Aortitis after granulocyte-colony stimulating factor administration: A case report

SHUICHI FUJIWARA[1], HITOMI HARA[1], NAOMASA FUKASE[1,2], RYOKO SAWADA[1], TOSHIYUKI TAKEMORI[1], TOMOHIRO MIYAMOTO[1], YUTA NAKAMATSU[1], RYOSUKE KURODA[1] and TOSHIHIRO AKISUE[1,3]

[1]Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo 650-0017, Japan; [2]Division of Orthopaedic Surgery, Kobe University Hospital International Clinical Cancer Research Center, Kobe, Hyogo 650-0047, Japan; [3]Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Hyogo 654-0142, Japan

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Abstract. Granulocyte-colony stimulating factor (G-CSF) is commonly used to reduce neutropenia-related complications following chemotherapy. It is a glycoprotein that stimulates the production of granulocytes [white blood cells (WBCs) in the bone marrow. In the present study, the case of a 59-year-old man is presented who received chemotherapy (eribulin) for liver metastases from sacral chordoma and subsequently developed acute aortitis after the administration of G-CSF. Grade 3 neutropenia occurred on day eight of the fifth chemotherapy cycle, and pegfilgrastim was administered on day nine. A total of 3 days after pegfilgrastim administration, the patient developed a fever that persisted for 6 days. He visited our hospital on day 18 with abdominal pain and elevated WBC count and C-reactive protein levels. Febrile neutropenia was suspected, and antibiotics were administered. However, both blood and urinalysis cultures returned negative results, and antibiotics were ineffective. Contrast-enhanced computed tomography revealed a thickened wall of the brachiocephalic artery and abdominal aorta, consistent with aortitis. After discontinuing the antibiotics, the patient was monitored closely without further treatment. His condition improved within a few days; therefore, it was concluded that aortitis was induced by G-CSF.

Correspondence to: Dr Shuichi Fujiwara, Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
E-mail: fujishu@hyogo-cc.jp

Abbreviations: G-CSF, granulocyte-colony stimulating factor; CRP, C-reactive protein; CT, computed tomography; JADER, Japanese Adverse Drug Event Report database; FN, febrile neutropenia; WBC, white blood cell

Key words: aortitis, chordoma, G-CSF, adverse event, chemotherapy

Introduction

The neutrophil-enhancing effect of granulocyte-colony stimulating factor (G-CSF) can directly influence treatment effectiveness by maintaining the dosage and intensity of chemotherapy and avoiding delays in treatment intervals (1). Typical adverse events of G-CSF include fever, back pain, headache, bone pain and muscle aching. More serious adverse events include acute lung injury, acute coronary syndrome, and acute aortitis (2). Aortitis induced by G-CSF treatment typically presents with systemic symptoms including fever and elevated C-reactive protein (CRP) levels. As these symptoms resemble those of an infection, they are often mistaken for an infection associated with chemotherapy-induced febrile neutropenia (FN), which can lead to a delay in appropriate treatment for aortitis. A computed tomography (CT) scan is an essential diagnostic tool for confirming the diagnosis (3).

According to the Japanese Adverse Drug Event Report database (JADER), of 3,409 patients with malignant tumors treated with G-CSF, 16 (0.47%) developed aortitis. The cases included four patients with breast and ovarian cancer, three with malignant lymphoma, two with uterine cancer, and one with esophageal and prostate cancer (4). In the present study, a rare case of aortitis induced by G-CSF administration in a patient undergoing chemotherapy for liver metastases from sacral chordoma is presented.

Case report

A 59-year-old-man was referred to the Kobe University hospital in Kobe City on October 2018 for the treatment of multiple metastatic chordomas of the liver. He had already initiated treatment with carbon ion radiotherapy [70.4 Gy (RBE)/32fr] for sacral chordoma. A total of 22 months after postradiotherapy, multiple metastases appeared in the liver, and the patient received eight cycles of trabectedin (dose: 1.2 mg/m^2, 24-h continuous infusion intravenously on day one as palliative chemotherapy for metastases at the previous hospital. As number of metastatic lesions gradually increased despite the administration of initiation chemotherapy, the patient received eribulin (dose: 1.4 mg/m^2, intravenously on days one and eight)

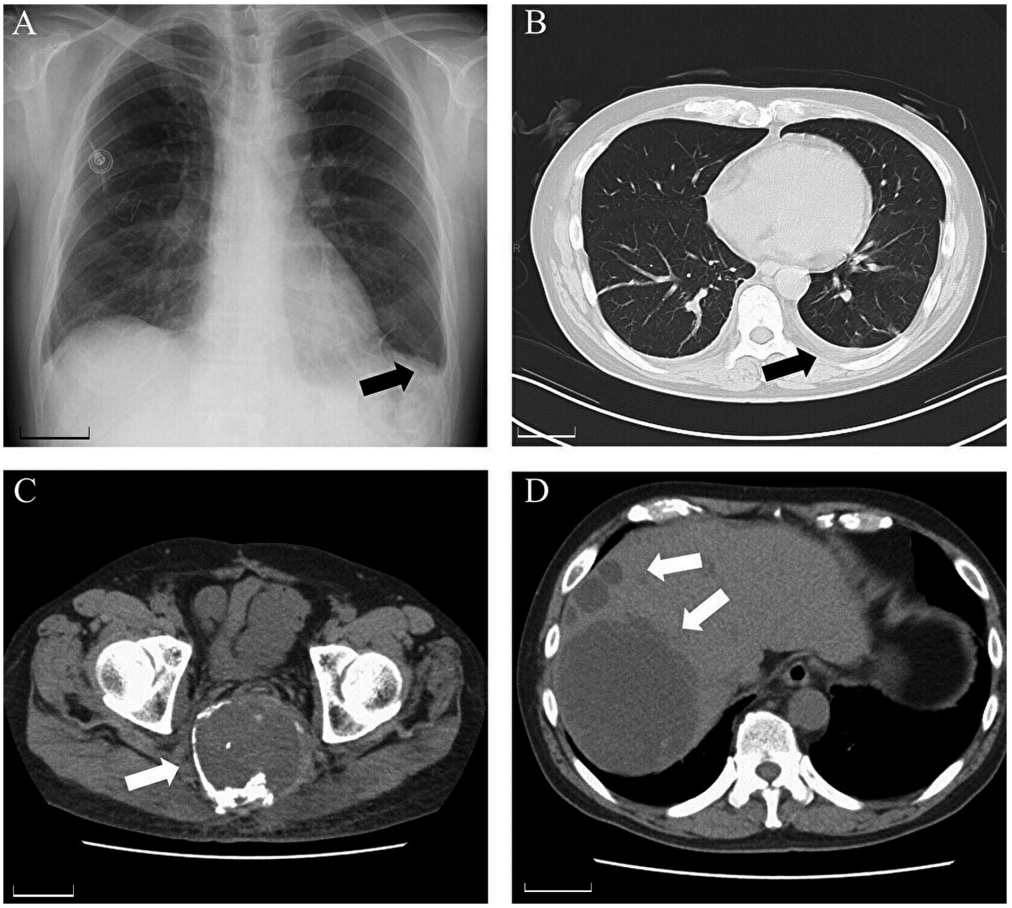

Figure 1. Imaging findings on admission. Scale bars, 5 cm. (A) Chest X-ray revealed a blunt left costophrenic angle. (B) Thoracic computed tomography showed left pleural effusion with no signs of pneumonia. (C) No significant progression was observed at the primary site in the sacrum. (D) No significant progression was observed at the metastatic sites in the liver.

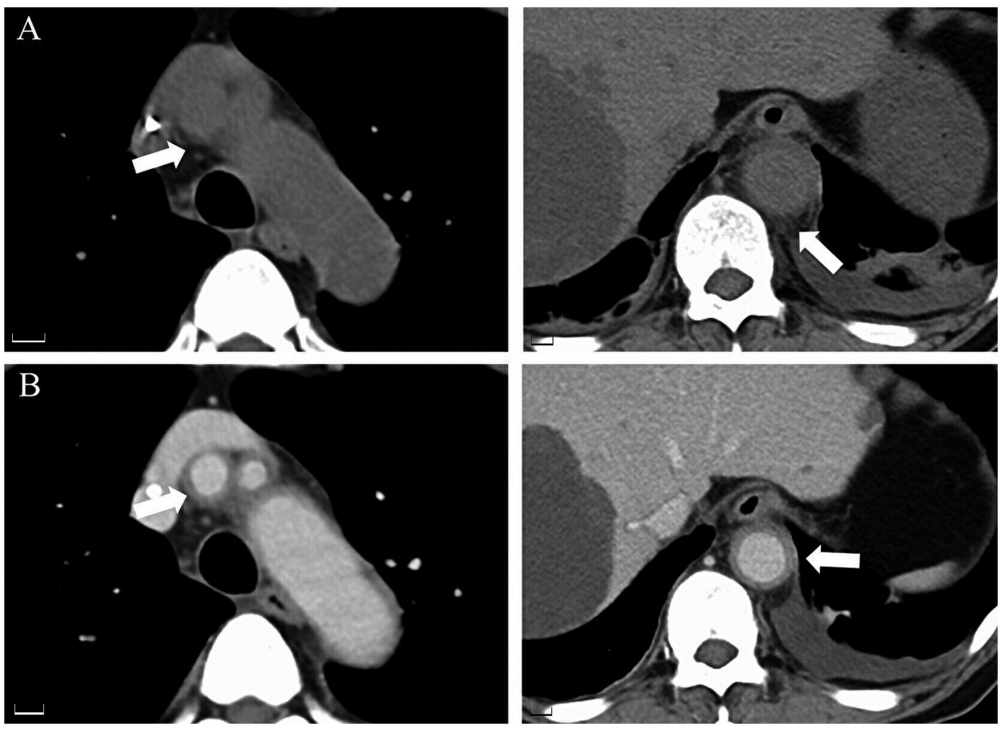

Figure 2. CT scan findings. Scale bars, 1 cm. (A) Non-contrast CT showed periaortic soft tissue inflammation around the brachiocephalic artery (left) and abdominal aorta (right). (B) Contrast-enhanced CT showed thickening of the walls of the brachiocephalic artery (left) and abdominal aorta (right). CT, computed tomography.

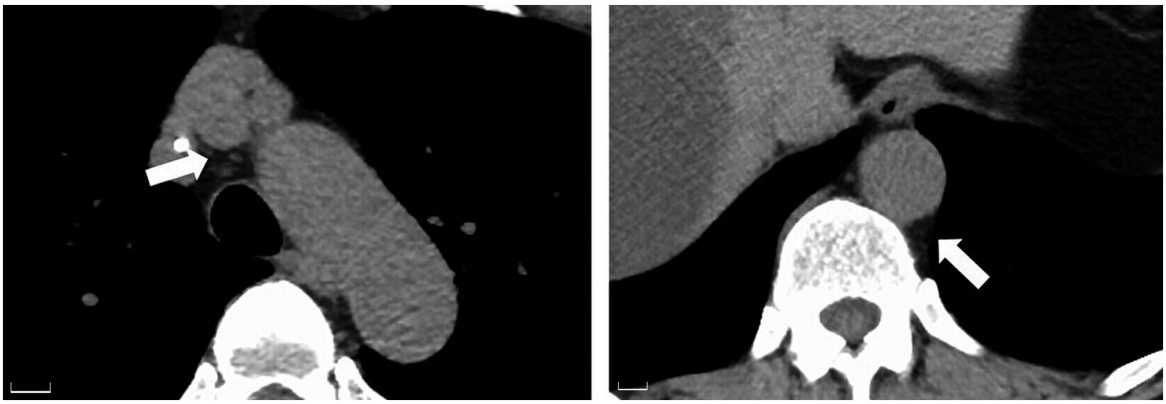

Figure 3. Computed tomography scan findings two months after granulocyte-colony stimulating factor discontinuation. Periaortic soft tissue inflammation around the brachiocephalic artery (left) and abdominal aorta (right) showed improvements. Scale bars, 1 cm.

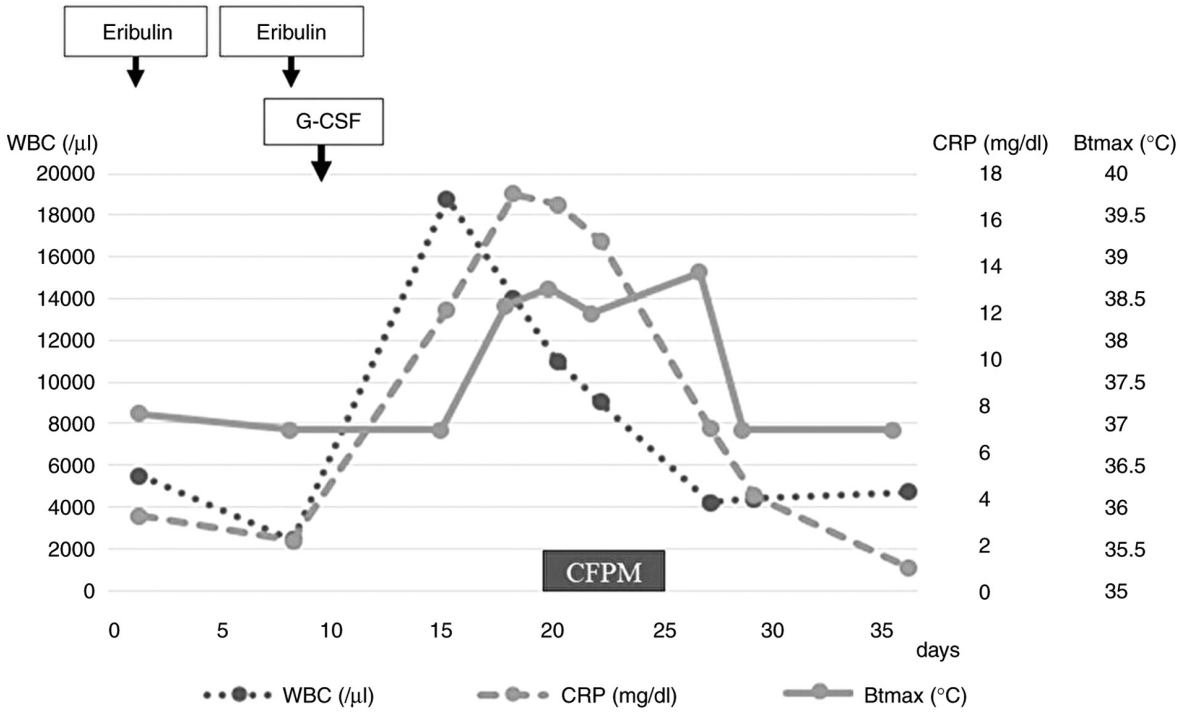

Figure 4. Clinical course of G-CSF-induced aortitis. WBC and CRP levels and body temperature were elevated after G-CSF administration. These parameters improved after discontinuation of antibiotic treatment. G-CSF, granulocyte-colony stimulating factor; WBC, white blood cell; CRP, C-reactive protein.

in our hospital. As there is no established standard treatment for chordoma, the next line of therapy was selected based on treatment strategies for soft tissue sarcomas. The blood tests conducted before the administration of eribulin did not reveal neutropenia, renal or liver dysfunction, which were considered risk factors for FN according to the NCCN guidelines (5).

On day eight of the fifth course of eribulin, blood tests showed a white blood cell (WBC) count of 2,400/μl and a neutrophil count of 860/μl, which was classified as grade 3 neutropenia according to the Common Terminology Criteria for Adverse Events Criteria (CTCAE) (6). Pegfilgrastim was administered as G-CSF on day nine to prevent FN. A total of 3 days after G-CSF administration, the patient had a fever (38˚C, grade 1 on CTCAE criteria) (6) at home, which continued for 6 days. The patient complained of a persistent fever and abdominal pain on day 18 (day nine of G-CSF administration) of the fifth cycle. Laboratory tests revealed a high WBC count (14,000/μl), CRP level (17.11 mg/dl) and procalcitonin level (0.65 ng/ml). Blood, urine and sputum cultures were negative. Chest X-ray revealed a blunt left costophrenic angle (Fig. 1A). Thoracic CT showed left pleural effusion with no pneumonia (Fig. 1B). No obvious changes were observed at the primary site (sacral) or metastatic lesion (liver) on abdominal CT (Fig. 1C and D).

FN was suspected and antibiotic treatment (cefepime, 4 g/day) was initiated on day 19. Neutrophil count before administrating antibiotics was 15,600/μl (83% of WBC counts). However, the patient did not achieve defervescence after six days of antibiotic treatment. Therefore, contrast-enhanced CT was performed, which revealed periaortic soft tissue inflammation (Fig. 2A) and thickened walls of the brachiocephalic artery and abdominal aorta (Fig. 2B). Based on

the CT images, G-CSF-induced aortitis was suspected, and antibiotic treatment was discontinued. The patient's general condition improved naturally, with the WBC count and CRP level decreasing to 4,400/μl and 4.08 mg/dl, respectively, on day 29.

Follow-up CT revealed the disappearance of the periaortic soft tissue inflammation (Fig. 3). Chemotherapy was continued without any further complaints of fever. The clinical course and treatment history of the patients are shown in Fig. 4.

Discussion

G-CSF attaches to receptors on neutrophil progenitors in the bone marrow, stimulating their differentiation into neutrophils and thereby boosting neutrophil counts in the peripheral blood. It is widely used in chemotherapy to induce myelosuppression (7). Various types of G-CSF agents are available in clinical settings. Filgrastim and lenograstim are short-acting G-CSF agents with biological structures and activities closely resembling those of endogenous human G-CSF (8). Pegfilgrastim, a modified form of G-CSF, has a polyethylene glycol molecule attached to its N-terminus, which extends its biological half-life in peripheral blood (7).

Aortitis may develop as a result of an enhanced pro-inflammatory response and neutrophil-induced tissue damage (9); however, the exact mechanism by which G-CSF administration induces aortitis remains unclear. In a study using the JADER database, Oshima *et al* (4) reported that G-CSF treatment was linked to a potentially increased risk of aortitis in patients with malignant tumors, and the incidence of aortitis associated with G-CSF was 0.47%. Their report included cases of four patients with breast and ovarian cancer, three with malignant lymphoma, two with uterine cancer, and one with esophageal and prostate cancer; however, no case of patients with chordomas was included in their report.

Regarding the characteristics of G-CSF-induced aortitis, fever was the most common symptom, with additional complaints of back, chest, abdominal and neck pain. The onset of aortitis has been reported within 10 days after the initiation of G-CSF in >50% of the patients (61.2%). CT was used as the diagnostic imaging modality in most cases (89.8%) (10). In our case, the patient got fever 3 days after G-CSF administration and felt abdominal pain 9 days after G-CSF administration, which was similar to the aforementioned study (10). Regarding the utility of contrast-enhanced CT, Takamatsu *et al* (11) reported that contrast-enhanced CT enables differentiation between G-CSF-induced aortitis and intramural hematoma based on their distinguishing imaging features (11). With respect to the differential diagnosis, Takayasu arteritis, giant cell arteritis and IgG4-related disease were considered to be listed (11). In our case, internist determined that the possibility of autoimmune diseases that cause aortitis was low, therefore no additional tests were performed. The limitation of the present case report is lack of the evaluation of antineutrophil cytoplasmic antibody, rheumatoid factor, and serum levels of IgG4 subclass to rule out these diseases.

The treatment of aortitis associated with G-CSF remains controversial. The first and most common approach for managing aortitis associated with G-CSF is to discontinue G-CSF administration (12). Takahashi *et al* (13) reported a case successfully treated with intravenous administration of steroids. In a systematic literature review on the treatment of aortic arteritis, Hoshina and Takei (10) reported that steroids were administered to 29 patients (59.2%), whereas 19 patients (38.8%) healed without the use of steroids (10). In the present case, the patient became afebrile and showed improvement in inflammatory markers in blood tests 20 days after G-CSF administration without steroid treatment. Steroid administration may need to be considered in more severe cases or in cases where aortitis persists even after discontinuation of G-CSF (14).

The acceptability of re-administering G-CSF to patients with a history of G-CSF-induced aortitis remains controversial. Takamatsu *et al* (11) reported that among 11 asymptomatic patients with clinically undiagnosed pegfilgrastim-induced aortitis, eight patients received additional pegfilgrastim treatment, and none of them showed recurrence of aortitis on CT. They also stated that the results did not indicate the safety of pegfilgrastim re-administration and that the risk of recurrence after re-administration remained unclear (11).

Although G-CSF-induced aortitis is uncommon, clinicians should exercise caution when treating patients with malignant tumors. If a patient presents with a persistent fever of unknown origin after receiving G-CSF, G-CSF-induced aortitis should be considered as a potential cause during diagnostic workup. The treatment for G-CSF-induced aortitis has not yet been established. However, the discontinuation of G-CSF and, in some cases, steroid administration should be considered depending on the severity of the condition. Therefore, clinicians should closely monitor the clinical course of patients to guide appropriate treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SF and HH designed the experiments and wrote the initial draft of the manuscript. SF and HH confirm the authenticity of all the raw data. SF, HH, NF, RS, TT, TM and YN provided medical care for the patients and collected the data. RK and TA were responsible for the design and interpretation of the study as well as revisions and approval of the final draft of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient was informed that data from the case would be submitted for publication and provided consent for the academic use of clinical information.

Competing interests

The authors declare that they have no competing interests.

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