



Case report of very late gastric cancer recurrence

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ABSTRACT

Very late recurrence of gastric cancer is rare. Here, we report a dramatic recurrence of gastric cancer, with isolated skeletal metastasis and bone marrow carcinomatosis, 22 years after the patient's initial presentation. Gastric cancer recurrence involving bone or bone marrow is also uncommon and associated with poor prognosis. Pathology from a bone marrow biopsy showed signet ring cell morphology. The patient in this case demonstrated a surprising response—lasting 11 months—to palliative chemotherapy with cisplatin and capecitabine. This case report and literature review describes the characteristics of late gastric cancer recurrence and an approach to the diagnosis and management of patients with bone metastasis or bone marrow carcinomatosis.

KEY WORDS

Gastric cancer, metastasis, late recurrence

1. INTRODUCTION

Globally, gastric cancer accounts for almost 1 million deaths each year¹. Recurrence of gastric cancer often appears early, commonly within the first 2 years after gastrectomy². Late recurrence is uncommon and, after 10 years, extremely rare. Recurrences usually present in the abdominal cavity, peritoneum, lymph nodes, and liver^{3,4}. Recurrence limited to bone and bone marrow is rare, and prognosis in such cases is poor⁵. The case report that follows further explores late gastric cancer recurrence and the principles of diagnosis and management in patients presenting with skeletal and bone marrow metastasis.

2. CASE DESCRIPTION

A 66-year-old man presented to the medical oncology service with a 7-month history of progressively increasing back pain and a diagnosis of pathologic

compression fracture at T10. In addition, he had bilateral deep vein thrombosis, significant weight loss, anemia, and thrombocytopenia. He was transfusion-dependent, presenting with a hemoglobin of 77 g/L and requiring weekly red-cell transfusions.

This patient had been diagnosed 22 years earlier with a gastric adenocarcinoma presenting with linitis plastica and treated surgically with a Billroth II subtotal gastrectomy. No adjuvant treatment was given. Regular surveillance endoscopy had not previously identified any sign of recurrence. He was otherwise well, with no significant past medical or familial history of malignancy. The patient was cachectic, but physical examination detected no lymphadenopathy, or organomegaly.

Alkaline phosphatase was markedly elevated at 5185 U/L. The remaining serum biochemistry values, including calcium, were normal. A whole-body bone scan using Tc-99m showed diffuse skeletal metastasis throughout the axial and proximal appendicular skeleton (Figure 1). Computed tomography imaging found the bone metastasis to be both osteolytic and osteoblastic in nature. No other evidence of metastatic disease was found. Endoscopy revealed no evidence of local recurrence. The gastric remnant and anastomosis were clearly visualised, and colonoscopy was unremarkable.

Pathology analysis of the bone marrow biopsy and aspirate revealed marrow diffusely infiltrated with non-hematopoietic tumour, severe fibrosis, and osteosclerotic changes [Figure 2(a)]. Signet ring cells were observed, suggestive of either gastric cancer or lymphoma. Infiltration of the tumour cells was 70%–80% glandular, staining positive for cytokeratin 7 and low molecular weight keratin, and negative for CD45, CD20, TIF1, and Cdx2 [Figure 2(b)]. The positive cytokeratin 7 bone marrow stain was performed by immunohistochemistry using a monoclonal mouse anti-human cytokeratin 7 (Dako, Glostrup, Denmark). Positive controls were performed on a non-bone-marrow multi-use control sample. Negative controls were performed on a negative bone marrow

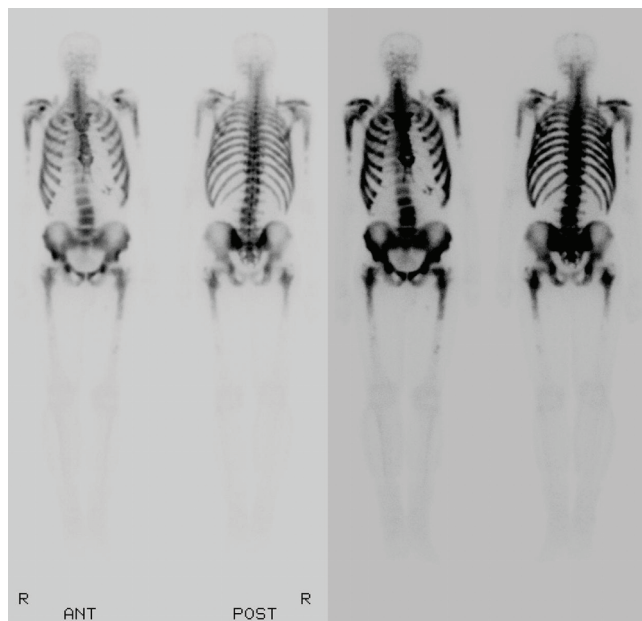


FIGURE 1 Whole-body Tc-99m bone scan showing diffuse axial and proximal appendicular bone metastasis. ANT = anterior view; POST = posterior view.

biopsy sample. The overall pathology from the bone marrow biopsy and aspirate was consistent with a diagnosis of recurrent gastric carcinoma.

The patient was started on combination palliative chemotherapy with intravenous cisplatin (60 mg/m² every 3 weeks) and oral capecitabine (625 mg/m² twice daily for 3 weeks) at a 20% dose reduction. This regimen was well tolerated, with minimal toxicity. After the first cycle of chemotherapy, the patient's weekly transfusion requirement declined. After the second cycle, he became transfusion-independent, with hemoglobin measurements in the range 100–110 g/L. Bone imaging was stable, with no evidence of disease progression. Figure 3 shows the improvement in the patient's alkaline phosphatase (ALP) levels during his chemotherapy treatment.

Although he was tolerating treatment well, the patient requested discontinuation of chemotherapy after 9 cycles. Three months after chemotherapy completion, his ALP began to rise. He became anemic, and thrombocytopenia again required ongoing red-cell transfusions. Palliative chemotherapy with cisplatin and capecitabine was restarted, and later, 1 cycle of a taxane was administered with no response. The patient died 1 month after his relapse presentation.

3. DISCUSSION

Gastric cancer recurrences usually appear within the first 2 years after gastrectomy. Late recurrences are uncommon: fewer than 10% of patients recur after 5 years, and fewer than 1% recur after 10 years⁶. The literature contains only two other cases of recurrence

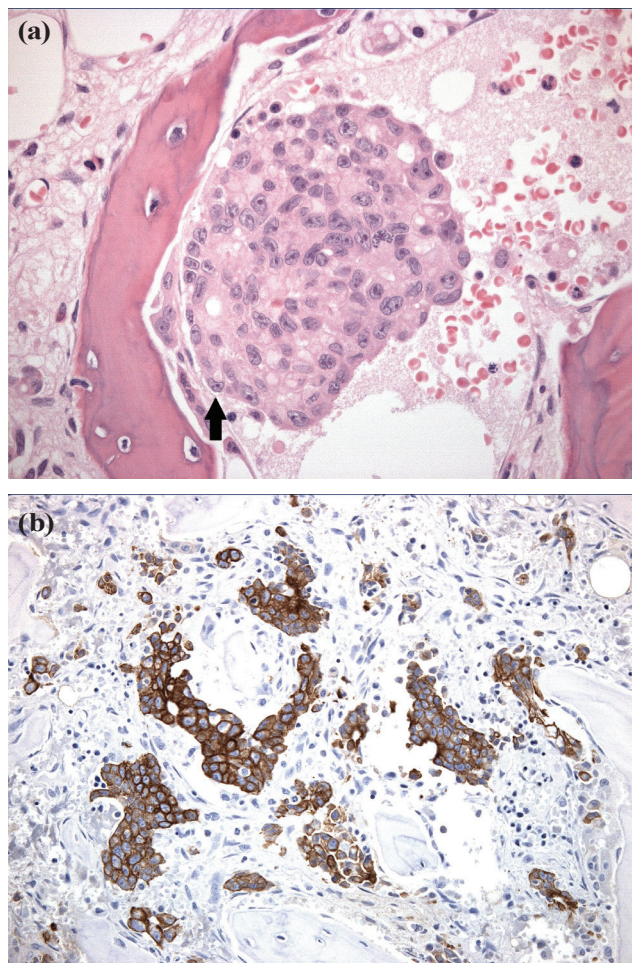


FIGURE 2 (a) Bone marrow pathology showing diffuse marrow infiltration with signet ring cells (arrow). Magnification 40 \times , dry. (b) Bone marrow signet ring cells staining positive for cytokeratin 7. Magnification 20 \times , dry.

after a period of 20 years: one describing peritoneal relapse; and the other, distant metastasis^{7,8}. In both cases, pathology was signet ring cell carcinoma. No publication has reported isolated recurrences in bone after 9 years. Characteristic prognostic features for early recurrence such as clinical stage, size of tumour, depth of invasion, presence of lymphovascular invasion, and lymph node status are not useful in predicting late cancer recurrence^{6,9}.

Bone metastases are rare in patients with gastric cancer, being observed in fewer than 2% of patients after curative surgical resection¹⁰. The proportion is higher for patients who present with advanced disease, with autopsy studies suggesting that the incidence is as high as 20%¹¹. Isolated recurrence in bone is rare, and bone metastasis is more commonly associated with disease involvement at other sites.

Prognosis for patients with bone metastasis is very poor, approximately 4 months⁵. A recent retrospective study by Park *et al.* reported a benefit

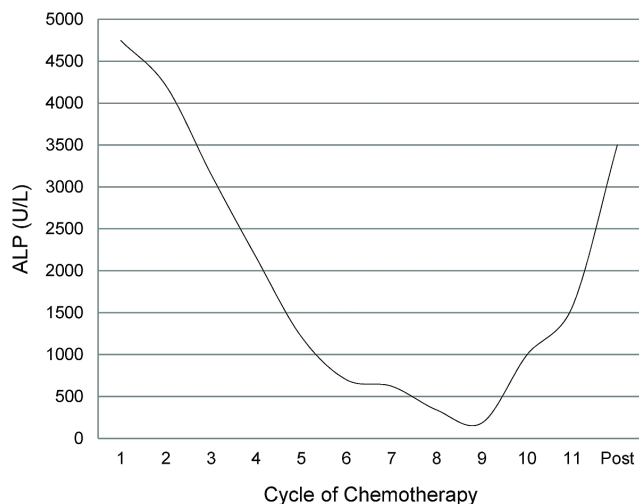


FIGURE 3 Alkaline phosphatase (ALP) measurements during chemotherapy treatment for late gastric cancer recurrence involving skeletal and bone marrow metastases.

for palliative chemotherapy in patients with bone metastasis: median overall survival was 167 days compared with 43 days for patients treated with radiotherapy and best supportive care¹². In that study, the chemotherapy regimens varied widely; most protocols consisted of either a taxane, an anthracycline, a fluoropyrimidine, or a platinum agent. Prognostic factors for poor survival were low performance status, multiple bone metastases, and elevated carcinoembryonic antigen. Patients with fewer than two of those adverse prognostic factors benefited from palliative chemotherapy. In the Park *et al.* study, 85% of patients had multiple sites of metastasis, and therefore the true benefit of palliative chemotherapy in the setting of isolated bone metastasis remains unknown. The present case report describes a typical presentation for bone metastasis: pain associated with elevated ALP.

Bone marrow involvement with gastric cancer is also very rare: approximately 80% of patients present with bone metastases. The laboratory findings at presentation are commonly anemia, thrombocytopenia, and elevated ALP and lactate dehydrogenase¹³. Bone marrow metastasis may also present with autoimmune hemolytic anemia or disseminated intravascular coagulation^{14,15}. The pathology observed is usually poorly differentiated adenocarcinoma or signet ring cell carcinoma¹¹. Because signet ring cells may also be associated with lymphoma, usually follicular lymphoma, the differential diagnosis must include that possibility¹⁶. The presence of such cells in bone marrow is also uncommon. Signet ring cell lymphoma can be distinguished from solid-tumour malignancies by immunohistochemistry. Lymphoma cells stain strongly positive for CD45 (leukocyte common antigen) and CD20 (B-cell marker)¹⁷. Immunohistochemistry was used in the

present case to clarify the diagnosis of recurrent gastric cancer and to exclude the possibility of an underlying lymphoma. Signet ring cells can also be seen in other gastrointestinal malignancies; in breast, lung, prostate, and bladder cancers; and in stromal tumours of the ovary and testis (tumours that were excluded in the present case).

The prognosis for gastric cancer with bone marrow metastasis is extremely poor. A recent study showed a mean survival of 1.5 months¹⁸, with adverse prognostic factors being low serum sodium (<133 mmol/L), peritoneal seeding, and lung metastasis. Patients who had none of the poor prognostic risk factors benefited from chemotherapy, with a mean survival of 96 days. Patients with adverse prognostic features did not benefit from palliative chemotherapy and had a mean survival of 23 days.

Our patient demonstrated a very dramatic 11-month response to chemotherapy in the setting of bone marrow metastasis. He experienced a significant improvement in quality of life and became transfusion-independent. We identified 1 other case report of gastric cancer metastasized to bone marrow after 9 years, and in that case, the authors also reported a response to chemotherapy (5-fluorouracil–methotrexate) lasting 10 months¹⁹. These 2 case reports suggest a dramatic benefit of palliative chemotherapy for gastric cancer patients with long periods of remission before bone marrow metastasis.

4. SUMMARY

The present case report highlights several key learning points. Late recurrence of gastric cancer can appear after more than 10 years, and patients with concerning symptoms warrant investigation for relapse. A bone scan may be useful in patients presenting with abnormal blood counts or elevated ALP.

Gastric cancer metastasis to bone is uncommon and associated with poor prognosis. The situation with bone marrow involvement is similar. If signet ring cell morphology is observed, a diagnosis of lymphoma should be excluded.

When appropriately selected, gastric cancer patients with bone metastasis or bone marrow carcinomatosis benefit from palliative chemotherapy. Patient selection is of utmost importance to optimize response and minimize the potential for toxicity. Our patient is an excellent example of a dramatic response to palliative chemotherapy using cisplatin and capecitabine. Further study is needed to determine the optimal chemotherapy regimen in this setting.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest relevant to the present work to declare.

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