

CASE REPORT

Eflapegrastim-induced large vessel vasculitis in patient treated with recurrent uterine leiomyosarcoma

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Abstract

Background: Granulocyte colony-stimulating factor (G-CSF) is widely used to prevent febrile neutropenia during chemotherapy. However, it can rarely induce large-vessel vasculitis (LVV), a condition that is challenging to recognize early and may lead to serious complications. **Case:** A 66-year-old woman with recurrent uterine leiomyosarcoma received long-acting G-CSF (eflapegrastim) for prophylaxis against neutropenia after initial systemic chemotherapy. Ten days after the first administration of eflapegrastim, she developed fever and fatigue. Contrast-enhanced computed tomography (CT) revealed new circumferential wall thickening of the aortic arch, proximal descending thoracic aorta, left proximal common carotid artery, and proximal subclavian artery. Positron emission tomography (PET) subsequently demonstrated increased fluorodeoxyglucose uptake, supporting a diagnosis of acute vasculitis. Corticosteroid therapy was promptly initiated after multidisciplinary discussion, resulting in rapid symptomatic improvement within 2 weeks and complete radiologic resolution after 4 weeks. **Conclusion:** Acute LVV induced by long-acting G-CSF is an emerging adverse event with potentially life-threatening consequences. Early suspicion and prompt use of imaging modalities, such as CT and PET, are essential for accurate diagnosis, enabling timely corticosteroid therapy and improved clinical outcomes.

Keywords

Granulocyte-colony stimulating factor; Eflapegrastim; Large-vessel vasculitis; Workup

1. Introduction

Granulocyte colony-stimulating factor (G-CSF) is widely administered to reduce the incidence of febrile neutropenia during cytotoxic chemotherapy, thereby facilitating treatment delivery and improving clinical outcomes [1]. G-CSF stimulates the proliferation and differentiation of neutrophil precursors and is generally considered safe, with most adverse effects being mild and transient, including bone pain, headache, fatigue, or leukocytosis [2, 3]. However, rare but clinically significant inflammatory complications have been increasingly reported, particularly large-vessel vasculitis (LVV) [4–7]. Early recognition is essential, as timely discontinuation of G-CSF and prompt initiation of corticosteroid therapy typically result in rapid clinical improvement and prevent serious complications, such as aneurysm formation or dissection [8, 9].

We present a case of acute, steroid-responsive LVV following first administration of long-acting G-CSF (eflapegrastim) in a patient receiving adjuvant chemotherapy for recurrent uterine leiomyosarcoma. This case underscores the importance of maintaining clinical suspicion and early imaging in patients presenting with fever after exposure to long-acting G-CSF.

2. Case report

A 66-year-old woman, gravida 2 para 2 with a history of two cesarean deliveries, was evaluated for an incidentally detected uterine mass. She had no history of vascular or autoimmune diseases and did not use tobacco or alcohol. She underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) and final pathology confirmed uterine leiomyosarcoma, International Federation of Gynecology and Obstetrics (FIGO) stage IA, measuring 3.5 cm, with 36 mitoses per 10 high-power fields (HPF), without necrosis or lympho-vascular invasion. No adjuvant therapy was administered, and she was followed with surveillance imaging. Two years later, follow-up chest computed tomography (CT) revealed multiple pulmonary nodules suggestive of metastasis, which were confirmed via positron emission tomography (PET). She underwent video-assisted thoracoscopic surgery (VATS) wedge resection and pathology confirmed metastatic leiomyosarcoma.

Systemic chemotherapy was initiated with doxorubicin plus ifosfamide. Prophylactic long-acting G-CSF (eflapegrastim) was administered the following day. Ten days after exposure to eflapegrastim (08 August 2025), the patient developed per-

sistent fever and severe fatigue. On admission, her vital signs were: blood pressure, 113/78 mmHg; heart rate, 110 beats/min; respiratory rate, 20 breaths/min; and body temperature, 38.3 °C. Laboratory evaluation revealed leukocytosis (white blood cell (WBC), 36,700/ μ L; reference range, 4000–10,800/ μ L) and elevated C-reactive protein (CRP, 10 mg/dL; reference range, 0–0.3 mg/dL), whereas procalcitonin was within normal limits (0.157 ng/mL). Contrast-enhanced CT demonstrated circumferential mural thickening and perivascular inflammation involving the aortic arch, proximal descending thoracic aorta, left proximal common carotid artery, and left proximal subclavian artery (Fig. 1). Subsequent PET revealed increased fluorodeoxyglucose (FDG) uptake in the aortic arch and its major branches, consistent with active inflammation, without evidence of recurrent malignancy (Fig. 2). Given the absence of infection and the temporal relationship to G-CSF, G-CSF-induced LVV was strongly suspected despite markedly elevated inflammatory markers. Further evaluation with echocardiography demonstrated normal cardiac structure and function. Blood and urine cultures were negative.

Following multidisciplinary discussion, systemic corticosteroid therapy was initiated with oral prednisolone 10 mg three times daily (30 mg/day). This specific dose was selected as a moderate-to-high induction regimen (typically 0.5–1.0 mg/kg/day) to ensure rapid suppression of the acute vascular inflammation, while minimizing the risk of profound immunosuppression in the setting of active recurrent malignancy and recent cytotoxic chemotherapy. The patient's starting dose (equivalent to approximately 0.5 mg/kg/day) was selected based on this general treatment principles, adjusted for the patient's body weight of 58 kg. Because there was no evidence

of thrombosis or ischemia, no additional treatments, such as anticoagulants, were administered. The patient's fever and systemic symptoms resolved rapidly with corticosteroid monotherapy. After 2 weeks, prednisolone was tapered to 10 mg twice daily (20 mg/day). At 4 weeks, follow-up chest CT demonstrated complete resolution of vascular inflammation (Fig. 3), and prednisolone was further reduced to 10 mg daily. Over a subsequent follow-up period of 3 months since the discontinuation of corticosteroids, the patient has remained stable with no clinical or radiological evidence of vasculitis recurrence. Owing to intolerable chemotherapy-related toxicity and the absence of active disease on imaging, the patient elected to discontinue further chemotherapy. Given the severe nature of this adverse event, long-acting G-CSF was permanently discontinued, and no rechallenge was attempted to avoid life-threatening exacerbations. She remains under surveillance with chest and abdomen CT scans every 3 months.

3. Discussion

LVV following exposure to G-CSF is rare, with a reported incidence of <1% [10, 11]. Notably, most published cases have emerged over the past decade, likely reflecting heightened clinical awareness and the increasing use of long-acting G-CSF formulations [12]. G-CSF-induced LVV is characterized by inflammation of the aorta and its major branches, and typically presents with nonspecific symptoms including fever, malaise, and chest or back pain [4, 5, 10, 12]. Because of its variable and protean manifestations, it is frequently misdiagnosed as infection, tumor recurrence, or chemotherapy-related fever, often delaying diagnosis [4, 5].

The revised 2012 International Chapel Hill Consensus Con-



FIGURE 1. Contrast-enhanced chest computed tomography (CT) demonstrating circumferential mural thickening and perivascular inflammation involving the aortic arch, proximal descending thoracic aorta, left proximal common carotid artery, and left proximal subclavian artery.

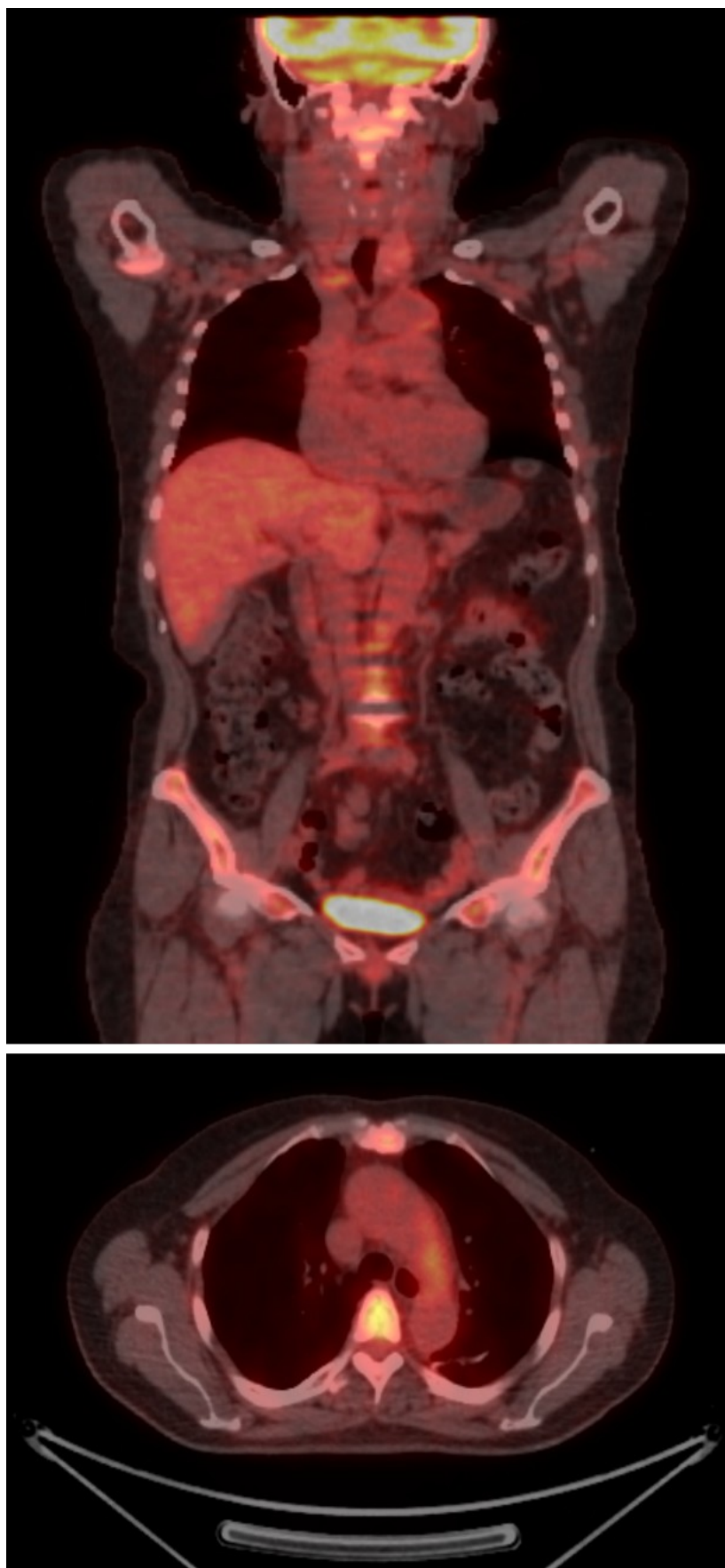


FIGURE 2. Fluorodeoxyglucose-positron emission tomography (FDG-PET) showing increased FDG uptake consistent with inflammation of the large vessels involving the aortic arch, proximal descending aorta, left proximal common carotid artery, and left proximal subclavian artery.



FIGURE 3. Follow-up contrast-enhanced chest computed tomography (CT) demonstrating complete resolution of vascular wall thickening at 4 weeks after initiation of corticosteroid therapy.

ference nomenclature is the most widely adopted system for describing vasculitis [13]. Determining the etiology of aortitis requires careful differentiation between primary LVV and secondary LVV associated with systemic disease. Secondary LVV may result from infection, immune-mediated disease, malignancy, or drug exposure. Diagnosing drug-induced vasculitis is particularly challenging and relies on excluding all other potential causes. The temporal association with eflapegrastim administration, rapid clinical and radiologic improvement following glucocorticoid therapy, and absence of recurrent vasculitis after discontinuation of G-CSF strongly support a drug-induced origin [5, 8–11].

Patients with G-CSF-induced LVV typically present with high-grade fever, appearing within a mean of 13.4 days post-dose (range, 1–38 days), frequently after only a few injections [10, 12]. Laboratory findings commonly include leukocytosis and elevated inflammatory markers, whereas procalcitonin remains within normal limits, aiding differentiation from bacterial infection. In this patient, blood and urine cultures were negative, and serologic testing for tuberculosis, syphilis, and Q-fever was unremarkable. Primary autoimmune vasculitis, including giant cell arteritis or Takayasu arteritis, were considered unlikely, as the patient lacked characteristic clinical features (*e.g.*, cranial ischemic symptoms or limb claudication), and autoantibody tests (*e.g.*, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and rheumatoid factor) were negative. Immunoglobulin G4 (IgG4)-related vasculitis was excluded based on a normal serum IgG4 level. Paraneoplastic vasculitis, which most commonly manifests as leukocytoclastic vasculitis of the skin and is associated with progressive malignancy, was considered improbable given the absence of cutaneous findings and stable disease status [14].

When infectious etiologies have been initially excluded, prompt imaging is critical. Contrast-enhanced CT serves as

the most accessible and cost-effective first-line diagnostic modality, enabling early detection by revealing circumferential mural thickening and perivascular inflammation of the aorta and its major branches. While we recognize that the routine use of FDG-PET/CT may raise concerns regarding cost-effectiveness and the risk of false-positive results—particularly in the early postoperative period or during generalized systemic inflammation—we advocate for its careful, but early, consideration in the specific context of oncology patients. Patients receiving long-acting G-CSF with chemotherapy often present with non-specific symptoms like fever and fatigue, which can mimic infectious complications or aggressive tumor progression. In this highly vulnerable population, initiating high-dose systemic corticosteroids based solely on a preliminary CT diagnosis, without definitively ruling out occult malignancy or atypical infections, carries significant clinical risk. Therefore, in the oncologic setting, early FDG-PET/CT plays a critical dual role: it not only confirms the precise metabolic extent of the active vasculitis, but more importantly, definitively differentiates drug-induced LVV from malignancy recurrence. This allows clinicians to safely and rapidly initiate potentially life-saving corticosteroid therapy without the fear of exacerbating an underlying tumor.

Although the pathophysiology of G-CSF-induced LVV remains incompletely elucidated, several mechanisms have been proposed. G-CSF activates neutrophils and induces a cytokine surge involving interleukin (IL)-1, IL-6, IL-23, and tumor necrosis factor (TNF)- α , promoting pathological activation of T helper 17 (Th17) cells, antigen-specific cluster of differentiation 4 (CD4⁺) T cells, and neutrophils [15–18]. In addition, G-CSF upregulates endothelial adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin via Janus kinase/signal transducer and activator of transcription

(JAK/STAT) and mitogen-activated protein kinase (MAPK) signaling pathways, enhancing leukocyte adhesion and transmigration [17]. This endothelial activation may contribute to vessel wall injury and granulomatous infiltration observed in histopathologic analyses of G-CSF-induced vasculitis [15–18]. Long-acting G-CSF agents maintain sustained serum levels compared with short-acting agents, potentially prolonging immune activation and increasing the risk of LVV.

Management of G-CSF-induced LVV involves discontinuation of G-CSF and initiation of systemic corticosteroids [19]. Most patients exhibit rapid clinical improvement, and vascular abnormalities typically resolve within weeks to months. Although recent series indicate that 30–40% of patients may recover without corticosteroid therapy [4, 11, 20], steroids are indicated in severe or refractory cases. LVV carries a risk of progression to aortic aneurysm, dissection, or rupture. Prompt initiation of corticosteroids is critical once infection has been excluded. In cases involving the subclavian artery, symptoms such as presyncope or lightheadedness may reflect subclavian steal physiology due to altered hemodynamics and retrograde vertebral artery flow, further underscoring the need for early treatment.

This report has several limitations. First, as a single case report, it cannot establish definitive causality or the true incidence of eflapegrastim-induced LVV. Larger pharmacovigilance studies are required to confirm our findings. Second, while we emphasize the importance of early FDG-PET/CT in differentiating LVV from tumor recurrence in oncology patients, we acknowledge its inherent limitations, including limited accessibility, high costs, and the risk of false-positive results due to postoperative changes or systemic inflammation. Therefore, diagnostic decisions must be carefully individualized, utilizing contrast-enhanced CT as the primary step and reserving PET-CT for selected cases.

This case underscores the importance of maintaining a high index of suspicion in patients presenting with fever and marked leukocytosis shortly after exposure to long-acting G-CSF. Early recognition prevents unnecessary antibiotic use, avoids misinterpretation as tumor progression, and facilitates timely initiation of therapy. Prompt imaging and corticosteroid treatment are essential to prevent potentially life-threatening complications.

AVAILABILITY OF DATA AND MATERIALS

All data supporting the findings of this case report are included in the article and available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

EJ and UJ—provided guidance and advice on data analysis. EH and JYK—drafted the manuscript. All authors designed the research study. All authors performed the research and analyzed the data. All authors have read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (No. CNUHH-2025-090). Informed consent for participation and publication was obtained from the patient.

ACKNOWLEDGMENT

The authors sincerely appreciate the peer reviewers and editors for their valuable insights and constructive suggestions.

FUNDING

This study was supported by a grant (HCRI-25042) from Chonnam National University Hwasun Hospital Biomedical Research Institute.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Enoch Hong, Ja Young Kim, Eujene Jung, Uchul Ju. Eflapegrastim-induced large vessel vasculitis in patient treated with recurrent uterine leiomyosarcoma. *European Journal of Gynaecological Oncology*. 2026; 47(3): 117-122. doi: 10.22514/ejgo.2026.034.