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Case Report

Recurrence of Large-Vessel Vasculitis Induced by Multiple Types of Granulocyte Colony-Stimulating Factor Preparation in Patient with Large-Cell Neuroendocrine Lung Carcinoma: A Case Report

Yurie Seto Tadaaki Yamada Masashi Egami Takumi Sugimoto Izumi Sato Satomi Tanaka Yusuke Chihara Kenji Morimoto Masahiro Iwasaku Shinsaku Tokuda Yoshiko Kaneko Koichi Tamayama

Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

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Filgrastim · Granulocyte colony-stimulating factor · Large-vessel vasculitis · Pegfilgrastim · Case report

Abstract
With the increased use of granulocyte colony-stimulating factor (G-CSF) preparations, there is concern about the increase in G-CSF-associated large-vessel vasculitis; however, there have been no previous reports of vasculitis caused by multiple types of G-CSF preparations. We experienced a case of drug-induced large-vessel vasculitis caused by two different G-CSF products, which was difficult to diagnose. When treating patients with a history of large-vessel vasculitis caused by pegfilgrastim, we need to pay attention to its recurrence when using other G-CSF preparations.

Introduction

Granulocyte colony-stimulating factor (G-CSF) is an effective treatment for neutropenia as it promotes the differentiation and proliferation of the granulocyte system in bone marrow, enhances neutrophil function, and has antiapoptotic effects on neutrophils [1, 2]. G-CSF

Correspondence to:
Tadaaki Yamada, tayamada@koto.kpu-m.ac.jp

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preparations are used to treat and prevent febrile neutropenia in patients treated with cytotoxic anticancer drugs and are important for maintaining the relative dose intensity, which has a significant impact on prognosis [3]. Pegfilgrastim is an approved long-acting G-CSF preparation and its use has increased in Japan and other countries. Although G-CSF preparations induced relatively few side effects, in recent years, there have been scattered reports of G-CSF preparation-induced large-vessel vasculitis, especially in Japan [4, 5]. As a result, in Japan, the package inserts for pegfilgrastim and filgrastim were revised to include "large-vessel vasculitis (inflammation of aorta, common carotid artery, subclavian artery, etc.) (frequency unknown)" as a serious adverse reaction in 2018. There have been no previous reports of vasculitis caused by multiple types of G-CSF preparations. Here, we report a case of drug-induced large-vessel vasculitis caused by two different G-CSF products, which were fever-induced and difficult to diagnose.

Case Report

A 71-year-old male, a former smoker, developed rheumatoid arthritis at the age of 61 and started medication for worsening joint symptoms at the age of 63 years. His joint symptoms had gradually worsened over a long period of time, and at the time of admission, he was taking immunosuppressive drugs (iguratimod, bucillamine, salazosulfapyridine) as well as prednisolone. In December 201X, he developed large-cell neuroendocrine carcinoma (LCNEC) stage IB and underwent partial resection of the lower lobe of the left lung. The patient subsequently relapsed in July 201X + 1 and started systemic chemotherapy (cisplatin [80 mg/m^2, day 1]) and etoposide [100 mg/m^2, days 1–3]) in September 201X + 1. In addition, after culture tests of bronchial lavage fluid collected during bronchoscopy detected *Mycobacterium tuberculosis* (TB), the patient was diagnosed with bronchial tuberculosis and antituberculosis drugs (rifampicin, Isoniazid, pyrazinamide [PZA], ethambutol for 2 months, then rifampicin and isoniazid for 7 months) were initiated.

Clinical Course (A)

First-course systemic chemotherapy for 3 days was initiated in September 201X + 1, as shown in Figure 1a. Pegfilgrastim (3.6 mg/body) was administered on day 4 because of concerns about pulmonary TB relapse. Grade 1 fever according to the Common Terminology Criteria for Adverse Events version 5.0, appeared on day 9, and the antibacterial agent meropenem was started. Although no examination findings were suggestive of signs of infection, including blood and urine cultures, grade 3 fever appeared on day 14. His remittent fever continued, and on day 20 his body temperature rose to a maximum of 40.3°C. The patient had no other specific subjective symptoms. As the CRP level gradually rises in parallel with fever, we attempted to screen for the source of fever. However, a contrast-enhanced CT scan on day 21 did not show any evidence of a fever source (Fig. 2, 3). Accordingly, the antituberculosis drug PZA was discontinued on day 21 due to suspected PZA-induced fever, but spike fever continued and gradually normalized at day 28.

Clinical Course (B)

Second-course systemic chemotherapy for 3 days was initiated in November 201X + 1, as shown in Figure 1b. Pegfilgrastim was readministered on day 4 of the second course of chemotherapy, and the patient developed a grade 2 fever on day 10, followed by remittent fever. On day 15, his body temperature rose to a maximum of 39.2°C. Contrast-enhanced CT on day 14 showed wall thickening of the aorta and left subclavian artery and contrast effects on the surrounding soft tissues, which were not seen before the start of chemotherapy (Fig. 3c). No skin lesions or other organ symptoms were noted. Giant cell arteritis and Takayasu arteritis were also

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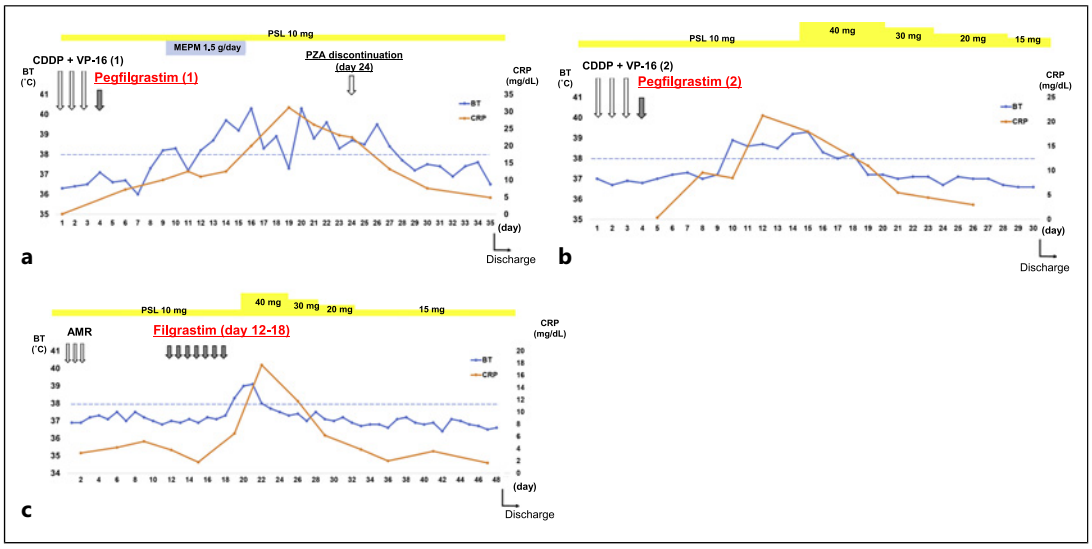

Fig. 1. Clinical course of the case patient. **a** Shows the clinical course after the first pegfilgrastim administration. **b** Shows the clinical course of the second pegfilgrastim administration. **c** Shows the clinical course after the filgrastim administration during amrubicin monotherapy. AMR, amrubicin; BT, body temperature; CDDP, cisplatin; CRP, C-reactive protein; CT, computed tomography; MEPM, meropenem; PSL, prednisolone; PZA, pyrazinamide; VP-16, etoposide.

listed as differential diagnoses but did not meet the American College of Rheumatology classification criteria. Blood tests were negative for MPO-ANCA, PR3-ANCA (chemiluminescent enzyme immunoassay), and antinuclear antibody (indirect fluorescent antibody method). We suspected drug-induced acute aortitis due to pegfilgrastim because the clinical course was similar to that of the first course of chemotherapy. To treat for acute aortitis, PSL was increased to 40 mg/day and the fever resolved quickly thereafter. The patient did not develop fever after the third and subsequent courses of chemotherapy, without pegfilgrastim. Based on these clinical courses, the patient was diagnosed with pegfilgrastim-induced aortitis.

Clinical Course (C)

Due to worsening of LCNEC, amrubicin (AMR [35 mg/m^2, day 1–3]) was started in July 201X + 2 as second-line chemotherapy. To avoid the incidence of severe neutropenia and the use of G-CSF agents, AMR was administered at a reduced dose of 35 mg/m^2. The clinical course of second-line chemotherapy for LCNEC is shown in Figure 1c. Despite AMR dose reduction, grade 4 neutropenia appeared on day 12 after administration of AMR. After fully explaining the risks and benefits of administration of G-CSF preparation to the patient, another G-CSF preparation, filgrastim (75 μg/day), was administered from day 12–18. He developed a grade 2 fever on day 20, followed by remittent fever. On day 21, his body temperature rose to a maximum of 39.1°C. No obvious signs of infection were noted and contrast-enhanced CT on day 21 showed recurrence of vessel wall thickening in the aorta and left subclavian artery (Fig. 3d). PSL was increased to 40 mg/day for the treatment of G-CSF-associated vasculitis, and the fever resolved promptly thereafter. After PSL was reduced to a baseline of 10 mg/m^2, treatment with AMR was continued at a reduced dose of 30 mg/m^2 for a total of five courses. No fever or vasculitis was observed during this period, and filgrastim was not used. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533375).

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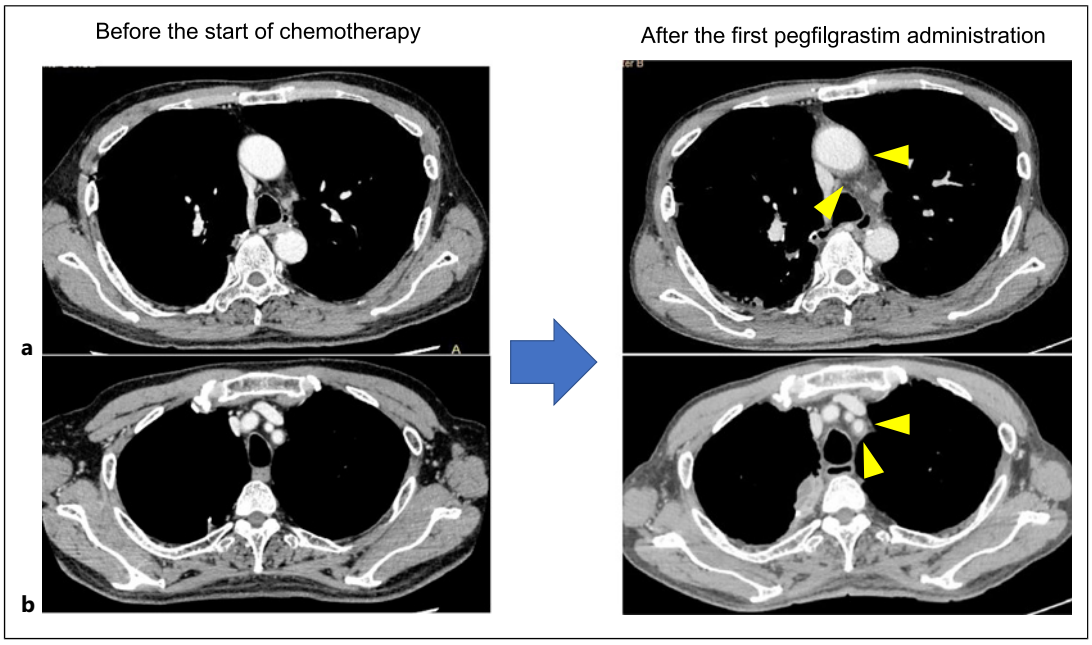

Fig. 2. CT scan findings: The two left images were taken before the start of chemotherapy. The two in the right show wall thickening and periaortic soft tissue infiltration of the aorta (**a**) and left subclavian artery (**b**) on day 18 after the first pegfilgrastim administration.

Discussion

Drug-induced vasculitis caused by G-CSF preparations was first reported by Darie et al. [6] in France in 2004. Interestingly, since then, more than 20 cases have been reported to date, the majority being Japanese women [4]. It was reported that vasculitis develops on average 5 days (range: 1–8 days) after the last administration of G-CSF preparations [7], although the longest case reported developed vasculitis 6 months after G-CSF administration [8]. In our case, the three onsets of vasculitis ranged from 5 to 8 days, which is consistent with previous reports.

Vasculitis caused by G-CSF preparations is most reported with pegfilgrastim but others have been reported with filgrastim and lenograstim, indicating that all G-CSF products are at risk for causing drug-induced vasculitis [9]. The most common sites of vasculitis are the thoracic and abdominal aorta, carotid artery, and subclavian artery [10]. There are scattered cases of aortitis that closely resemble giant cell arteritis, and one case of temporal arteritis has been reported [11]. Our case is consistent with a previously reported clinical course of G-CSF-associated vasculitis. Steroid therapy is often used and is very effective, but some cases have improved without steroid therapy [4]. The prognosis of drug-induced vasculitis by G-CSF is relatively good; however, there have been reports of aortic dissection [12] and aneurysm formation [8] as severe complications. Interruption of chemotherapy due to vasculitis is also a serious issue for patient prognosis. Therefore, intervention with steroid therapy should be seriously considered. There have been reports of inadequate steroid dosage at 0.5 mg/kg of PSL, and many cases have reported a 1 mg/kg equivalent as being effective. However, the appropriate duration for PSL treatment remains uncertain. There are reports of cases in which the PSL dose can be reduced quickly from a high dose and treatment can be completed within 2 months [13, 14]. In this case, the patient was already on PSL 10 mg/day for treatment for rheumatoid arthritis. When the patient was diagnosed with vasculitis, the dose was increased

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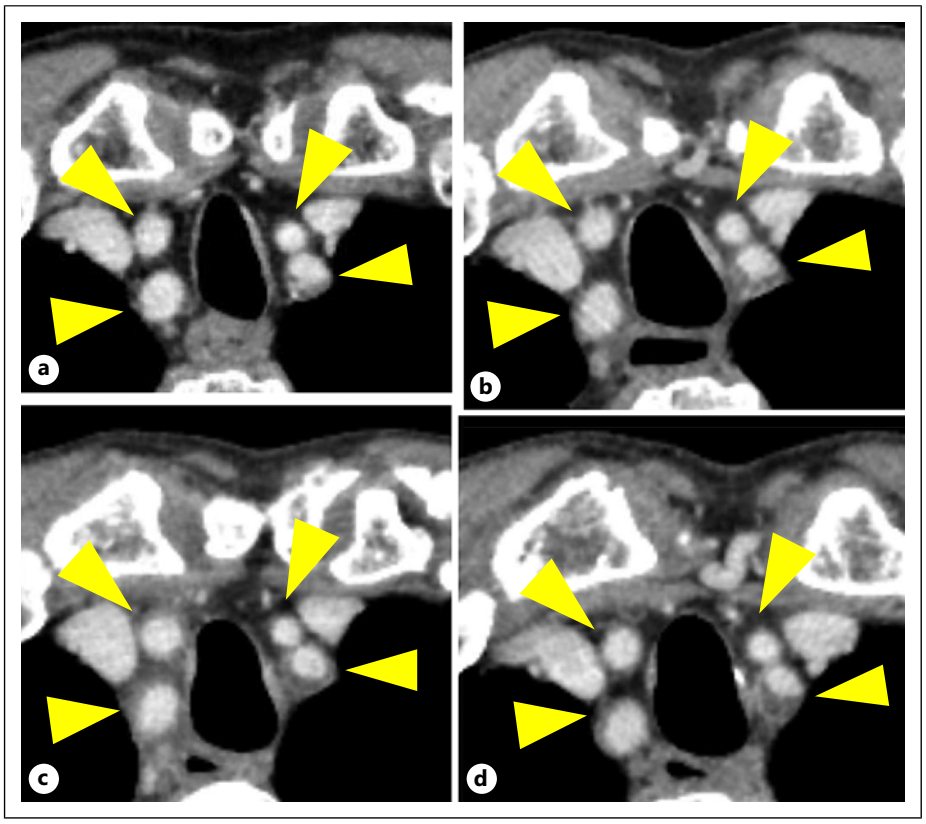

Fig. 3. CT scan findings: the bilateral common carotid artery and the bilateral subclavian arteries (yellow arrows). **a** Before administration of G-CSF agents, (**b**) on day 18 after the first pegfilgrastim administration, (**c**) on day 11 after the second pegfilgrastim administration, (**d**) on day 9 after the start of filgrastim administration.

to 40 mg/day (0.8 mg/kg/day), and thereafter, reduced to baseline over 1–2 weeks. The reason for the delay in diagnosis was that the fever spontaneously resolved within 2 weeks, and there were several clinical factors, such as rheumatoid arthritis, TB, and immunosuppression due to drug fever or anticancer drugs. Steroid therapy for vasculitis requires exclusion of the possibility of infection. In this case, blood cultures were negative and imaging studies showed no obvious evidence of infection.

Based on our case, we need to pay attention to the emergence of G-CSF-associated vasculitis as a cause of fever, although this is less common. Moreover, the administration of filgrastim after the development of pegfilgrastim-related vasculitis can cause vasculitis flareups.

This is the first report of vasculitis caused by multiple G-CSF preparations. The novel observations drawn from this case are that (1) fever can serve as an initial symptom when drug-induced large-vessel vasculitis develops, and (2) repetitive occurrences of drug-induced vasculitis can stem from the administration of two types of G-CSF preparations. It is well known that in autoimmune diseases such as rheumatoid arthritis, IL-6 induces an excessive inflammatory response owing to immune abnormalities [15]. Conversely, G-CSF promotes autoimmunity by inducing immune mediators such as IL-2 and IL-6 to generate pathological Th17 cells and enhance IL-6-dependent survival of antigen-specific CD4 + T cells [16]. These mechanisms are postulated to be involved in the aetiology of drug-induced aortitis [8], and IL-6 has been reported to mediate the progression of aortic dissection in animal models [17]. In the past, immune diseases such as leukocytoclastic vasculitis and rheumatoid arthritis have

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been reported to be exacerbated by G-CSF administration [18, 19]. The patient was receiving treatment for rheumatoid arthritis at the onset of vasculitis. Although the joint symptoms that are seen in exacerbation of rheumatoid arthritis were not evident, we speculate that several cytokines derived from G-CSF stimulation might have played pivotal roles in the pathogenesis in vasculitis. In a previous report, vasculitis occurred with pegfilgrastim but not with filgrastim [20]. This suggests that pegfilgrastim, which has a longer elimination half-life in the blood, may have induced vasculitis more than filgrastim because G-CSF continued to activate neutrophils, but in this case, vasculitis occurred even after switching to filgrastim, a formulation with a shorter half-life. It is possible that the pathogenesis of rheumatoid arthritis made the vasculitis more likely to be triggered. Alternatively, the amount of G-CSF exposure might show a causal relationship with the onset of vasculitis. Although G-CSF-associated vasculitis has a good prognosis, it must be promptly diagnosed and treatment initiated to improve the patient's quality of life and, most importantly, to continue chemotherapy to control the cancer.

Conclusion

We experienced a case of drug-induced large-vessel vasculitis caused by two different G-CSF products, which were fever-induced and difficult to diagnose. When fever of unknown origin is observed during G-CSF administration, a systemic search for large-vessel vasculitis should be performed in addition to infectious diseases and other common causes of fever.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study was exempted from ethical approval by the Ethics Committee of the University Hospital, Kyoto Prefectural University of Medicine.

Conflict of Interest Statement

T.Y. received commercial research grants from Pfizer, Ono Pharmaceutical, Janssen Pharmaceutical K.K., AstraZeneca, and Takeda Pharmaceutical Company Limited and has received speaking honoraria from Eli Lilly. K.T. reports receiving research grants from Chugai-Roche Co., and Ono Pharmaceutical Co., and personal fees from AstraZeneca Co., Chugai-Roche Co., MSD-Merck Co., Eli Lilly Co., Boehringer-Ingelheim Co., and Daiichi-Sankyo Co. No potential conflicts of interest were disclosed by the other authors.

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Author Contributions

M.E. and Y.S. were the attending physician at the time of admission and wrote the manuscript. T.Y. was an outpatient attending physician and made critical revisions to the manuscript. T.S., I.S., S.T., and Y.C. were the attending physicians on admission and performed the data collection and treatment. K.M., M.I., S.T., Y.K., and K.T. provided advice on treatment decisions and wrote the paper. The final manuscript has been read and approved by all authors.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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