

[CASE REPORT]

Granulocyte Colony-stimulating Factor-induced Aortitis with Lung Injury, Splenomegaly, and a Rash During Treatment for Recurrent Extrasosseous Mucinous Chondrosarcoma

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Abstract:

We herein report a case of aortitis induced by granulocyte colony-stimulating factor (G-CSF) that coincided with lung injury, splenomegaly, and cutaneous manifestations during treatment for recurrent extrasosseous mucinous chondrosarcoma. Computed tomography revealed large-vessel vasculitis, splenomegaly, and pulmonary interstitial changes. Treatment with prednisolone was successful. Because sarcoma is a rare disease, this case is valuable for showing clinicians that G-CSF preparations could cause aortitis regardless of the patient's underlying diseases or therapeutic pharmacological backgrounds.

Key words: G-CSF, aortitis, pegfilgrastim, sarcoma

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Introduction

Granulocyte colony-stimulating factor (G-CSF) preparations are commonly used to prevent and treat neutropenia caused by cancer chemotherapy. Meta-analyses of randomized controlled trials of G-CSFs as primary prophylaxis against febrile neutropenia have demonstrated significant reductions in the rates of short-term all-cause mortality, as well as rates of infection-related mortality, in patients with solid tumors and malignant lymphoma (1, 2). A meta-analysis of 59 randomized controlled trials demonstrated that systemic cancer chemotherapy with primary adjunct G-CSF treatment was associated with a significantly greater intensity of the effect of the delivered chemotherapy doses and with greater relative and absolute risk reductions in all-cause mortality rates than was chemotherapy without adjunct G-CSF treatment over a long period (3). As for drug safety,

Teshima et al. reported that according to the results of their post-marketing use survey in Japan, the rate of overall adverse effects was 7.47%; these effects included lumbago (3.84%), fever (1.62%), and bone pain (0.61%), and most were not serious and seemed to be ameliorated by the discontinuation of G-CSF treatment (4).

However, a few cases with serious adverse effects, such as interstitial pneumonia and extramedullary hematopoietic splenic rupture, have been reported after the administration of G-CSF (5, 6). Pegfilgrastim, a relatively new G-CSF used to prevent febrile neutropenia, is a modified protein consisting of methoxy polyethylene glycol (PEG) molecular chains attached to a Met1 amino group of genetic recombinant filgrastim whose renal excretion is reduced and whose effects are prolonged (7). In Japan, pegfilgrastim is approved for use only to prevent febrile neutropenia after chemotherapy. To optimize its pharmacological effect and prevent adverse effects, the use of pegfilgrastim is restricted to patients at

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Figure 1. Erythematous skin lesions on the right cubital fossa (a) and over the left knee socket (b), on admission.

high risk for febrile neutropenia at least 24 hours after a course of chemotherapy. Over the past two decades, authors have reported cases of aortitis induced by G-CSF preparations such as filgrastim, lenograstim, and pegfilgrastim (8, 9). Oshima et al., using the Japanese Adverse Drug Event Report database, reported that G-CSF treatment is associated with an increased risk for aortitis (10).

We herein report a case of G-CSF-induced aortitis that coincided with lung injury, splenomegaly, and rash during treatment for extrasosseous mucinous chondrosarcoma. This is a rare case of G-CSF induced aortitis occurred in a patient who was being treated for sarcoma and it is valuable for showing clinicians that G-CSF preparations could cause aortitis regardless of the patient's underlying diseases or therapeutic pharmacological background.

Case Report

A 56-year-old man who was receiving treatment for the local recurrence of extrasosseous mucinous chondrosarcoma on the right lower limb presented to our hospital because of an 8-day history of high fever, general fatigue, and a rash with pain. He did not report either any upper or lower respiratory symptoms, abdominal pain, diarrhea, arthralgias, headache, or visual impairment. He had finished the first 4-day course of chemotherapy with 2-day adriamycin (25 mg/m² each) and four-day ifosfamide (2.8 g/m² each), followed 36 hours later by subcutaneous administration of pegylated G-CSF (3.6 mg), and he was discharged immediately. Four days later, the symptoms began.

On presentation, he did not appear ill, and he was alert and oriented. His body weight was 69.4 kg, and his height was 169 cm. His vital signs were as follows: blood pressure, 90/47 mm Hg; pulse rate, 95 beats/min; body temperature, 39.1°C; respiratory rate, 12/min; and oxygen saturation level, 99% on room air. A physical examination revealed palm-sized dark red-to-purplish indurated rashes with ten-

derness on the right cubital fossa and over the left knee socket (Fig. 1a, b). The surface lymph nodes, liver, and spleen were not palpable. The initial laboratory data revealed the following: a white blood cell count of 15,780/μL (90.0% segmented neutrophils, 7.0% stab neutrophils 1.0% monocytes, 2.0% lymphocytes, and 0% atypical lymphocytes, visually confirmed), hemoglobin level of 11.8 g/dL, platelet count of 109,000/μL, and serum C-reactive protein level of 38.77 mg/dL. Table lists the other laboratory data. The results of antigen tests for influenza virus were negative. Two sets of blood culture were conducted. Computed tomography (CT) without contrast media revealed inflammatory changes in the soft tissue surrounding the aorta, partial reticular change and ground-glass opacities scattered throughout both lungs, and splenomegaly (Fig. 2).

Because he was immunocompromised, we diagnosed systemic inflammatory response syndrome and acute renal failure caused by bacterial infection. We promptly administered 2 L of crystalloid infusion for resuscitation and empirical piperacillin/tazobactam as shown in Fig. 3. His renal function was restored rapidly, but high-grade fever persisted for 4 days, as did the inflammatory markers, despite antibiotic treatment. However, this patient did not appear ill, and his food intake did not decrease during the first 4 days after his admission to this hospital. Furthermore, even with a high-grade fever (>40°C), his pulse rate had stayed in the range of 60/min to 70/min, which represented relative bradycardia, which in turn has been considered a characteristic of drug-related fever (11). A blood culture yielded negative results, as did serological tests (including cytomegalovirus antigen and autoantibodies); thus, we diagnosed aortitis resulting from G-CSF administration.

Because of concerns about the high-grade fever and the pulmonary findings, we initiated treatment with prednisolone, 60 mg (1 mg/kg) orally on the fourth day of hospitalization. His fever resolved within the day, followed by a rapid improvement in his general condition and laboratory data. The rash had improved simultaneously, although the skin discoloration remained. Six days after initiating prednisolone, we tapered the dosage to 40 mg and discharged the patient on day 18 (Fig. 3). At the 3-month follow-up visit, the patient remained well with the prednisolone dose of 7.5 mg/day, which was discontinued 3 months later.

Discussion

As in other immunocompromised patients after the administration of anticancer drugs, we had to rule out vasculitis secondary to infections before diagnosing the drug-induced aortitis, since infectious disease was strongly associated with systemic vasculitis, including aortitis (12). Hence, it might be important in such patients to evaluate them for common infectious diseases that are often overlooked-not only bacterial bloodstream infections but also tuberculosis, syphilis, viral hepatitis, and human immunodeficiency virus-that are known causes of vasculitis before G-CSF-induced

Table. Laboratory Data on Admission.

Complete blood count		Serological test		Urine test	
WBC	15,780 ×10 ³ /μL	CRP	38.77 mg/dL	occult blood	2+
N-Stab	7 %	IgG	828 mg/dL	ketone	negative
N-Seg	90 %	IgA	327 mg/dL	glucose	negative
Eosino	0 %	IgM	103 mg/dL	protein	1+
Baso	0 %	IgE	53 mg/dL	Urinary sediment	
Mono	1 %	CH50	>60 CH50/mL	RBC	<4 /HPF
Lymph	2 %	C3	162 mg/dL	WBC	<4 /HPF
RBC	442 ×10 ⁴ /μL	C4	45 mg/dL	Squamous cell	0-1 /HPF
Hemoglobin	11.8 g/dL	sIL-2R	1,922 U/mL	cast	positive
Platelet	109 ×10 ⁴ /μL	ANA	<80	β2 microglobulin	18.7 mg/dL
Biochemistry		PR3-ANCA	<1.0 U/mL		
TP	6.2 g/dL	MPO-ANCA	<1.0 U/mL		
Alb	2.4 g/dL	anti ssDNA	2.5 AU/mL		
T-bil	0.8 mg/dL	anti dsDNA	<1.2 IU/mL		
D-bil	0.5 mg/dL	ASO	38 IU/mL		
AST	22 U/L	ASK	×320		
ALT	99 U/L	PCT	0.58 ng/mL		
Ch-E	157 U/L	IGRA	negative		
ALP	1,077 U/L	RPR	<1.0		
LAP	149 U/L	TPHA	0		
γ-GTP	302 U/L	HCV Ab	0.03		
LD	208 U/L	HBs Ag	0 IU/mL		
CK	19 U/L	CMV IgG	64 UA/mL		
UN	33 mg/dL	CMV IgM	negative		
Creatinine	2.29 mg/dL	ESR	114 mm/hr		
Na	139 mmol/L				
K	3.7 mmol/L				
Cl	101 mmol/L				
Blood Sugar	159 mg/dL				
HbA1c	6.4 %				

WBC: white blood cell, RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, N-stab: stab neutrophil, N-seg: segmented neutrophil, Eosino: eosinophil, Baso: basophil, Mono: monocyte, Lymph; Lymphocyte, TP: total protein, Alb: albumin, T-bil: total bilirubin, D-bil: direct bilirubin, Ch-E: cholinesterase, ALP: alkaline phosphatase, LAP: leucine aminopeptidase, γ-GTP: γ-glutamyl transpeptidase, LD: lactate dehydrogenase, UN: urea nitrogen, CK: creatine kinase, Na: sodium, K: potassium, Cl: chloride, HbA1c: hemoglobine A1c, CRP: C-reactive protein, IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, IgE: Immunoglobulin E, CH50: 50% hemolytic complement activity, sIL-2 R: soluble Interleukin-2 receptor, ANA: antinuclear antibody, PR3-ANCA: serine proteinase3-anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, anti-ssDNA: anti-single-stranded DNA antibody, anti-dsDNA: anti-double stranded DNA antibody, ASO: antistreptolysin O, ASK: antistreptokinase, PCT: procalcitonin, IGRA: interferon-gamma releasing assay, RPR: rapid plasma reagin card agglutination test, TPHA: treponema pallidum antibody hemagglutination test, HCV ab: hepatitis C virus antibody, HBs Ag: hepatitis B virus antigen, CMV IgG: cytomegalovirus antibody, immunoglobulin G, CMV IgM: cytomegalovirus antibody, immunoglobulin M, ESR: erythrocyte sedimentation rate

aortitis is diagnosed (13).

In this case, pegfilgrastim was administered 36 hours after the completion of the first cycle of AI (adriamycin, ifosfamide) chemotherapy, and a series of symptoms had begun 4 days later. Most cases of G-CSF-induced aortitis had been reported to occur 1 to 15 days after the administration of G-CSF, and a few cases were reported to develop 1 month to 1 year later (8, 14). This variation in the latent period, which could interfere with the clinical diagnosis, might result from pharmacodynamic and pharmacokinetic factors such as the type and amount of G-CSF used, type of the preceding chemotherapy, and individual physiological differences. In fact, pegfilgrastim and lipegfilgrastim, which both have a longer

half-life and produce equivalent effects with fewer administrations, have been most often reported as the drug causing aortitis (8-10). It is of interest that this condition has been reported more often in women than in men, although more detailed cases and epidemiological studies are needed to prove that G-CSF-induced aortitis is indeed more common in women.

Searching on web, G-CSF-induced aortitis in a patient being treated for sarcoma was thus found to be extremely rare. One reason why no cases of G-CSF-induced aortitis were previously reported in patients with sarcomas might be due to the low absolute number of such patients. Ogura et al. reported that according to a nationwide organ-specific cancer

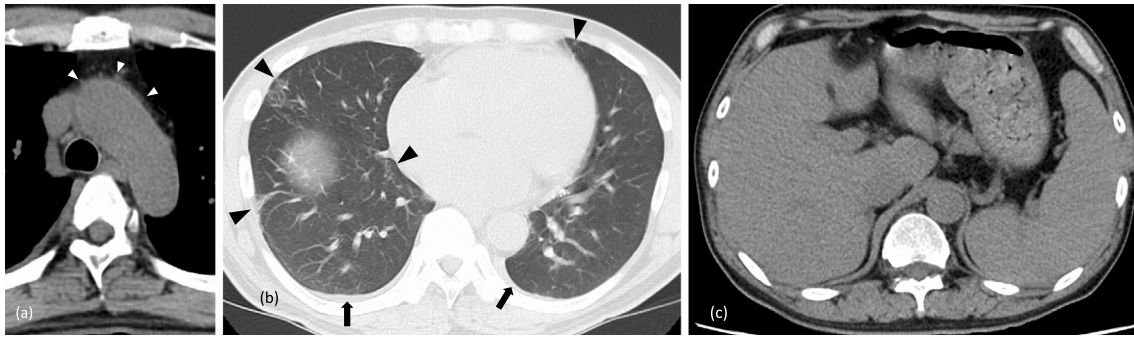


Figure 2. Computed tomography (CT) without contrast media, showing aortitis (a; white arrowheads), patchy interstitial changes scattered throughout both lungs (b; black arrowheads) and a small amount of pleural effusion (b; yellow arrowheads), and splenomegaly (c).

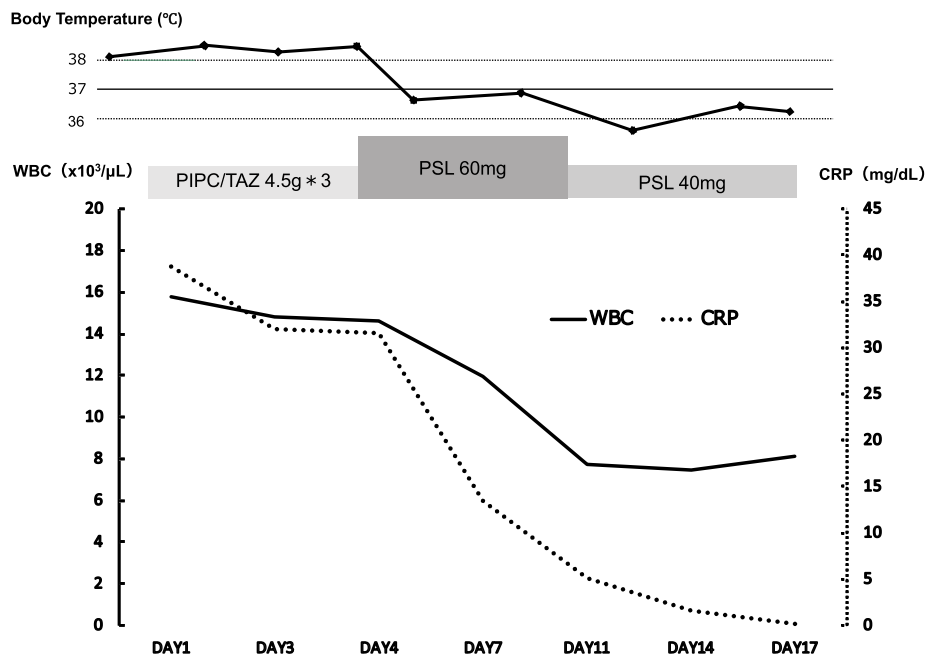


Figure 3. Clinical course of this case. CRP: C-reactive protein, PIPC/TAZ: piperacillin/tazobactam, PSL: prednisolone, WBC: white blood cell count

registry for bone and soft tissue tumors in Japan, the number of patients with sarcomas in 2012 was 1,598, which is an extremely low proportion of the 865,238 cases of all cancers (15, 16). We believe that this case report, which concerns an orthopedic cancer, is important because the biological evidence that the administration of G-CSF could provoke aortitis is still lacking.

Although this patient did not exhibit any pulmonary manifestations, the lung interstitial changes found on CT seemed critical and warranted the administration of steroids, since there had been many reports of G-CSF-related pulmonary toxicity, which in some cases progressed to acute respiratory distress syndrome and to death (17-19). In a review of 20 cases of interstitial pneumonia secondary to treatment with G-CSF, Niitsu et al. reported that three patients died of respiratory and multiple organ failure; consequently, they emphasized the importance of starting steroid pulse therapy as early as possible when the diagnosis is made (20).

Although the skin lesions that this patient exhibited were not histologically confirmed, we speculated, from their macroscopic appearance, that they represented neutrophilic eccrine hidradenitis, which is neutrophilic dermatosis characterized by the sudden onset of erythematous papules or plaques with a neutrophilic infiltrate around eccrine glands, together with necrosis of these structures. Rising concentrations of the cytotoxic agents in sweat are thought to be the mechanism of neutrophilic eccrine hidradenitis, and doxorubicin is known to be one of the common causative substances (21). It is of interest that several such cases have been reported to be associated with the administration of G-CSF, and one of them occurred in patients who received pegfilgrastim after AI chemotherapy (22, 23).

Without any guidelines available for the treatment of drug-induced aortitis, we set the initial dose of prednisolone as 60 mg, administered it orally, according to the Guideline for Management of Vasculitis Syndrome (Japanese Circula-

tion Society 2008) for the diagnosis of giant cell arteritis (24). However, several cases of G-CSF-induced aortitis that remitted without the administration of prednisolone have been reported. We think that the degree of inflammatory response might vary in individual cases, and so the clinical decision of whether to administer prednisolone must be individualized. In our patient, prednisolone treatment was necessary because of sustained high-grade inflammatory markers and interstitial changes in the lungs.

In summary, we herein described a case of G-CSF-induced aortitis that coincided with lung injury, splenomegaly, and rash during treatment for extrasosseous mucinous chondrosarcoma. The patient required PSL administration because of the lung injuries and persisting high grade fever. The response to the treatment with PSL was good, and the patient had recovered without any sequelae. It has been almost 30 years since filgrastim was introduced to the market. However, G-CSF induced aortitis has not been well recognized. We speculate that one reason for this might be the lack of algorithm to predict patients at high risk to present this condition. Secondly, there is lack of specific signs and symptoms. In addition, as we described above, the condition sometimes subsides without the administration of steroids or immuno-suppressants which are usually indispensable for the treatment of other types of vasculitis syndrome. Therefore, we speculate that many cases of G-CSF induced may have been overlooked. This case report might be one type of supportive evidence of G-CSF induced aortitis, however, it is necessary to collect and examine future cases regarding what kind of patients: sex, races, age etc., are likely to present with aortitis due to G-CSF.

The authors state that they have no Conflict of Interest (COI).

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