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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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CASE REPORT

Disseminated carcinomatosis of the bone marrow caused by granulocyte colony-stimulating factor: A case report and review of literature

Kengo Fujita, Ayaka Okubo, Toshitsugu Nakamura, Nobumichi Takeuchi

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Abstract

BACKGROUND

Disseminated carcinomatosis of the bone marrow (DCBM) is a widespread metastasis with a hematologic disorder that is mainly caused by gastric cancer. Although it commonly occurs as a manifestation of recurrence long after curative treatment, the precise mechanism of relapse from dormant status remains unclear. Granulocyte colony-stimulating factor (G-CSF) can promote cancer progression and invasion in various cancers. However, the potential of G-CSF to trigger recurrence from a cured malignancy has not been reported.

CASE SUMMARY

A 55-year-old Japanese woman was diagnosed with Ewing sarcoma localized on the fifth lumbar vertebrae 6 years after curative gastrectomy for T1 gastric cancer. After palliative surgery to release nerve compression, pathological diagnosis of the resected specimen was followed by curative radiation and chemotherapy. During treatment, G-CSF was administered 32 times for severe neutropenia prophylaxis. Eight months after completing definitive treatment, she complained of severe back pain and was diagnosed as multiple bone metastases with DCBM from gastric cancer. Despite palliative chemotherapy, she died of disseminated intravascular coagulation 13 d after the diagnosis. Immunohistochemical examination of the autopsied bone marrow confirmed a diffuse positive staining for the G-CSF receptor (G-CSFR) in the relapsed gastric cancer cell cytoplasm, whereas the primary lesion cancer cells showed negative staining for G-CSFR. In this case, G-CSF administration may have been the key trigger for the disseminated relapse of a dormant gastric cancer.

CONCLUSION

When administering G-CSF to cancer survivors, recurrence of a preceding cancer should be monitored even after curative treatment.

Key Words: Disseminated bone marrow carcinomatosis; Gastric cancer; Granulocyte colony-stimulating factor; Cancer survivor; Immunostaining; Case report

Core Tip: Disseminated carcinomatosis of the bone marrow (DCBM) is a rare manifestation of recurrence of a treated cancer, mainly gastric cancer. We reported a case of DCBM 8 years after curative surgery for T1 gastric cancer. Immunostaining for granulocyte colony-stimulating factor (G-CSF) receptor was diffusely positive in the relapsed lesions, but it was negative in the primary lesion. The administration of G-CSF during treatment for Ewing sarcoma within 2 years before the relapse could have been the trigger for the gastric cancer recurrence. G-CSF administration in patients with history of cancer could be a risk factor for recurrence.

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INTRODUCTION

Disseminated carcinomatosis of the bone marrow (DCBM) is a rare metastatic disorder that originates from gastric cancer in about 90% of cases[1-4]. Although the reported incidence of bone recurrence from curatively resected gastric cancer was 0.7%-2.1%, 13.4%-17.6% of autopsied gastric cancer cases had bone metastasis[5-9]. The duration between primary surgery and DCBM diagnosis was reportedly longer than 5 years in 66.7% of cases[10]. Therefore, disseminated tumor cells (DTCs) could stay in a prolonged subclinically dormant status. However, the precise mechanisms of this metachronous relapse are not well-known[11].

We reported a case of DCBM 8 years after curative surgery of T1 gastric cancer. Within 2 years prior to the relapse, definitive treatment with multiple granulocyte colony-stimulating factor (G-CSF) infusions for Ewing sarcoma was administered. We focused on the relationships between G-CSF administration and gastric cancer relapse.

CASE PRESENTATION

Chief complaints

A 55-year-old woman followed up for cured Ewing sarcoma at the outpatient oncology department of our hospital complained of pain all over the body, especially in the lumbar area.

History of present illness

The patient's pain started 8 mo after completing chemotherapy for Ewing sarcoma. The lumbar pain extended to the upper back and right shoulder for several weeks.

History of past illness

The patient had undergone curative distal gastrectomy with lymphadenectomy for early gastric cancer (T1aN1M0)[12], and completed a 5-year postoperative follow-up without any signs of recurrence based on tumor markers, gastroduodenoscopy, and computed tomography (CT) scans. Seven years after the gastrectomy, she had persistent pain on the right hip joint and right lumbar area, which was attributed to a soft tissue tumor on the right fifth lumbar vertebra seen on CT and magnetic resonance imaging (MRI). The pathologic diagnosis of the palliatively resected tumor was Ewing sarcoma, which was confirmed by chromosomal analysis of *ESWR1* break apart. After induction radiotherapy (50.4 Gy/28 Fr), she received adjuvant chemotherapy with 8 courses of vincristine (16 mg in total), 4 courses of doxorubicin (344 mg in total), 8 courses of cyclophosphamide (13840 mg in total), 33 courses of ifosfamide (81.2 mg in total), and 32 courses of etoposide (2240 mg in total). Six times of red blood cell

(RBC) transfusion were required for grade 4 anemia. Grade 4 neutropenia was treated with antibiotics and 18 doses of 2700 μg of filgrastim (filgrastimBS®, Nippon Kayaku, Tokyo, Japan). For severe neutropenia prophylaxis, 14 doses of 50.4 mg of pegfilgrastim (G-Lasta®, Kyowa Kirin, Tokyo, Japan) were given (Figure 1). After completion of chemotherapy, CT and MRI revealed no residual tumor.

Personal and family history

The patient had no prior history of smoking or alcohol consumption. There was no relevant family history in relation to this case report.

Physical examination

On admission, the patient's temperature was 36.3 °C, heart rate was 82 beats per minute, respiratory rate was 19 breaths per minute, blood pressure was 122/86 mmHg, and oxygen saturation at room air was 95%. Our primary clinical consideration was bone metastasis from recurrent Ewing sarcoma or gastric cancer.

Laboratory examinations

Laboratory examinations showed evident increases in serum alkaline phosphatase (ALP) at 8081 IU/L (normal, 106-322 IU/L) and pancytopenia (RBC 2.23 × 10^{12}/μL, hemoglobin 7.2 g/dL, white blood cell 8500/μL with 69% neutrophils, and platelet 2.9 × 10^{4}). The following tumor markers were elevated: Carcinoembryonic antigen (CEA) at 120.3 ng/mL (normal, < 5 ng/mL) and carbohydrate antigen 125 (CA125) at 45.5 U/mL (normal, < 35 U/mL). Notably, the ALP range was 1000-1500 IU/L during chemotherapy for Ewing sarcoma and remarkably increased when the patient complained of pain (Figure 1). Additionally, the CEA and CA125 were normal throughout the five-year follow-up of the resected gastric cancer but were not available during the treatment for Ewing sarcoma.

Imaging examinations

Bone scintigraphy, using technetium-99m hydroxymethylene diphosphonate, revealed an increased uptake in the spine, limbs, pelvis, and skull and decreased radioactivity in the kidneys (Figure 2). These characteristic image findings are called superscans (also termed super bone scans and super scan patterns) and can indicate bone marrow involvement[13,14].

MULTIDISCIPLINARY EXPERT CONSULTATION

Bone marrow biopsy from the iliac crest revealed adenocarcinoma, which seemed to be a recurrence from gastric cancer. The immunohistochemical findings of the adenocarcinoma cells were as follows: CK7(+), CK20(+), MUC2(-), MUC5AC(+), MUC6(focal+), CDX2(−), and CA19-9(−). The results were identical to those of the primary lesion of the resected stomach 8 years prior, except for CDX2, which was focally positive in the primary lesion.

Postmortem autopsy revealed the following metastatic lesions from gastric cancer: (1) Bilateral bronchopulmonary lymph nodes; (2) Scattered minute tumor emboli in the lungs; and (3) Diffuse bone marrow infiltration in the vertebrae (cervical, thoracic, and lumbar), ribs, and iliac bone. There were no recurrences of gastric cancer in the peritoneal cavity and stomach and of Ewing sarcoma all over the body. The histological and immunohistochemical findings of the autopsied bone marrow were identical to those of the bone marrow biopsy. To further investigate the mechanism of relapse, additional immunostainings on the primary and relapsed bone marrow lesions were done using anti-G-CSF antibody (clone 5.24, 1:600, Sigma-Aldrich, St. Louis, Missouri, United States) and anti-G-CSF receptor (G-CSFR) antibody (1:300, Bioss antibodies, Woburn, Massachusetts, United States). Immunostaining for G-CSF was negative in both lesions. In contrast, G-CSFR was diffusely positive in the cytoplasm of the cancer cells in the relapsed lesions but was negative in the primary lesion (Figure 3).

FINAL DIAGNOSIS

The final diagnosis was DCBM from gastric cancer that was curatively resected 8 years prior.

TREATMENT

Weekly intravenous chemotherapy that comprised methotrexate 140 mg, fluorouracil 840 mg, and calcium folinate 12 mg per course was started but needed to be stopped on day 7 because of deteriorating general condition of the patient[15-18].

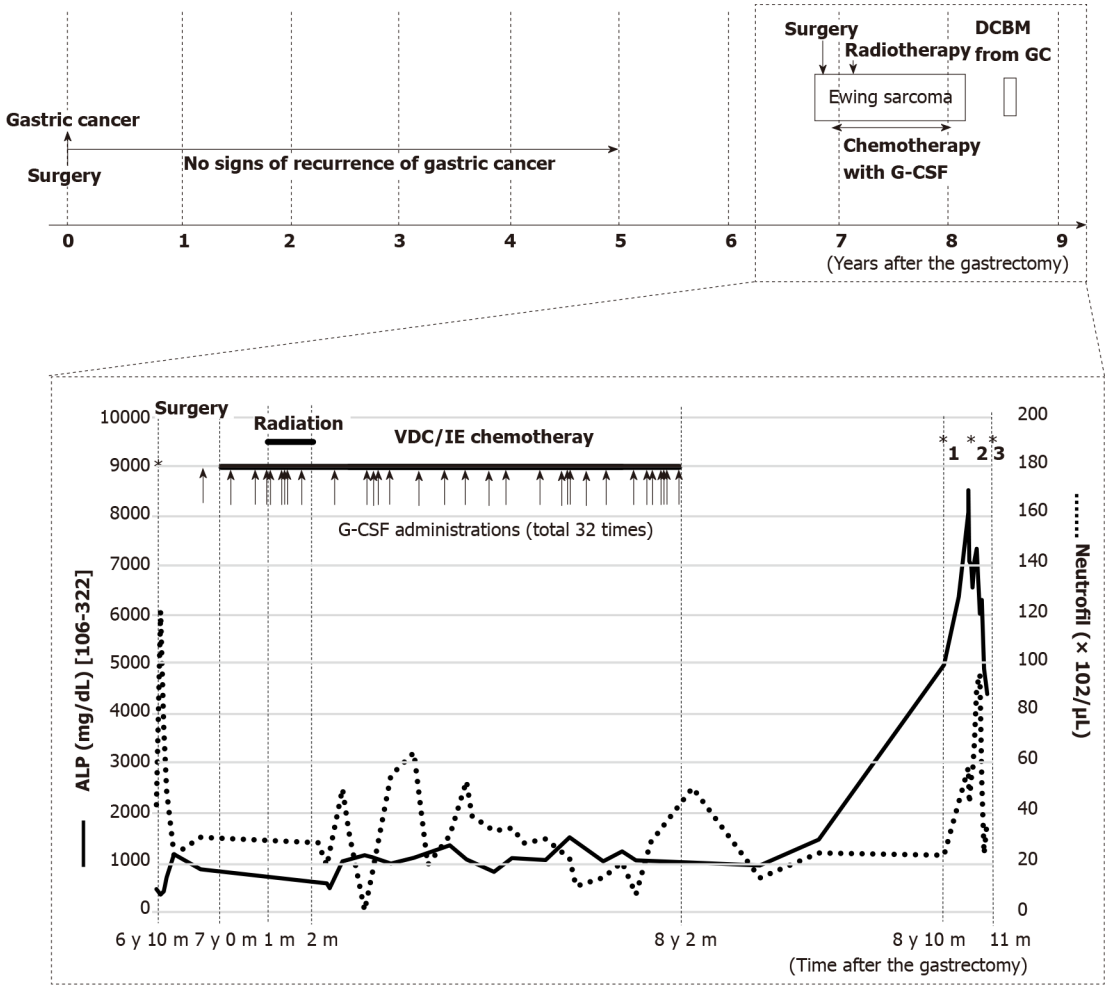

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Figure 1 Clinical course after gastrectomy. During the five-year follow-up of resected gastric cancer, there are no signs of recurrence based on tumor markers, computed tomography, and gastroduodenoscopy. Eight months after completing chemotherapy with granulocyte colony-stimulating factor administration for Ewing sarcoma, disseminated carcinomatosis of the bone marrow (DCBM) from gastric cancer is diagnosed. Alkaline phosphatase is moderately elevated during the treatment of Ewing sarcoma and remarkably increased when the patient complained of lumbar pain, which led to the diagnosis of DCBM.∗1: Complaint of pain; ∗2: Bone marrow biopsy; ∗3: Died of DCBM. G-CSF: Granulocyte colony-stimulating factor; DCBM: Disseminated carcinomatosis of the bone marrow; ALP: Alkaline phosphatase; VDC/IE: Vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide; GC: Gastric cancer.

OUTCOME AND FOLLOW-UP

Despite chemotherapy, disseminated intravascular coagulation progressed, and the patient died 13 d after the diagnosis of DCBM.

DISCUSSION

This case suggested the potential of G-CSF administration to cause recurrence presenting as DCBM from a curatively resected gastric cancer 8 years prior. Although the precise mechanism of DCBM as a manifestation of a metachronous recurrence of cured cancer is unclear, recent studies have indicated the reactivation of dormant DTCs by various factors, which are mainly related with angiogenesis and the immunologic antitumor surveillance system[19-23]. The administration of G-CSF has been reported to be one of the factors that can promote cancer progression and invasion in various cancers[24], and this interaction was confirmed *in vivo* using gastric cancer cells expressing G-CSFR[25]. However, previous clinical documentations have seldom documented that G-CSF could trigger recurrence of cured malignancies. In this report, we focus on the direct and indirect effects of G-CSF on the metachronous relapse of cured malignancies.

G-CSF can directly promote the proliferation and spread of gastric cancer cells, especially those with stem-like properties, such as CD44 and aldehyde dehydrogenase expression, by activating G-CSFR and the RERK1/2 and RSK1 phosphorylation pathways[26,27]. In the present case, G-CSFR staining was negative in the primary lesion but was diffusely positive in the relapsed lesion. This observation

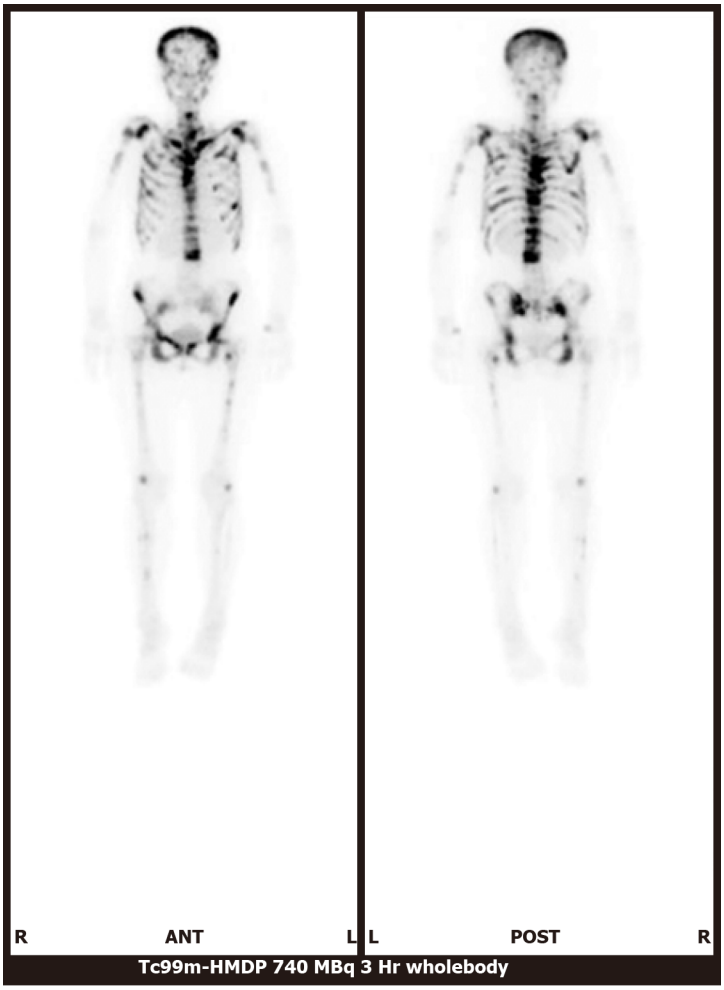

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Figure 2 Bone scintigraphy using 99 m technetium-hydroxymethylene diphosphonate. There is increased uptake in the spine, limbs, pelvis, and skull and decreased uptake in the kidneys.

provided two possible explanations. First, a small amount of slow growing G-CSFR-positive gastric cancer cells could survive in a dormant state for a long period. Second, residual DTCs may develop and express G-CSFR throughout years of dormant state. G-CSF can promote the growth of solid tumors not only through G-CSFR on tumor cells but also by modulating immune cell activities or bone remodeling. G-CSF can activate myeloid derived suppressor cells and regulate T cells and macrophages, both of which can lead to the progression of solid tumors by suppressing CD8-positive T cells[28-31]. In addition, G-CSF can accelerate bone infiltration of tumor cells by activating osteoclasts and inhibiting osteoblasts[32,33]. These direct and indirect effects of G-CSF could be a positive trigger for the reactivation of dormant cancer cells.

About 90% of gastric cancer cases have positive G-CSFR staining, and some cancers have been reported to express G-CSFR[27,34]. G-CSF administration for the second primary cancers could be a risk factor for recurrence of a preceding G-CSFR-expressing primary cancer that was assumed to be cured for a long time. Therefore, G-CSF administration should be performed carefully in patients who have a preceding cancer. Considering the high incidence of G-CSFR-expressing gastric cancer, no other similar cases of gastric cancer recurrence caused by G-CSF have been reported. The possibility of G-CSF causing recurrence of a preceding cancer might have been overlooked. Because this one case is not enough to accurately evaluate the risk of G-CSF to cause recurrence, further research on the interaction between G-CSF and tumor proliferation and relapse are needed.

CONCLUSION

G-CSF administration in cancer survivors could be a risk factor for recurrence of a preceding cancer, even after curative treatment.

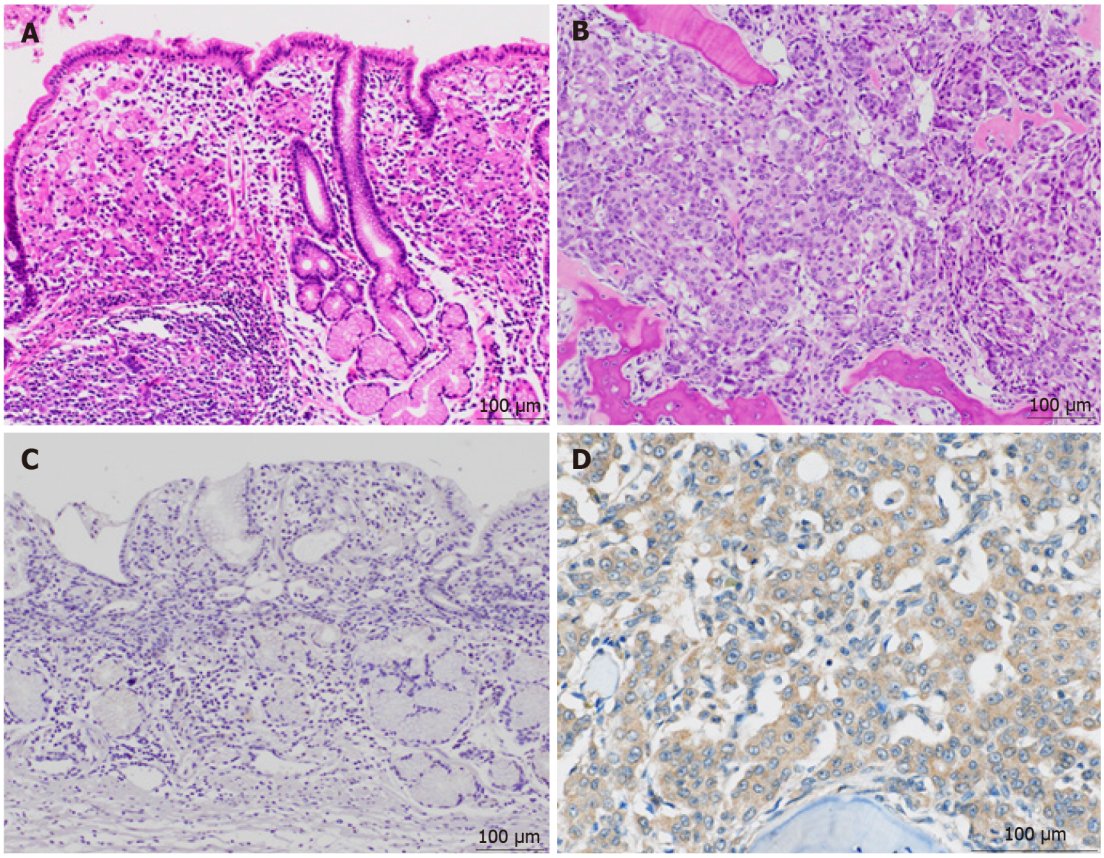

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Figure 3 Histologic and immunohistochemical images of the primary and relapsed lesions. A: Histology of the primary gastric specimen shows moderately to poorly differentiated adenocarcinoma and, partially, signet cell carcinoma (hematoxylin and eosin); B: On autopsy, the metastatic bone marrow lesion shows corresponding adenocarcinoma (hematoxylin and eosin); C: Immunohistochemical staining for granulocyte colony-stimulating factor receptor (G-CSFR) is negative in the primary lesion; D: Immunohistochemical staining for G-CSFR is diffusely positive in the bone marrow metastatic lesion.

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FOOTNOTES

Author contributions: Fujita K and Okubo A collected and interpreted clinical data, reviewed the literatures, and drafted a manuscript; Nakamura T was involved in pathological diagnosis and revised the manuscript critically for intellectual content; Takeuchi N was the patient's primary oncologist and revised the manuscript critically for intellectual content; and all authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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