Granulocyte colony stimulating factor-associated aortitis evaluated via multiple imaging modalities including vascular echography: a case report

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Background
Granulocyte colony stimulating factor (G-CSF) preparations are used for patients with granulocytopenia, especially to prevent febrile neutropenia. Arteritis has been recognized as a side effect of G-CSF treatment; however, there are no clear diagnostic criteria or treatment guidelines because not enough cases have been reported. Present case showed one of the diagnostic and treatment selection methods via multiple imaging modality including vascular echography.

Case summary
A 52-year-old woman underwent chemotherapy for ovarian cancer and received G-CSF because of myelosuppression. The patient experienced high and remittent fever that persisted during treatment using antibiotics and acetaminophen. Enhanced computed tomography revealed thickening of the tissue around the aortic arch and abdominal aorta. Echography of the abdominal aorta revealed thickening of the wall and a hypoechoic region around the aorta. Gadolinium-enhanced magnetic resonance imaging and 18F-fludeoxyglucose positron emission tomography also revealed that the inflammation was localized to the lesion. A suspicion of G-CSF-associated aortitis was based on the patient’s history and the exclusion of other diseases that might have caused the aortitis. Her condition rapidly improved after starting corticosteroid treatment.

Discussion
The differential diagnosis in similar cases should consider immune diseases that cause large-vessel arteritis (Takayasu arteritis, giant cell arteritis, and another vasculitis), infection, drug-induced disease, and immunoglobulin G4-related disease. The use of different imaging modalities, including vascular echography, helped guide the diagnosis and follow-up. It is necessary to evaluate the patient’s general condition before the selection of treatments.

Keywords
Granulocyte colony stimulating factor (G-CSF) • Aortitis • Arteritis • Vascular echography • Onco-cardiology • Case report

Learning points
• In patients with persistent fever and a history of granulocyte colony stimulating factor administration, aortitis should be considered in the differential diagnosis.
• The arteritis localization and activity should be evaluated using multiple modalities (e.g. vascular echography, computed tomography, and magnetic resonance imaging) including neck to the pelvis to guide treatment.
• The treatment including the necessity of corticosteroid therapy should be selected based on the general condition of the patients, considering that the patients are treated for cancer.
**Introduction**

Granulocyte colony-stimulating factor (G-CSF) preparations are used for chemotherapy-related granulocytopenia, especially to prevent febrile neutropenia. The G-CSF preparations bind to G-CSF receptors that are present on neutrophil progenitor cells in the bone marrow, which promote their differentiation into neutrophils. The clinical regimens include filgrastim, lenograstim, nartograstim, filgrastim biosimilars, and long-lasting pegylated preparations of filgrastim. The first report regarding G-CSF-associated aortitis was in 2004, and arteritis has been reported as a side effect of G-CSF treatment. However, there are no clear diagnostic criteria or treatment guidelines. Therefore, we report a case of G-CSF-associated aortitis that required careful exclusion of similar aortitis and multiple imaging modalities to support the diagnosis.

**Timeline**

| Event                                      | Description                                                                 |
|--------------------------------------------|-----------------------------------------------------------------------------|
| One month before onset                     | The 5th course of chemotherapy [paclitaxel 262 mg (180 mg/m²)/carboplatin 583 mg (target area under the concentration-time curve 6 mg min/mL)] was administered. |
| Two weeks before onset                     | Myelosuppression was detected, and the granulocyte colony stimulating factor (G-CSF) was administered for the first time and continued for 3 days. |
| Ten days before onset                      | The 6th course of chemotherapy was administered.                             |
| Three days before onset                    | Myelosuppression was detected, and the G-CSF treatment was started and continued for 4 days. |
| Day 0 (onset)                              | Last administration of G-CSF. The patient developed a high fever during the night. |
| Day 1                                      | The patient visited an outpatient clinic and was prescribed acetaminophen and levofloxacin. |
| Day 4                                      | The patient was admitted to the gynaecology department for a persistent high fever. Although the thickening around the aorta was suspected via computed tomography (CT), it was uncertain whether the inflammation was localized there, and the patient first received cefmetazole for suspected infection or febrile neutropenia. |
| Day 9                                      | The antibiotic treatment was changed to piperacillin/tazobactam.             |
| Day 16                                     | The fever and inflammation did not improve completely. Aortitis was re-considered as a differential diagnosis of fever. An magnetic resonance imaging was performed to evaluate the aortitis. |
| Day 17                                     | The patient was transferred to the cardiology department for treatment of the aortitis. Bone marrow testing was performed. |
| Day 23                                     | Positron emission tomography revealed active inflammation of the aortic arch and abdominal aorta. Prednisolone (PSL) was started (50 mg/day, 1 mg/kg). |
| Day 24                                     | The fever improved, and the temperature was maintained at <37.5°C.            |
| Day 38                                     | A CT examination revealed that the thickening around the aorta had improved. C-reactive protein concentration returned to normal. |
| Day 46                                     | The PSL dose was gradually reduced.                                          |
| Day 71                                     | The patient was discharged (PSL 25 mg/day).                                  |
| After 9 months                              | The PSL dose was gradually reduced to 10 mg/day for 9 months.                |
| After 1 year                                | No episode of infection, and no recurrence of aortitis and cancer. The patient is almost free from the PSL. |

**Case presentation**

A 52-year-old woman underwent six courses of post-operative chemotherapy (paclitaxel 262 mg/carboplatin 583 mg) for ovarian cancer. Myelosuppression was detected after the 5th and 6th chemotherapy courses, which prompted G-CSF treatment (filgrastim, 75 μg/day). The patient developed a high fever after the last G-CSF administration and was admitted 4 days later in the gynaecology department. Negative bacterial, fungal, and viral test results were observed, and a broad-spectrum antibiotic treatment did not completely improve her condition. Aortitis was suspected based on enhanced computed tomography (CT) findings, and she was referred to our cardiology department.

Her peripheral arterial oxygen saturation was 96% (room air), body temperature was 38.0°C with remittent fever, blood pressure was 92/50 mmHg, and bilateral pulse was 70 beats/min. The head and neck had no bruise or tenderness, and the patient reported no visual deterioration or diplopia. Chest auscultation was clear, and cardiac auscultation revealed normal S1 and S2 with no S3 or murmurs. There were no abdominal abnormalities or notable skin lesions and swelling on the extremities. Her medical history included pulmonary embolism and deep vein thrombosis that had been controlled using anticoagulant medication.

**Table 1** shows the patient’s laboratory findings on admission, which included an elevated C-reactive protein concentration (CRP). Although the white blood cell count (WBC) slightly elevated on admission, it gradually decreased to 1400/μL (normal range 3300–8600). Decreasing of the platelet counts and normocytic anaemia were also observed. Bone marrow tests showed that the three lineages of haematopoietic cells were...
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Electrocardiography, echocardiography, and chest radiography revealed no abnormalities that could explain the fever. Echography of the abdominal aorta revealed aortic wall thickening and a hypoechoic region around the aorta (Figure 1). Furthermore, CT revealed an increase in the soft tissue surrounding the aortic arch and abdominal aorta (Figure 2A,B). Gadolinium-enhanced magnetic resonance imaging revealed thickening of the aortic wall and enhancement of the wall and perivascular tissue (Figure 3A), and uptake was observed during $^{18}$F-fludeoxyglucose positron emission tomography (Figure 3B). These imaging findings suggested active inflammation at the lesions.

The patient was transferred to the cardiology department, and G-CSF-associated aortitis was suggested based on her history and clinical course (Naranjo adverse drug reaction probability scale score 7; probable). On Day 23, she was exhausted because of the persistent fever and received prednisolone treatment (PSL, 50 mg/day), which promptly resolved her symptoms. Follow-up testing revealed improvement in her CRP concentration and erythrocyte sedimentation rate (Supplementary material online, Figure S1). After 2 weeks, CT revealed an improvement in the thickening around the aorta (Figure 2C). The PSL dose was gradually reduced. This treatment was marked by the absence of recurrence of the aortitis, cancer, and infection at her 1-year follow-up.

**Discussion**

This case involved a patient who presented with a significant fever. Aortitis was suspected via multiple imaging modalities, and the association with G-CSF treatment was suggested based on the patient’s history and exclusion of other diseases.

**Clinical course in previous cases**

A PubMed search revealed 28 reported cases involving arteritis associated with G-CSF treatment (Table 2). Most cases involved fever at the onset of disease, although other symptoms (e.g. abdominal tenderness, syncope) appeared before the fever in some cases. In this case, PSL was started because of a high fever and malaise; however, one-half of the reported cases resolved without corticosteroids.

In the previous cases that involved corticosteroid treatment, three cases were administered high-dose treatments (e.g. pulse methylprednisolone), and six cases involved PSL doses starting at 30–60 mg/day with gradual tapering.

| Table 1 | Laboratory findings on admission (Day 4) |
|---------|-----------------------------------------|
|         | WBC 8780/μL (3300–8600) | Neut 76.0% (41.8–75.0) |
|         | Lymph 15.7% (18.5–48.7) | Mono 8.1% (2.2–7.9) |
|         | Eo 0.1% (0.4–8.7) | RBC 2.14 × 10¹¹/μL (3.86–4.92) |
|         | Hb 7.2 g/dL (11.6–14.8) | HCT 22.2% (35.1–44.4) |
|         | Pts 7.0 × 10⁹/L (15.8–34.8) | MCV 103.7 fl (83.6–98.2) |
|         | MCH 33.6 pg (27.5–33.2) | MCHC 32.4% (31.7–35.3) |
|         | TP 7.0 g/dL (6.6–8.1) | TPAb Negative |
|         | Alb 3.5 g/dL (4.1–5.1) | IgM 74 mg/dL (50–269) |
|         | UN 12.6 mg/dL (8.0–20.0) | IgG4 21 mg/dL (-134) |
|         | Cr 0.80 mg/dL (0.46–0.79) | C2 31.8 mg/dL (11.0–31.0) |
|         | eGFR 59 mL/min/1.73 m² | LDH 170 U/L (124–222) |
|         | Cr 0.80 mg/dL (0.46–0.79) | Na 140 mEq/L (138–145) |
|         | Cl 3.8 mEq/L (3.6–4.8) | K 3.8 mEq/L (3.6–4.8) |
|         | CRP 19.39 mg/dL (0.00–0.14) | PT-INR 1.15 (0.85–1.15) |

**Ants:** SS-A/Ro antibody, anti SS-B/La antibodies, anti Sm antibodies, anti-double strand-DNA antibodies, anti-RNP antibodies were all negative. ESR is the data of Day 24. Normal ranges are shown in brackets.
| No | Age | Sex | Year | Nationality | Background disease | G-CSF | Symptoms | Lesions | Glucocorticoid treatment |
|----|-----|-----|------|-------------|--------------------|-------|----------|---------|------------------------|
| 1  | 55  | F   | 2004 | France      | Stem cell donor    | Filgrastim | Fever, abdominal and lumbar pain, vomiting | Descending ao, abdominal ao | yes                     |
| 2  | 54  | M   | 2009 | US          | Lung cancer        | Filgrastim | Fever, epigastric tenderness            | Abdominal ao               | no                      |
| 3  | 52  | M   | 2016 | Israel      | Healthy donor      | Filgrastim | Weight loss, back pain, constipation     | Abdominal ao, iliac artery | yes                     |
| 4  | 78  | F   | 2016 | Japan       | Cyclic neutropenia | Filgrastim | Fever, headache, jaw claudication, visual abnormality | Temporal arteries | yes                     |
| 5  | 59  | F   | 2017 | Japan       | Lymphoma           | Pegfilgrastim | Neck and chest pain, fever               | Carotid artery, subclavian artery, ao arch, descending ao | yes                     |
| 6  | 61  | F   | 2017 | Japan       | Ovarian cancer     | Lenograstim  | Fever                                    | Carotid artery             | no                      |
| 7  | 67  | F   | 2017 | Japan       | Lung cancer        | Pegfilgrastim | Malaise and fever                        | Carotid artery, thoracic ao | yes                     |
| 8  | 61  | F   | 2018 | Japan       | Breast cancer      | Pegfilgrastim | Neck and chest pain → fever               | Carotid artery, thoracic ao | no                      |
| 9  | 47  | F   | 2018 | Japan       | Ovarian cancer     | Pegfilgrastim | Fever                                    | ao arch, descending ao     | yes                     |
| 10 | 71  | F   | 2019 | Japan       | Endometrial cancer | Pegfilgrastim | Fever                                    | ao arch                    | yes                     |
| 11 | 72  | F   | 2019 | Japan       | Lymphoma           | Pegfilgrastim | Fever, chest pain                        | ao arch                   | no                      |
| 12 | 62  | F   | 2019 | Japan       | Lymphoma           | Pegfilgrastim | Fever, chest pain                        | Descending ao              | yes                     |
| 13 | 69  | M   | 2019 | Japan       | Lymphoma           | Pegfilgrastim | Fever                                    | Subclavian artery          | unknown                 |
| 14 | 77  | F   | 2019 | Japan       | Ovarian cancer     | Pegfilgrastim | Fever                                    | Carotid artery, subclavian artery | no                     |
| 15 | 60  | F   | 2019 | Sweden      | Breast cancer      | Filgrastim   | Abdominal tenderness → fever             | Subclavian artery, ao arch, descending ao | yes                     |
| 16 | 70  | F   | 2019 | Sweden      | Breast cancer      | Filgrastim | Syncope, diarrhoea, dehydration → fever | Thoracic ao, brachiocephalic trunk | yes                     |
| 17 | 72  | F   | 2019 | Japan       | Breast cancer      | Pegfilgrastim | Fever                                    | Descending ao              | no                      |
| 18 | 43  | F   | 2020 | Japan       | Uterine cancer     | Pegfilgrastim | Unknown                                  | Thoracic ao                | no                      |
| 19 | 47  | F   | 2020 | Japan       | Uterine cancer     | Pegfilgrastim | Unknown                                  | Thoracic ao                | no                      |
| 20 | 74  | F   | 2020 | Japan       | Tongue cancer      | Pegfilgrastim | Unknown                                  | Thoracic ao                | no                      |
| 21 | 65  | F   | 2020 | Japan       | Pancreatic cancer  | Pegfilgrastim | Fever, chest pain                        | ao arch, abdominal ao      | no                      |
| 22 | 66  | F   | 2020 | Japan       | Breast cancer      | Pegfilgrastim | Fever, malaise, abdominal discomfort     | ao arch, abdominal ao      | yes                     |
| 23 | 52  | F   | 2020 | Finland     | Breast cancer      | Filgrastim   | Fever, chest pain                        | Aorta                     | yes                     |
| 24 | 62  | F   | 2020 | Finland     | Breast cancer      | Filgrastim   | Fever                                    | Aorta                     | yes                     |
| 25 | 70  | F   | 2020 | Finland     | Breast cancer      | Lipegfilgrastim | Fever                                   | Aorta, supra-aortic vessels | no                      |
| 26 | 56  | F   | 2020 | Finland     | Breast cancer      | Lipegfilgrastim | Fever, neck pain, jaw pain, malaise      | Carotid artery, thoracic ao | yes                     |
| 27 | 53  | F   | 2020 | Finland     | Breast cancer      | Pegfilgrastim | Fever, sore throat, ear ache, dysphoena, and chest pain | Aorta | yes                     |
| 28 | 40  | F   | 2020 | Finland     | Breast cancer      | Lipegfilgrastim | Fever, sore throat, chest and neck pain, malaise | Carotid artery | yes                     |

ao, aorta or aortic; F, female; M, male.
The figures in square brackets refer to page numbers.
*Name of the G-CSF preparations were unknown, however these were used for several days.*
corticosteroid may be possible because G-CSF-associated arteritis may have a relatively good prognosis compared to other arteritis. Nevertheless, a case that involved aortic dissection highlighted the need for careful observation. Some cases with G-CSF re-administration had aortitis recurrence, and dose reduction or change of the anti-cancer drug were needed to avoid myelosuppression.

Differential diagnosis of aortitis
Takayasu arteritis and giant cell arteritis (GCA) are immune disorders that cause large-vessel arteritis. Takayasu arteritis onset is most common among women in their 20s, and the lesions are often continuous in the aorta and its primary branches. More than 90% of patients have lesions in the aortic arch, and 40% in the abdominal aorta. Onset of GCA is most common among women in their 60s to 70s, and lesions are typically detected in the branches of the carotid and vertebral arteries, and other large arteries may have lesions. Perivascular inflammation caused by IgG4-related diseases is found in the abdominal and iliac arteries, although lesions can be present in the thoracic aorta. These lesions tend to be detected in men in their sixties. Other differential diagnoses include infection (bacterial, syphilis, human immunodeficiency virus, and tuberculosis), drug-induced disease, malignancy, Behçet disease, Cogan syndrome, systemic lupus erythematosus, and anti-neutrophil cytoplasmic antibody-related vasculitis (Supplementary material online, Figure S2). The differential diagnosis needs to be performed based on the characteristics of the diseases in addition to the imaging evaluation.

Lesions and imaging
Previous reports of G-CSF-associated arteritis indicated that most lesions were detected in the thoracic aorta (68%), especially in the arch (29%) and descending aorta (29%). However, lesions can be detected in the abdominal aorta (21%), carotid artery (25%), and subclavian artery (14%) (Table 2). Most cases involved circumferential thickening of the peri-arterial tissue, which was detected via CT. Echography was useful in guiding the diagnosis in this case, although none of the previously English reported cases involved an abdominal aorta echography. Nevertheless, an echography was used to evaluate some lesions in the temporal and carotid arteries.

Mechanism of aortitis
The pathological mechanisms underlying G-CSF-associated arteritis are unclear. Previous reports have speculated that arteritis is related to cytokines and complex immune reactions between anti-cancer agents and G-CSF. In aortitis after acute aortic dissection, G-CSF may act on the arterial adventitia and invading granulocytes, which results in inflammation. Nevertheless, this mechanism for G-CSF-associated arteritis remains speculative.

Conclusions
Chronic inflammation can lead to a reduced nutritional status and quality of life in cancer patients, which may influence their general condition and make them unable to continue chemotherapy. When cancer patients experience persistent fever after G-CSF treatment, it is necessary to make a differential diagnosis carefully and select treatments based on the patient’s general condition as well as the prognosis of arteries.

Patient perspective
The patient was mentally exhausted before treatment. Psychiatric support also improved her mental status, despite the high dose of PSL used.

Lead author biography
Graduated from Jichi Medical University School of Medicine, Japan and worked as a general physician. In 2016, conducted clinical studies on cardiovascular risk factors among young people at Shinshu University Graduate School of Medicine. Currently working in general cardiology and preventive medicine.

Supplementary material
Supplementary material is available at European Heart Journal - Case Reports online.

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Figure 2 Imaging findings via enhanced computed tomography. (A) Enhanced computed tomography (CT) findings before chemotherapy. (B) The computed tomography findings after onset (chest: early phase, abdomen: plain, early, and delay phase), which revealed enhancement of the peri-aortic tissue from the aortic arch and the abdominal aorta (vs. the pre-chemotherapy findings). There was no wall thickening in the branches of the aorta, aortic stenosis, aneurism, or dissection. (C) Enhanced computed tomography after the treatment for aortitis. The thickening around the aorta had improved after 2 weeks.
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Figure 3 Imaging findings via gadolinium-enhanced magnetic resonance imaging and fluorodeoxyglucose positron emission tomography. (A) Gadolinium-enhanced T1-weighted image revealed thickening of the vessel wall at the aortic arch and the abdominal aorta at the diaphragm (arrow). (B) Fluorodeoxyglucose positron emission tomography (18F-FDG PET) revealed FDG uptake in the aortic arch and the abdominal aorta, with a standardized uptake value (SUV) of 2–3 like that in the liver (arrow).