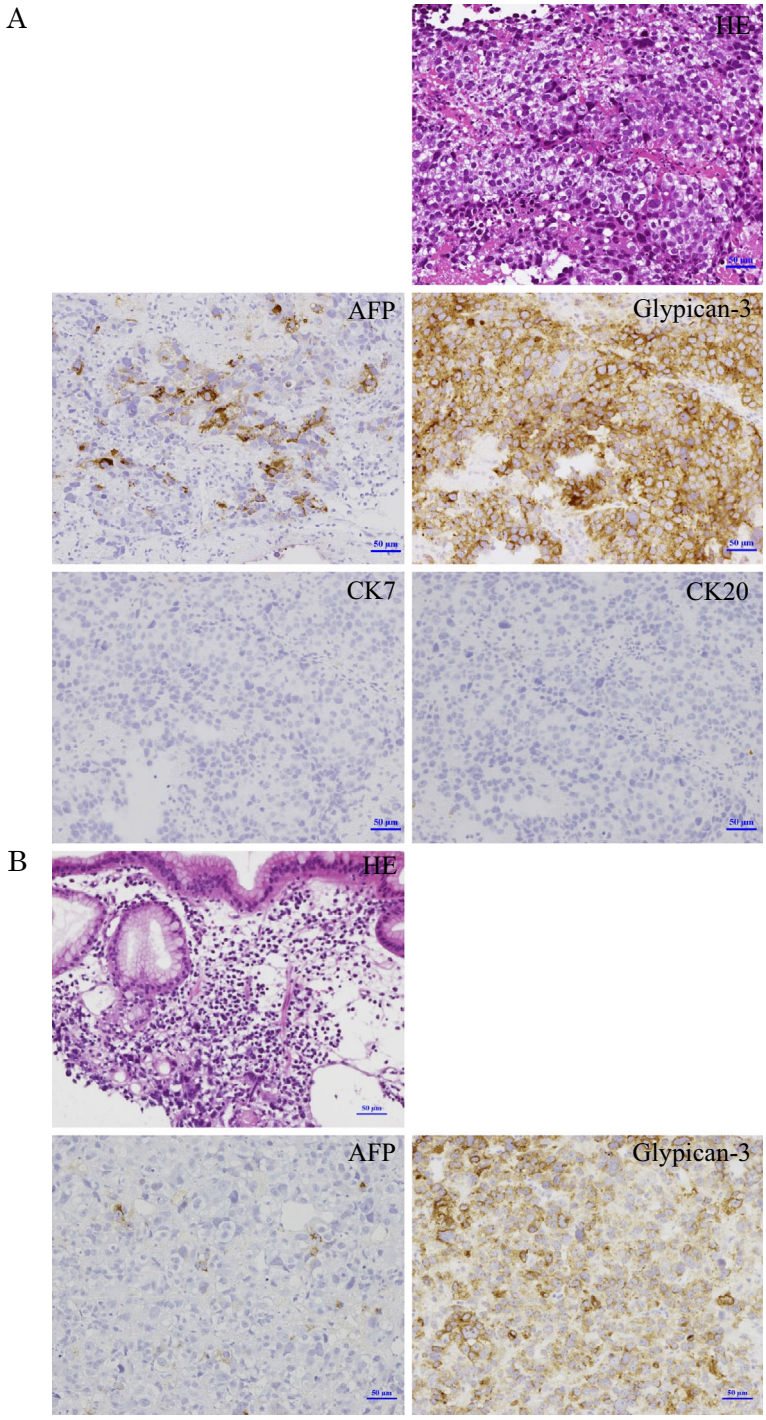

Figure 2. **(A) Hematoxylin and Eosin (H&E) staining showed different sized prominent, round, polymorphic atypical cells to be observed growing in sheets, while necrotic changes were evident, however, lumen formation was unclear. An immunohistochemical examination of the liver tumor showed it to be positive for glypican-3, focal positive for AFP, and negative for CK 7 and CK 20, leading to a diagnosis as HCC. (B) H&E staining showed histological findings similar to those of the liver tumor. An immunohistochemical examination of the gastric tumor showed it to be positive for glypican-3 and focal positive for AFP, leading to a diagnosis of gastric metastasis of HCC.**

portal vein was detected by CT at the time of thediagnosis of gastric metastasis, suggesting that the tumor had metastasized via a retrograde portal vein mechanism. We speculated that a hematogenous pathway exists for gastric metastasis of tumor thrombi involving the hepatofugal flow to the stomach after TAE independent of the major pathway of direct invasion. A histopathological diagnosis including immunostaining is useful for the diagnosis of HCC and metastatic gastric tumors (16, 17). In the present case, the histopathological findings of the HCC and gastric tumor were compared, thus leading to a diagnosis of gastric metastasis from HCC. Immunohistochemical staining showed that glypican-3

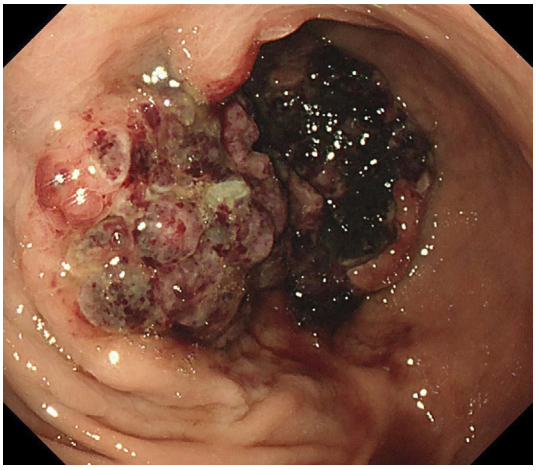

Figure 3. **Upper gastrointestinal endoscopy revealed irregularly elevated tumors with partial ulceration at the anterior wall of the lower body of the stomach.**

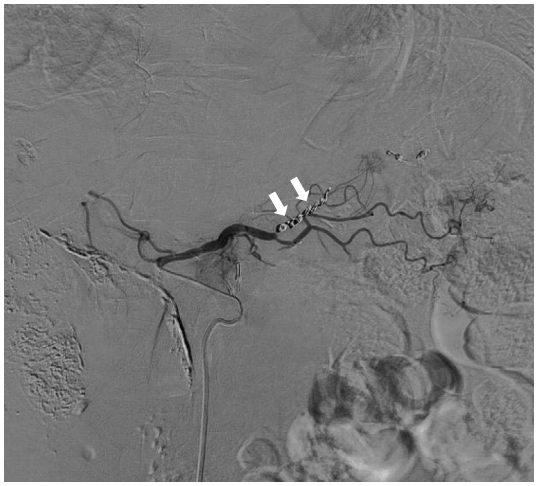

Figure 4. **The left gastric artery was treated using TAE with metallic coils (arrow) to prevent sustained bleeding. AFP: alpha fetoprotein, CK: Cytokeratin, CT: computed tomography, HCC: hepatocellular carcinoma, TAE: transcatheter arterial embolization**

was positive in the present case, but hepatocyte paraffin 1 (HepPar-1) and arginase-1 were negative. Immunohistochemical staining for HepPar-1 and arginase-1 have been reported to have a higher rate of positivity with increasing degree of tumor differentiation (18), which was considered to be negative in the present case due to poor differentiation of the HCC. In addition, AFP-producing gastric cancer also was included in the differential diagnosis, but glypican-3 positivity was a contradictory finding. There are reports that even AFP-producing gastric carcinoma may demonstrate a positive result for glypican-3 (19), so it was thought that hepatic metastasis from AFP-producing gastric carcinoma was a possibility. However, because no gastric lesions were identified as a result of the upper gastrointestinal endoscopy performed prior to the initial treatment, gastric metastasis from HCC was therefore thought to be a more valid diagnosis. The current treatments for gastric metastases from HCC include surgery, systemic chemotherapy, TACE, and TAE (20-22); however, surgery is often difficult because of the poor performance status and poor hepatic reserve. In the present case, the anemia in the patient improved after performing TAE, which is a minimally invasive treatment. I selected the left gastric artery as the site of TAE because the range of the blood flow shown through contrast radiography of the left gastric artery appeared to be in nearly the same position as the marking clip attached under the endoscope in the vicinity of the gastric tumor prior to TAE. Left gastric arteriography showed no extravascular leakage, but coil embolization of the vessel around the marking clip resulted in a certain degree of hemostasis. As observed in our case, it is very useful to place a marking clip around a gastric lesion before performing hemostatic TAE. In reported cases of transcatheter arterial embolization for bleeding caused by advanced gastric cancer, the left gastric artery is often selected (23).

Conclusion

In addition to direct invasion, hematogenous metastasis to the stomach from HCC is possible and therefore should be considered during treatment. TAE for gastric metastasis of HCC is thought to be an effective treatment method, with minimal invasion and a good degree of hemostasis can be obtained in patients that are considered to be unsuitable for radical surgery.

The authors state that they have no Conflict of Interest (COI).

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References

1. Sawabe M, Nakamura T, Kanno J, Kasuga T. Analysis of morphological factors of hepatocellular carcinoma in 98 autopsy cases with respect to pulmonary metastasis. Acta Pathol Jpn **37**: 1389-1404, 1987.
2. Katyal S, Oliver JH, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastasis of hepatocellular carcinoma. Radiology **216**: 698-703, 2000.
3. Natsuizaka M, Omura T, Akaike T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastasis. J Gastroenterol Hepatol **20**: 1781-1787, 2005.
4. Watanabe J, Nakashima O, Kojiro M. Clinicopathologic study on lymph node metastasis of hepatocellular carcinoma: A retrospective study of 660 consecutive autopsy cases. Jpn J Clin Oncol **24**: 37-41, 1994.
5. Anthony PP. Primary carcinoma of the liver: A study of 282 cases in Ugandan Africans. J Pathology **110**: 37-48, 1973.
6. Nakashima T, Okuda K, Kojiro M, et al. Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer **51**: 863-877, 1983.
7. Lin CP, Cheng JS, Lai KH, et al. Gastrointestinal metastasis in he-

patocellular carcinoma: Radiological and endoscopic studies of 11 cases. J Gastroenterol Hepatol **15**: 536-541, 2000.

8. Feo F, Pascale RM. Multifocal hepatocellular carcinoma: intrahepatic metastasis or multicentric carcinogenesis? Ann Transl Med **3**: 4, 2015.

9. Oda I, Kondo H, Yamao T, et al. Metastatic tumors to the stomach: analysis of 54 patients diagnosed at endoscopy and 347 autopsy cases. Endoscopy **33**: 507-510, 2001.

10. Hu ML, Tai WC, Chuah SK, et al. Gastric metastasis of hepatocellular carcinoma via a possible existing retrograde hematogenous pathway. J Gastroenterol Hepatol **25**: 408-412, 2010.

11. Shibata T, Nakano S, Kitamura K, et al. A case of a metastatic hepatocellular carcinoma to the stomach via blood stream. Nihon Shokakibyo Gakkai Zasshi **78**: 1998-2002, 1981 (in Japanese, Abstract in English).

12. Kumai T, Suzuki T, Kobayashi E, et al. A case of a metastatic hepatocellular carcinoma to the stomach--review of Japanese literature. Nihon Shokakibyo Gakkai Zasshi **88**: 749-753, 1991 (in Japanese, Abstract in English).

13. Makino H, Takazakura E, Nakamura S, et al. Hepatocellular carcinoma with metastatic gastric cancer simulating Borrmann type 2 and hyperlipidemia. Acta Pathol Jpn **36**: 577-586, 1986.

14. Nakajima K, Hosono T, Murao S, Nakajima T, Hanada M, Yoshii M. Retrograde metastasis of hepatocellular carcinoma with an interesting lesion of the stomach--a case report. Gan No Rinsho **32**: 203-208, 1986 (in Japanese, Abstract in English).

15. Miyaki E, Waki K, Tsuji K, et al. A case report of hepatocellular carcinoma with metastases to the lip, stomach, and colorectum. Nihon Shokakibyo Gakkai Zasshi **111**: 535-542, 2014 (in Japanese, Abstract in English).

16. Terada T, Maruo H. Unusual extrahepatic metastatic sites from hepatocellular carcinoma. Int J Clin Exp Pathol **6**: 816-820, 2013.

17. Ibrahim TR, Abdel-Raouf SM. Immunohistochemical study of Glypican-3 and HepPar-1 in differentiating hepatocellular carcinoma from metastatic carcinomas in FNA of the liver. Pathol Oncol Res **21**: 379-387, 2015.

18. Yan BC, Gong C, Song J, et al. Arginase-1: A new immunohistochemical marker of hepatocytes and hepatocellular neoplasms. Am J Surg Pathol **34**: 1147-1154, 2010.

19. Kinjo T, Taniguchi H, Kushima R, et al. Histologic and immunohistochemical analyses of α-fetoprotein--producing cancer of the stomach. Am J Surg Pathol **36**: 56-65, 2012.

20. Haruki K, Misawa T, Gocho T, et al. Hepatocellular carcinoma with gastric metastasis treated by simultaneous hepatic and gastric resection: report of a case. Clin J Gastroenterol **9**: 319-323, 2016.

21. Kim JH, Park JW, Choi JI, et al. Gastric metastasis of hepatocellular carcinoma treated by transarterial chemoembolization: a case report. Korean J Hepatol **13**: 91-95, 2007.

22. Inagaki Y, Shiraki K, Takei Y. Gastric metastasis of hepatocellular carcinoma presenting as hematemesis. Clin Gastroenterol Hepatol **12**: A16-A17, 2014.

23. Hiraki Y, Kimura Y, Makari Y, et al. Three Cases of Bleeding from Advanced Gastric Cancer Treated by Transcatheter Arterial Embolization(TAE)and Continued Chemotherapy. Gan To Kagaku Ryoho **42**: 1965-1967, 2015 (in Japanese, Abstract in English).