A Case of Bone Metastasis from Gastric Carcinoma After a Nine-year Disease-free Interval

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A case featuring very late and unusual metastasis of gastric cancer is presented. A 49-year-old woman presented with metastatic disease in the seventh cervical vertebra 9 years after a total gastrectomy for gastric carcinoma. The resected primary tumor was a Borrmann type III, poorly differentiated adenocarcinoma which had invaded the subserosal layer of the stomach and had generated lymph node metastases. The patient was treated for the metastatic tumor with sequential administration of cisplatin, calcium leucovorin and 5-fluorouracil and subsequent irradiation. Remission was achieved and she survived for a further 13 months without major symptoms.

Key words: gastric cancer – bone metastasis – long disease-free interval

INTRODUCTION

Recurrence of gastric carcinoma most frequently involves abdominal dissemination and this usually occurs within 5 years of primary surgery (1). Recurrence more than 8 years after surgery is extremely rare (2–4) and bone metastasis occurs in only 0–17% of cases of gastric carcinoma (5). We present a case of metastasis to the seventh cervical vertebra which occurred 9 years after initial surgery. There was a good response to chemo-radiotherapy, in contrast to the ineffectiveness of most salvage therapies for the predominantly diffuse lesions which are usually seen in recurrent disease.

CASE REPORT

A 49-year-old woman was admitted to the Department of Surgery, University of Tokyo in April 1998 for bilateral hand and foot palsy. In September 1989, at the age of 40 years, she had undergone a gastrectomy for carcinoma at our hospital. The preoperative diagnosis was a small advanced (T₂) tumor and she underwent a total gastrectomy and splenectomy with limited lymphadenectomy (dissection of the perigastric and left gastric artery lymph nodes). A Roux-en-Y esophageojunostomy was performed for reconstruction. The primary tumor was situated on the anterior wall of the gastric body and had invaded the subserosa. The tumor was Borrmann type III, size 35 × 30 mm and had invaded the subserosal layer of the stomach, with the formation of an ulcer, 25 × 18 mm (Fig. 1). Histologically it was predominantly a poorly differentiated tubular adenocarcinoma with areas of signet-ring cell carcinoma and moderately differentiated adenocarcinoma (Fig. 2A). Focal involvement of lymphatic vessels, but not venous invasion, was seen. Twenty-four lymph nodes were examined and two nodes along the lesser curve (No. 3) were metastatic (pN1).

Post-operatively she was treated with oral 5-fluorouracil (5-FU), 150 mg/day, for 5 years. Surveillance revealed no evidence of recurrence until her new symptoms resulted in admission to hospital in September 1998. Investigations showed Hb 12.1 g/dl, WBC count 4800/µl, platelets 160 000/µl, LDH 274 IU/l, alkaline phosphatase (ALP) 288 U/l (mildly elevated), FDP <10 µg/l and prothrombin time 25% of normal. Hepatic and renal functions were normal. The tumor markers carcinoembryonic antigen (CEA) and CA19-9 remained within the normal range throughout her illness. Cervical computed tomography (CT), magnetic resonance imaging (MRI) (Fig. 3) and bone scintigraphy revealed abnormal uptake in the seventh cervical vertebra. We therefore suspected a primary bone tumor and performed a biopsy of the seventh cervical vertebra. The pathological findings were an adenocarcinoma (poorly differentiated type) which resembled the histology of the previous gastric cancer (Fig. 2B). No tumor was detected in the anastomotic site or elsewhere with endoscopic, X-ray, CT or MRI examinations. A diagnosis of solitary bone metastasis from gastric carcinoma, after a 9-year disease-free interval, was therefore made.

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Bone metastasis from gastric carcinoma

Chemotherapy was commenced, employing a regimen of sequential cisplatin, calcium leucovorin and 5-FU. On day 1 intravenous cisplatin (10 mg/m²) was given, followed 3 h later by intravenous 5-FU (500 mg/m²). On days 2–5, 5-FU (500 mg/m²) was given intravenously. Leucovorin (10 mg/m²) was given intravenously every 6 h on days 1–5. This regimen was repeated on a weekly basis. The patient’s symptoms were relieved after two courses. Radiotherapy was started 3 weeks after the commencement of the chemotherapy and a total of 40 Gy were given over 4 weeks. However, no radiotherapeutic effect was observed on cervical MRI scanning. The patient received a total of four courses of chemotherapy, of which two commenced after radiotherapy. After this she rejected continuing chemotherapy. The patient was discharged and was able to return to work but she died of pneumonia with carcinomatous lymphangitis at another hospital associated with our Department 1 year later and 10 years after the initial gastrectomy. No autopsy was performed.

Immunohistochemical staining for p53 (NCL-p53-DO7, Castra, USA) and Ki67 (Nuclear Antigen Ki-67, Immunotech, France) were compared in the primary tumors and the bone metastasis. Staining for both was significantly more extensive in the bone metastasis (80%) than in the primary tumor (10%), indicating a more aggressive nature.

DISCUSSION

The present case exhibits two unusual features of gastric carcinoma: very late recurrence and solitary bone metastasis. Gastric cancer recurs most frequently within 5 years of initial surgery. Katai et al. reported that 60% of patients died within 2 years and 91% within 5 years in their series of 687 cases of recurrent or metastatic tumors after curative gastrectomy for advanced gastric carcinoma (1). It has also been previously reported by our department that of 298 patients with early gastric cancer who underwent ‘absolute curative surgery’, six (2%) suffered recurrent early gastric cancer between 5 and 10 years later (6). Yamamura et al. studied patients with bone or bone marrow metastasis and found that 21 of 24 (88%) had presented within 4 years of initial surgery (7). In the present case the disease-free interval was 9 years and the patient died 1 year later. The oral chemotherapeutic agent 5-FU (150 mg/day) had been administered for 5 years following initial surgery and this may have contributed to the delay in recurrence.
At the time of her surgery it was our standard practice to administer oral 5-FU to patients with advanced gastric cancer in adjuvant setting for 2 years. However, this young patient strongly wished for continuation of chemotherapy for 3 more years.

Metastasis to the bone and/or bone marrow is relatively uncommon with gastric carcinoma, although it does account for most cases of diffuse bone marrow metastasis and disseminated intravascular coagulation (DIC) which occur due to solid tumors (8). Indeed, this was reported as early as 1939 by Jarchow (9). Mechanisms of bone metastasis in symptomatic gastric cancer must remain speculative, given the few reports available (4). Lehnert et al. (16) proposed that the rich supply of blood capillaries in the gastric mucosa may contribute to the early spread of cancer to liver and bone; however, a review of the literature suggested that scirrhous carcinomas and poorly differentiated adenocarcinoma, histologically and macroscopically Borrman types III and IV, were the predominant types of gastric cancer which resulted in bone metastases (10).

For bone and/or bone marrow metastasis from gastric cancer, sequential methotrexate and 5-FU have been reported to show some effects (2,11). We used in this case a regimen comprising cisplatin, calcium leucovorin and 5-FU. The combination of these agents is based on a dual biochemical modulation therapy (12,13). Radiation was also added in the hope of gaining further local control of the tumor (14,15), but no apparent effect was seen on MRI. The metastatic tumors showed a more aggressive nature than the primary, based on p53 and Ki67 immunostaining, and the chemotherapy was thought to have been the main factor which contributed to the relief of symptoms.

References