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Case Report

Long-Term Recurrence-Free Survival After Metachronous Surgery of the Stomach and Liver for Gastric Adenocarcinoma and Multiple, Synchronous Liver Metastases: A Case Report and Review of Literature

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This report describes a 58-year-old woman with gastric adenocarcinoma and liver metastases, who survives for more than 18 years after diagnosis. At diagnosis and first surgery, a moderately differentiated gastric adenocarcinoma with subserosal invasion was detected, along with 2 regional lymph node metastases and 2 liver metastases. She underwent gastrectomy and regional lymph node dissection but did not undergo liver operation then. After gastrectomy, she received adjuvant chemotherapy for 1 month but discontinued it due to severe diarrhea. Another metastasis in another area of the liver was detected, for which she underwent excision of the right lobe of the liver (subsegments 5, 6, and 7) about 30 months later. No signs of recurrence have been detected for 18 years (as of March 2012). This patient represents a rare case of long-term survival of gastric adenocarcinoma without recurrence after surgical treatment, despite multiple, synchronous, liver and regional lymph node metastases.

Key words: Gastric cancer – Liver metastasis – Long-term survivor – Surgical resection

The prognosis for gastric adenocarcinoma with metastasis in the liver is poor, the duration of survival for most patients is quite limited, and there are few curative treatment options. However, there have been a few reports of long-term survival in patients who were surgically treated with complete

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excision of lesions in both the stomach and liver. Here, we report a rare case of long-term survival, without signs of recurrence, in a patient with gastric adenocarcinoma accompanied by multiple synchronous liver metastases.

Case Report

A 58-year-old woman was diagnosed with gastric adenocarcinoma during medical examination at another institution and was subsequently transferred to our hospital. Upper gastrointestinal series, endoscopy, biopsy, computed tomography (CT) scan, and abdominal ultrasonography (US) were performed, which demonstrated gastric adenocarcinoma with 2 metastatic lesions in subsegment 5 of the liver (Fig. 1a). Both the serum carcinoembryonic antigen (CEA) and the carbohydrate antigen 19-9 (CA 19-9) levels were within the normal range. On June 11, 1993, she underwent gastrectomy accompanied by regional lymph node dissection; however, surgery on the liver was not performed. Her postoperative course was uneventful. Macroscopic findings showed advanced gastric cancer type 3, where a part of the surrounding wall was not sharply defined (Fig. 1b). Pathologic findings showed moderately differentiated adenocarcinoma invading into the subserosal layer of the gastric wall (Fig. 2a) and invading both lymphatic vessels (Fig. 2b) and veins (Fig. 2c), as well as metastases to 2 infra-pyloric lymph nodes (Fig. 2d). As postoperative adjuvant chemotherapy, the anticancer drug Mitomycin C (20 mg) was administered intravenously on the day of surgery, and 20 mg/d UFT (Tegafur 800 mg + uracil 1792 mg) was administered orally starting on June 22. However, the administration of adjuvant chemotherapy was discontinued in July due to the development of diarrhea caused by drug toxicity. After discontinuation of adjuvant chemotherapy, the patient underwent abdominal US, abdominal CT scan, and measurement of serum levels of CEA and CA19-9 every 3 to 6 months. Beginning in December 1994 (18 months after gastrectomy), the serum CEA levels began to rise slowly, reaching 31 ng/mL on January 8, 1996. In addition to the previously identified metastatic lesions in subsegment 5 of the liver, the size of which hardly increased, a new metastatic lesion was discovered in subsegment 7 (Fig. 3a). Therefore, 2 years after the initial gastrectomy procedure, hepatectomy (subsegments 5, 6, and 7) was performed on June 10, 1996. Surgical specimens contained all metastatic liver tumors in subsegments 5 and 7 (Fig. 3b). Pathologic findings showed metastatic adenocarcinoma similar to the gastric adenocarcinoma (Fig. 3c) with partial necrosis and no invasive growth pattern. Every metastatic lesion was surrounded with the connective tissue. By 3 months after liver surgery, September 2, 1996, her serum CEA level had rapidly fallen to 0.9 ng/mL, and it has since remained within the normal range. Since July 1993, she has not received any adjuvant chemotherapy, and there have been no signs of recurrence on either US or CT scan, as of March 2012.

Discussion

The survival rates for gastric adenocarcinoma with liver metastasis remain low.[1] Gastric adenocarcinoma with liver metastasis often spreads to other organs, such as the peritoneum, lymph nodes, bones, and lungs. Consequently, the ideal surgical and medical treatment options for gastric adenocarcinoma with liver metastases are not well defined. A lot of clinicians may consider that the standard treatment for the patient with gastric adenocarcinoma and metastatic liver lesions is not surgery but chemotherapy. In this patient too, for the primary gastric adenocarcinoma, gastrectomy and lymph node dissection were done first. Simultaneously, for the metastatic liver tumors, the adjuvant chemotherapy was introduced, but was discontinued because of drug toxicity. Afterwards, the complete excision of metastatic liver tumor was performed. Recently, some effective options of chemotherapy that can prolong survival time of the patient have been developed. However, there are still no options of chemotherapy that can make liver metastatic disease completely disappear. That is, a choice of chemotherapy cannot successfully cure gastric adenocarcinoma accompanied with liver metastasis, but a choice of surgery can mean either palliative or radical treatment even in the patient with multiple liver metastases. Surgical treatment may be able to successfully cure gastric adenocarcinoma accompanied with liver metastasis, when stomach and liver surgery completely excise primary and metastatic lesions, and when a patient can undergo surgical stress. In fact, a small number of cases of long-term survival ($\geq$10 years) in patients with gastric adenocarcinoma and liver metastases have been reported. According to anecdotal reports by some Japanese surgeons, a few patients with gastric adenocarcinoma and liver metastases can undergo curative stomach and liver surgery, and a

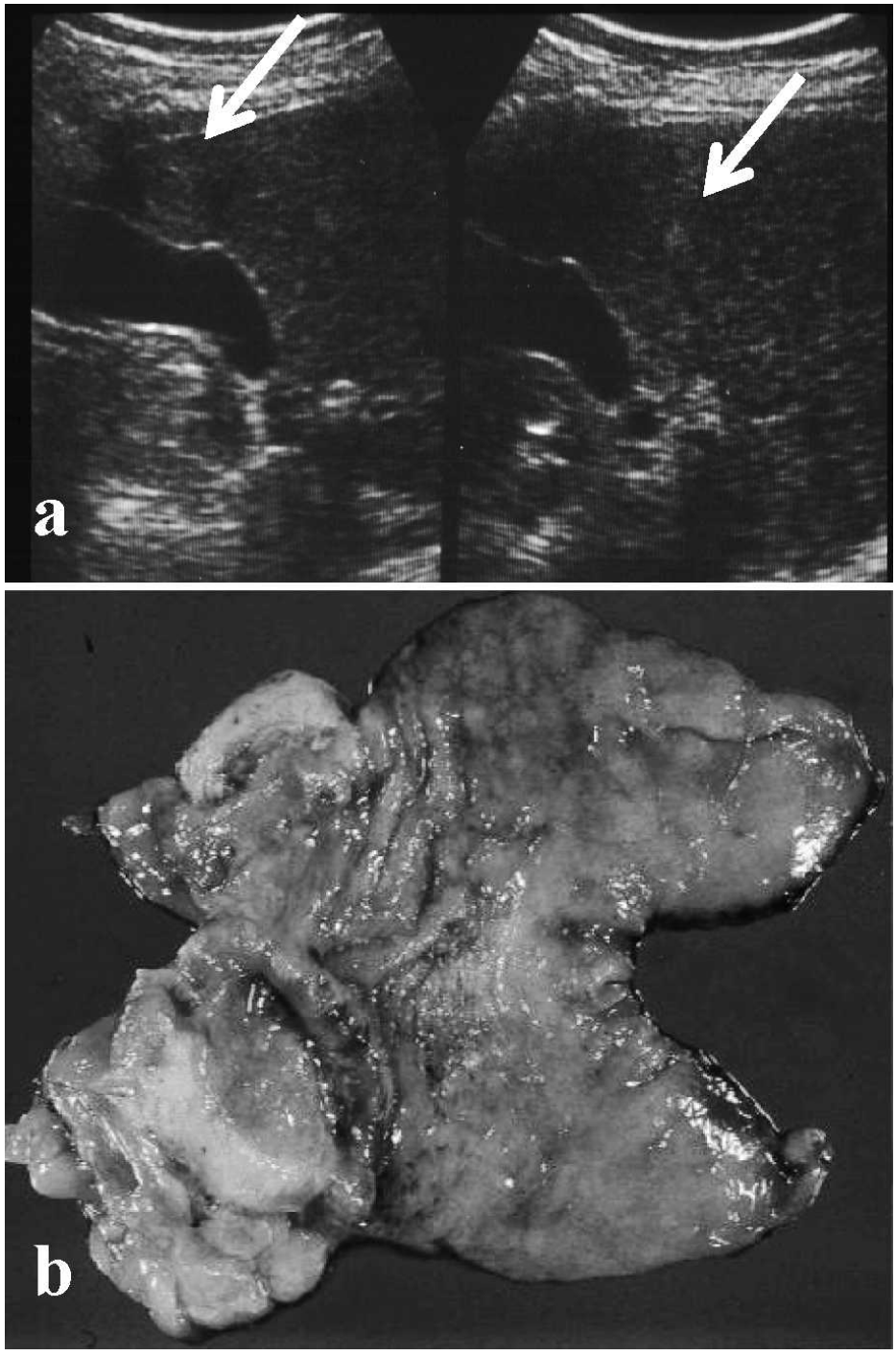

Fig. 1 (a) Ultrasonography of the liver before distal gastrectomy. Two tumor shadows are shown (arrows) in subsegment 5 of the liver. (b) Surgical specimen of the stomach. Diagnosis is advanced gastric adenocarcinoma Type 3 measuring 8.6 × 4.7 cm.

small percentage of these patients go on to live for 10 years or more. As this case suggests, under limited conditions, both stomach and liver surgery are useful treatments for patients with gastric adenocarcinoma and liver metastases.

As previously stated, Japanese surgeons report that the complete surgical excision of the stomach lesion and the affected portions of the liver is such a significant basic treatment that some patients with gastric adenocarcinoma and liver metastases might

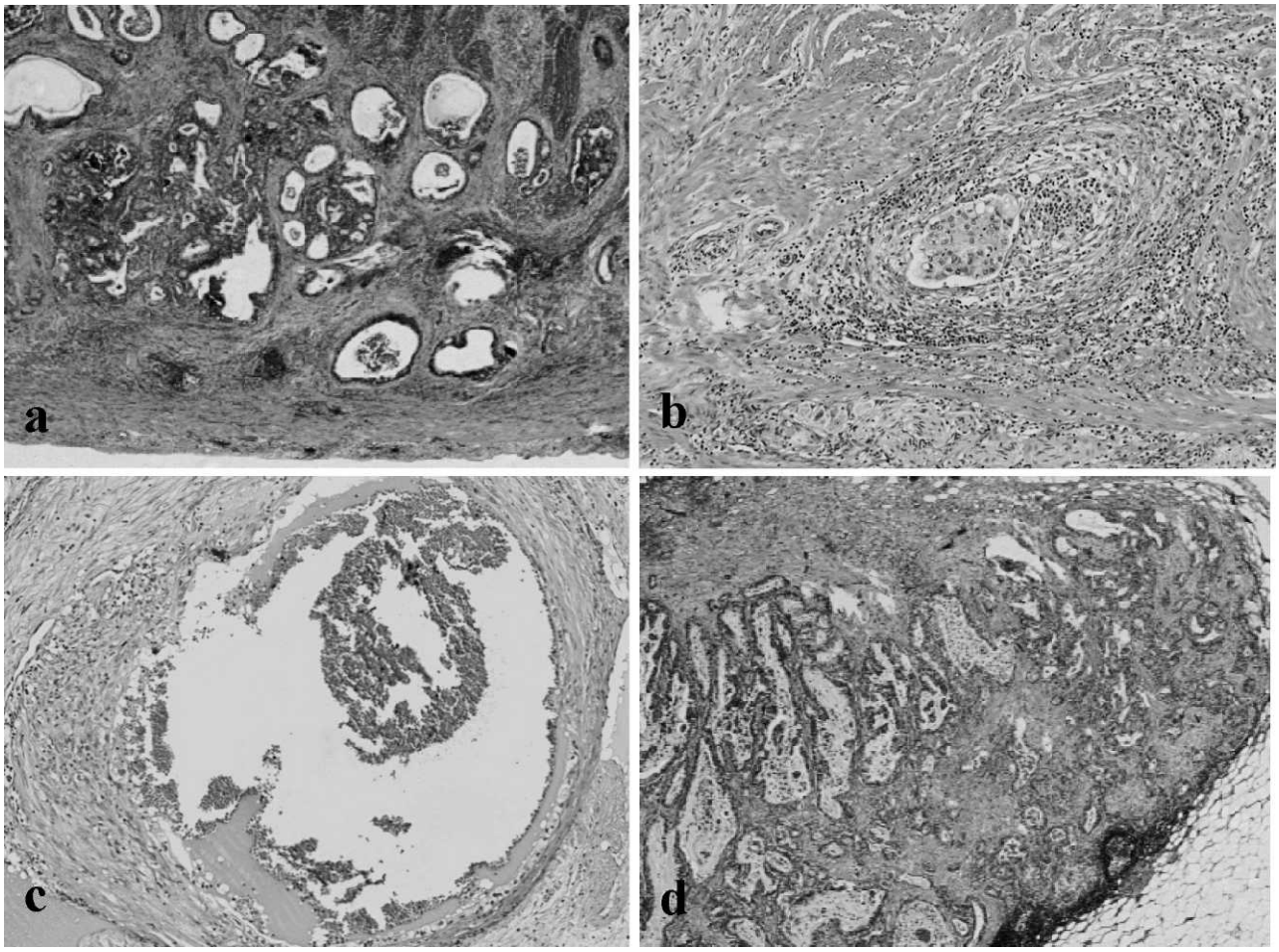

Fig. 2 Pathologic features. (a) Moderately differentiated tubular adenocarcinoma invading into the subserosal layer. (b) Lymphatic invasion of the adenocarcinoma. (c) Venous invasion of the adenocarcinoma. (d) Metastasis of the adenocarcinoma into infra-pyloric lymph nodes.

live for an extended period following surgery. Some surgeons contend that particular clinicopathologic factors influence the duration of survival in these patients. Ambiru *et al* reviewed the cases of 6 patients who survived longer than 5 years after curative excision of the stomach and liver and demonstrate that long-term survival is possible in patients whose metastatic liver tumor is not synchronous, but metachronous, with the gastric adenocarcinoma.[2] Ochiai *et al* reviewed the cases of 21 long-term survivors and show that hepatic resection should be attempted in patients with gastric adenocarcinoma and metachronous metastasis in the liver and that hepatic surgery should also be performed in patients with no pathologic findings of serosal, venous, and lymphatic invasion in the primary gastric lesion.[3] Sakamoto *et al* report that long-term survival is possible in a small number of patients who have a singular metastatic liver lesion and report that the number of liver metastases affects patient prognosis.[4] Fujii *et al* studied 12 patients who underwent curative hepatectomy for liver tumors that metastasized from a gastric adenocarcinoma and report on a single patient who survived more than 20 years without recurrence after simultaneous surgery of the stomach and liver.[5] These authors also report that the disease-free interval between gastric adenocarcinoma and liver metastasis is important and that the diameter of the metastatic liver lesion is the most important prognostic factor. They emphasize that a longer disease-free interval or a smaller diameter metastatic liver lesion improves prognosis. Finally, they conclude that hepatectomy should be attempted in patients where the disease-free period is 1 year or more and the diameter of the metastatic liver lesion is $\leq$5 cm.[5] Rafique *et al* state that the complete excision

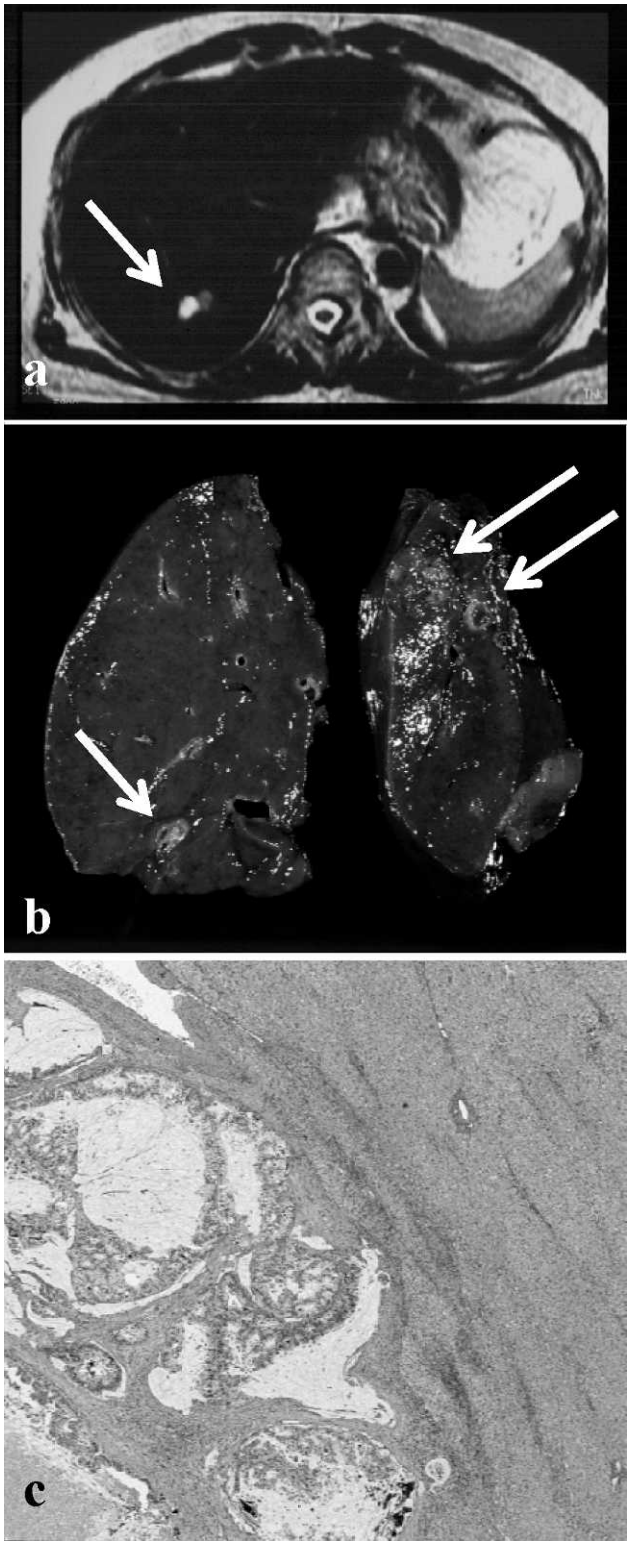

Fig. 3 (a) Space-occupying lesion in liver subsegment 7 shown on MRI. (b) Surgical specimens of the liver. (Left) Metastatic tumor of subsegment 7. (Right) Two metastatic lesions of subsegment 5. (c) Micrograph of liver. Metastatic adenocarcinoma of liver subsegment 5. Metastatic lesion is surrounded with the connective tissue.

of a metastatic liver tumor is most effective in cases with solitary tumors and suggest that intra-arterial chemotherapy against liver metastasis is also effective as a local chemotherapy. They report a rare case of a patient who survived without recurrence for 10 or more years after synchronous surgery of both the stomach and liver.[6] In contrast, Shirabe *et al* and Kunieda *et al* recommend aggressive chemotherapy rather than a surgical treatment as an effective treatment for the patient with gastric adenocarcinoma and liver metastases.[7,8] Yoshizumi *et al* report an exceptional case of a patient with gastric adenocarcinoma with metastases to both the liver and paraaortic lymph nodes and with direct invasion into the tail of the pancreas who survived for 12 years after surgery, as a result of extensive excision and aggressive chemotherapy.[9] The patient had the 5 following clinicopathologic features indicative of the potential for long-term survival in patients with gastric adenocarcinoma and liver metastases:

1. The pathologic features of gastric adenocarcinoma do not show invasion into the serosal surface, veins, or lymphatic vessels.
2. The interval between time-of-onset for gastric adenocarcinoma and the metastatic liver tumor is more than a year.
3. The diameter of the metastatic liver tumor is less than 5 cm.
4. Only a single metastatic liver tumor is present.
5. Plans include maintenance of aggressive chemotherapy for a long period following surgery.

The patient reported herein had a liver tumor diameter less than 5 cm and no penetration of the cancer into the serosal surface is detected by pathology. These 2 factors are favorable according to the prognostic clinicopathologic features described above. In contrast, 5 other clinicopathologic features in this patient are not congruent with those described by Yoshizumi:

1. Pathologic venous and lymphatic invasion were demonstrated.
2. Both the primary gastric adenocarcinoma and multiple metastatic liver tumors were detected at the same time.
3. The patient had multiple metastatic liver tumors.
4. The adjuvant chemotherapy was discontinued due to drug toxicity at an early stage.

5. Aggressive long-term chemotherapy could not be completed.

And yet, the metastatic liver tumors of this patient are characterized by the following clinicopathologic features:

1. Clinically, the diameter of neither of the 2 metastatic liver tumors that were first detected had increased after the progress of 3 years.
2. The CEA curve of the serum had increased slowly.
3. Pathologically, every metastatic tumor was surrounded with connective tissue and the stromal reaction appeared to protect normal liver tissues against the invasion of tumor cells.
4. The growth pattern of metastatic liver tumor was not of the invasive but of the expanding type.
5. The necrotic changes in the tumor tissue were partially seen.

These 5 clinicopathologic features of the metastatic liver tumors may demonstrate the slow growth and low malignant potential of the gastric adenocarcinoma of this patient. However, the primary reason for long-term survival (>18 years) without recurrence after surgical treatment in this patient with gastric adenocarcinoma is unknown.

Acknowledgments

This article includes information relating to general principles of medical care that should not be construed as specific instructions for individual patients. Application of this information in a particular situation remains the professional responsibility of the practitioner. The author assumes no liability or responsibility for any error or omission in such information.

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