Pseudocirrhosis in Gastric Cancer with Diffuse Liver Metastases after a Dramatic Response to Chemotherapy

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Key Words

Pseudocirrhosis · Gastric cancer · Chemotherapy

Abstract

We present the first reported case of pseudocirrhosis arising after a dramatic response to chemotherapy in metastatic gastric cancer. A 74-year-old man was diagnosed with gastric adenocarcinoma having multiple liver metastases. His general condition was poor, with an Eastern Cooperative Oncology Group performance status of 3, inadequate oral intake, and jaundice (total bilirubin 2.8 mg/dl). Chemotherapy with oxaliplatin, L-leucovorin, and 5-fluorouracil (modified FOLFOX-6) was initiated. After four treatment cycles, he experienced a marked regression of liver metastases; however, he developed massive ascites with a lobular liver surface and segmental atrophy, which were consistent with pseudocirrhosis. Chemotherapy was continued along with ascites management. Thereafter, ascites disappeared, and a complete response of the metastatic lesions was achieved at 11 months after initial treatment. He had no evidence of disease progression at 30 months after initial chemotherapy. This report suggests clinicians should recognize this entity, even in gastric cancer metastatic to the liver.

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Introduction

Pseudocirrhosis is a radiological term that refers to the development of diffuse hepatic nodularity in patients with cancer metastatic to the liver [1]. It is characterized by morphological changes resembling liver cirrhosis, such as a lobular hepatic contour, retraction of the capsular surface, segmental atrophy, and enlargement of the caudate lobe [2]. Although pseudocirrhosis often lacks the typical pathological features of cirrhosis, the clinical manifestations of portal hypertension, such as ascites and varices, and hepatic failure can be fatal as they are common in classic liver cirrhosis [3–8]. Pseudocirrhosis has mostly been observed in patients with breast cancer metastatic to the liver [5–7, 9–11] but is uncommon in other malignancies. There are only sporadic reports in thyroid [3], pancreatic [12], esophageal [13], small-cell lung [14], and colon cancers [15]. Here, we report the first case of a patient with metastatic gastric cancer who developed pseudocirrhosis during a dramatic response to chemotherapy.

Case Report

A 74-year-old man who developed anorexia, a sense of abdominal distension, and general malaise was referred to our hospital with a diagnosis of gastric adenocarcinoma. Upper gastrointestinal endoscopy revealed a type 2 advanced gastric cancer located in the antrum (fig. 1a). Histological examination of biopsy samples revealed well-differentiated adenocarcinoma. Blood chemistry revealed the following findings: albumin, 1.8 mg/dl; aspartate aminotransaminase (AST), 119 IU/l; alanine aminotransaminase (ALT), 57 IU/l; lactate dehydrogenase, 3,130 IU/l, and total bilirubin, 2.8 mg/dl. Serum concentrations of carcinoembryonic antigen and carbohydrate antigen 19-9 (CA 19-9) were highly elevated to 1,358.0 ng/ml and 291.9 U/ml, respectively. An abdominal computed tomography (CT) revealed multiple liver metastases, enlargement of both hepatic lobes, and a small amount of ascites in the perihepatic space (fig. 1b). His oral intake was poor, and he had an Eastern Cooperative Oncology Group performance status of 3. Although we proposed the best supportive care, the patient and his family strongly wished to receive chemotherapy. Therefore, a modified FOLFOX-6 regimen (85 mg/m² oxaliplatin and 200 mg/m² L-leucovorin as a 2-hour infusion on day 1, followed by a 400-mg/m² bolus of 5-fluorouracil on day 1, and a 46-hour infusion of 2,400 mg/m² 5-fluorouracil) was initiated at 2-week intervals.

After four cycles, CT revealed remarkable regression of the liver metastases with a nodular liver contour, liver volume loss, massive ascites, and pleural effusion (fig. 2a). Splenomegaly was not observed. The patient's condition radiologically mimicked liver cirrhosis. Hypoalbuminemia persisted (albumin 1.8 g/dl); however, his liver enzyme levels normalized (AST, 33 IU/l; ALT, 24 IU/l; lactate dehydrogenase, 182 IU/l, and total bilirubin, 1.8 mg/dl), and the level of tumor markers decreased (carcinoembryonic antigen, 64.0 ng/ml and CA 19-9, 63.4 U/ml). The serum ammonia level was within the upper limit of normal. He had no history of alcohol abuse. Serological studies investigating viral and autoimmune etiologies of cirrhosis were negative. The ascites were transudative, and cytology demonstrated no malignant cells. Treatment comprising abdominal paracentesis and diuretic medications (furosemide and spironolactone) was performed for worsening abdominal distension and peripheral edema. After the ascites reached a manageable level, the patient was discharged and reinitiated chemotherapy with a combination therapy of S-1 and oxaliplatin (oral 40 mg/m² S-1 twice daily for 2 weeks with 100 mg/m² oxaliplatin on day 1 every 3 weeks) on an outpatient basis. CT revealed further regression of the liver metastases and decreased the ascites.

tes 5 months after initial treatment (fig. 2b); the ascites disappeared 8 months after initial treatment (fig. 2c). During tapering of the diuretics, no evidence of increasing ascites was observed, and the serum albumin level recovered to 3.7 g/dl; therefore, diuretics were discontinued. Oxaliplatin was withdrawn from the treatment because of peripheral neuropathy, and S-1 monotherapy was continued.

After 11 months of initial treatment, CT revealed complete remission of the liver metastases (fig. 2d). Upper gastrointestinal endoscopy revealed a red scar instead of the tumor, and no tumor cells were detected in the lesion by biopsy (fig. 2e), leading to the achievement of a complete response. He was maintained on S-1 monotherapy, and a complete response has been maintained for 30 months after initial chemotherapy.

Discussion

To the best of our knowledge, this is the first reported case of pseudocirrhosis arising from metastatic gastric cancer. Most of the reports on pseudocirrhosis have involved metastasis of breast cancer to the liver. Two studies with relatively large cohorts revealed that hepatic contour abnormalities frequently occur in metastatic breast cancer, with incidences of 50% (29 of 58 patients) and 75% (68 of 91 patients), respectively [4, 9]. Diffuse contour abnormalities mimicking cirrhosis were observed in 18% (16 of 91) of patients [4]. In a report by Fennessy et al. [9], this morphological change was closely associated with larger metastases and both increases and decreases in the subjacent lesion size.

The precise mechanism underlying the onset of pseudocirrhosis remains unclear; however, now it is presumed to be attributed to two etiologies: (1) hepatic response and/or hepatotoxic effects to chemotherapy, and (2) diffuse tumor infiltration with desmoplastic reaction [5, 6, 11]. In the former, chemotherapy induces hepatic retraction with a lobular contour by both an increase and decrease in the subjacent tumor size [2, 9]. In the latter, pseudocirrhosis occurs in the absence or presence of prior systemic chemotherapy, and hepatic histology demonstrates extensive tumor infiltration and desmoplastic fibrosis [5, 6, 11]. It is considered that nodular regenerative hyperplasia (NRH), which is characterized by the widespread transformation of normal hepatic parenchyma into regenerative nodules with no or minimal bridging fibrosis, is related to pseudocirrhosis development [2]. In the series by Young et al. [2], 6 of 7 patients with breast cancer, from whom pathological specimens were available, had pathological findings suggestive of NRH. Oxaliplatin, which was administered to our patient, is a well-known causative agent of NRH; however, previous reports did not reveal clear association between specific chemotherapeutic agents or doses and pseudocirrhosis, and further investigation is warranted to clarify its association [4, 9].

The absence of liver biopsy is a major obstacle to our investigation of the pathogenesis of pseudocirrhosis. However, our patient had radiographical findings and a clinical course typical of pseudocirrhosis that rapidly progressed in response to chemotherapy. This supports a report by Young et al. [2] that pseudocirrhosis evolved over 1–3 months in 19 patients with serial CT scans. The increasing amount of ascites due to pseudocirrhosis can be mistaken for disease progression, particularly in gastric cancer with carcinomatous peritonitis, because it is caused by both progression and regression of liver metastases. Considering recent advances in chemotherapeutic agents, this condition may become increasingly frequent. Moreover, complications, such as hepatic encephalopathy and variceal bleeding, are sometimes fatal [3–8]. This indicates that pseudocirrhosis, including classic cirrhosis, has clinical significance and that early recognition and appropriate management are crucial.

In conclusion, this report indicates that pseudocirrhosis can occur while achieving a chemotherapeutic response in metastatic gastric cancer as well as in metastatic breast cancer. Clinicians should recognize pseudocirrhosis and provide appropriate management, even during chemotherapy for gastric cancer.

Statement of Ethics

We declare that written informed consent for publication was obtained from the patient.

Disclosure Statement

The authors declare that they have no potential conflicts of interest.

References

- Sharma A, Houshyar R, Bhosale P, Choi JI, Gulati R, Lall C: Chemotherapy induced liver abnormalities: an imaging perspective. *Clin Mol Hepatol* 2014;20:317–326.
- Young ST, Paulson EK, Washington K, Gulliver DJ, Vredenburg JJ, Baker ME: CT of the liver in patients with metastatic breast carcinoma treated by chemotherapy: findings simulating cirrhosis. *AJR Am J Roentgenol* 1994;163:1385–1388.
- Harry BL, Smith ML, Burton JR Jr, Dasari A, Eckhardt SG, Diamond JR: Medullary thyroid cancer and pseudocirrhosis: case report and literature review. *Curr Oncol* 2012;19:e36–e41.
- Qayyum A, Lee GK, Yeh BM, Allen JN, Venook AP, Coakley FV: Frequency of hepatic contour abnormalities and signs of portal hypertension at CT in patients receiving chemotherapy for breast cancer metastatic to the liver. *Clin Imaging* 2007;31:6–10.
- Sass DA, Clark K, Grzybicki D, Rabinovitz M, Shaw-Stiffel TA: Diffuse desmoplastic metastatic breast cancer simulating cirrhosis with severe portal hypertension: a case of ‘pseudocirrhosis’. *Dig Dis Sci* 2007;52:749–752.
- Nascimento AB, Mitchell DG, Rubin R, Weaver E: Diffuse desmoplastic breast carcinoma metastases to the liver simulating cirrhosis at MR imaging: report of two cases. *Radiology* 2001;221:117–121.
- Chandrakar V, Isaacs C: Breast cancer-related pseudocirrhosis and esophageal varices. *Breast J* 2005;11:301–302.
- Jeong WK, Choi SY, Kim J: Pseudocirrhosis as a complication after chemotherapy for hepatic metastasis from breast cancer. *Clin Mol Hepatol* 2013;19:190–194.
- Fennessy FM, Morteale KJ, Kluckert T, Gogate A, Ondategui-Parra S, Ros P, et al: Hepatic capsular retraction in metastatic carcinoma of the breast occurring with increase or decrease in size of subjacent metastasis. *AJR Am J Roentgenol* 2004;182:651–655.
- Schreiner SA, Gorman B, Stephens DH: Chemotherapy-related hepatotoxicity causing imaging findings resembling cirrhosis. *Mayo Clin Proc* 1998;73:780–783.
- Lee SL, Chang ED, Na SJ, Kim JS, An HJ, Ko YH, et al: Pseudocirrhosis of breast cancer metastases to the liver treated by chemotherapy. *Cancer Res Treat* 2014;46:98–103.
- Kang SP, Taddei T, McLennan B, Lacy J: Pseudocirrhosis in a pancreatic cancer patient with liver metastases: a case report of complete resolution of pseudocirrhosis with an early recognition and management. *World J Gastroenterol* 2008;14:1622–1624.
- Kobashigawa C, Nakamoto M, Hokama A, Hirata T, Kinjo F, Fujita J: Pseudocirrhosis in metastatic esophageal cancer. *South Med J* 2010;103:488–489.
- Ojeda VJ: Metastatic oat cell carcinoma simulating liver cirrhosis. *NZ Med J* 1977;86:480–481.
- Battisti S, Guida FM, Pagliara E, Tonini G, Zobel BB, Santini D: Pseudocirrhosis after anti-EGFR-based neoadjuvant therapy for hepatic metastasis from colon cancer: a different point of view. *Clin Colorectal Cancer* 2014;13:e13–e15.

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Fig. 1. **a** Endoscopic examination reveals type 2 advanced gastric cancer located in the antrum. **b** An initial abdominal CT reveals multiple metastatic lesions in the whole liver and ascites around the perihepatic space.

Fig. 2. **a** CT after four treatment cycles revealed remarkable regression of the liver metastases and increased ascites. The scan also revealed decreased hepatic volume and a lobulation of the hepatic contour, which indicated pseudocirrhosis. Splenomegaly was not observed. **b** CT performed 5 months after initial treatment revealed further regression of the liver metastases and decreased ascites. **c** CT performed 8 months after initial treatment revealed that the ascites had disappeared. **d** CT performed 11 months after initial treatment revealed that the liver metastases had disappeared. **e** Endoscopic examination performed 9 months after initial treatment revealed that the primary tumor had been replaced by a red scar. No tumor cells were detected in a biopsy of the scar tissue.