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Original article

Granulocyte colony-stimulating factor- and chemotherapy-induced large-vessel vasculitis: six patient cases and a systematic literature review

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Abstract

Objective. Patients receiving chemotherapy are prone to neutropoenic infections, presenting with non-specific symptoms such as a high fever and elevated inflammatory parameters. Large-vessel vasculitis (LVV) may have a similar clinical presentation and should be included in differential diagnostics. A few published case reports and adverse event reports suggest a causal association between LVV and the use of granulocyte colony-stimulating factor (G-CSF) and chemotherapy. Our objective was to evaluate the relationship between LVV, G-CSF and chemotherapy.

Methods. Between 2016 and 2018, we identified six patients in Finland with probable drug-induced LVV associated with G-CSF and chemotherapy. All six patients had breast cancer. A systematic literature review was performed according to PRISMA guidelines using comprehensive search terms for cancer, chemotherapy, G-CSF and LVV.

Results. The literature search identified 18 similar published case reports, of which most were published after 2014. In all patients combined ($n = 24$), the time delay from the last drug administration to the LVV symptoms was on average 5 days with G-CSF (range = 1–8 days) and 9 days with chemotherapy (range = 1–21 days). Common symptoms were fever (88%), neck pain (50%) and chest pain (42%). Based on imaging, 17/24 (71%) had vascular inflammation in the thoracic aorta and supra-aortic vessels, but 5/24 (21%) reportedly had inflammation limited to the carotid area.

Conclusion. This review suggests that LVV may be a possible serious adverse event associated with G-CSF and chemotherapy. Successful management of drug-induced LVV requires early identification, through diagnostic imaging, and discontinuation of the drug.

Key words: granulocyte colony-stimulating factor, vasculitis, aortitis, chemotherapy, febrile neutropoenia, adverse drug reaction, large vessel vasculitis

Key messages

- Clinicians and radiologists should be aware of the large-vessel vasculitis associated with granulocyte colony-stimulating factor or chemotherapy.
- Symptoms of large-vessel vasculitis developed within days after the administration of the suspected drug.
- Early discontinuation of the suspected drug is essential for fast recovery.

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CLINICAL SCIENCE

Introduction

Patients receiving chemotherapy have an increased risk for severe neutropoenic infections that present with non-specific symptoms such as high fever, general malaise and elevated inflammatory parameters. Large-vessel vasculitis (LVV) may have an identical clinical presentation and should be included in the differential diagnostics.

Vasculitides include a heterogeneous group of diseases characterized by inflammation of blood vessels. LVV affects the aorta and its major branches [1], causing inflammation of the media and adventitia that leads to subsequent luminal narrowing and occlusion [2]. Patients with LVV have increased risk for developing complications such as an aortic dissection or an aneurysm [3]. Carotidynia is a term referring to a pain in the carotid area. It is a poorly understood vascular inflammation of the carotid artery with an unknown aetiology [4]. A controversy exists over whether this is a distinct disease entity or a symptom attributable to other causes of neck pain, such as vasculitis. Imaging data often show perivascular inflammation without clear irregularity of the vascular lumen [5, 6]. The clinical presentation may be identical to vasculitis.

Granulocyte colony-stimulating factor (G-CSF) is a widely used drug to reduce neutropoenia associated with myelosuppressive chemotherapy. Until 2018, there were limited case reports showing that LVV was associated with G-CSF or chemotherapy. A few reports considered docetaxel to be the causative agent [7, 8]. Recent reports have shown that G-CSF is associated with aortitis. In February 2018, the European Medicines Agency stated that there may be a causal association between aortitis and G-CSF treatment (Pharmacovigilance Risk Assessment Commitee recommendations on signals EMA/PRAC/59224/2018). Recently, two independent drug adverse event database studies have found cases with probable G-CSF-induced aortitis [9] and that G-CSF treatment was associated with a sign for an increased risk for aortitis in patients with malignancies [10]. However, the number of reported cases is limited, and this finding requires confirmation.

Here, we describe six new patient cases within the past 3 years, who had a probable drug-induced LVV associated with G-CSF and chemotherapy for breast cancer. The symptoms developed shortly after the new drugs were started. We explored the connection between LVV, G-CSF and chemotherapy through our case studies and the systematic literature review.

Methods

Our case series

Six consecutive patient cases were identified between 2016 and 2018 from the Departments of Rheumatology at Turku University Hospital and Helsinki University Hospital, Finland. As clinicians, we paid attention to this unusual phenomenon. All patients suffered from breast cancer and fulfilled the inclusion criteria for the study. Informed written consent was acquired from the patients. All patients had a minimum of 6 months of clinical follow-up and a follow-up imaging, which varied from case to case. Detailed patient cases are described in the supplementary material, section Patient series from the Turku and Helsinki University Hospitals, available at *Rheumatology Advances in Practice* online. We had Institutional Review Board approval for the study.

Literature search

Three authors (K.T., S.H. and L.P.) conducted two separate systematic literature searches in MEDLINE via PubMed to find reports about cancer patients receiving chemotherapy or G-CSF or both, before the onset of new LVV. The first search was performed in April 2019 by using comprehensive search terms for cancer, chemotherapy and LVV. Our interest was breast cancer, but other malignancies were not excluded if they showed up in the search.

The other systematic literature search was performed in April 2019 to assess the connection between G-CSF and LVV by using comprehensive keywords for LVV and G-CSF with no restrictions embedded in the search terms.

The PRISMA guidelines were followed. Retrieved and relevant papers were searched manually for additional references, but no new essential articles were found. The search terms used are provided in the supplementary material, section Search terms for systematic literature review, available at *Rheumatology Advances in Practice* online.

Selection of cases

The inclusion criteria were as follows: a patient with malignancy, who had received chemotherapy or G-CSF and was diagnosed with new LVV <12 months after initiation of new chemotherapy or G-CSF. The exclusion criteria were as follows: a temporal relationship between the drug and LVV that was unclear or lasting >12 months; a cause other than an adverse drug reaction (ADR) that was the more probable aetiology for LVV (e.g. infection, mechanical causes); unclear or scarce information to evaluate the possibility of an ADR; and/or a vasculitis other than LVV. In this study, patients with the diagnosis of carotidynia were included in the LVV group, because all cases showed strong carotid artery inflammation with constitutional symptoms similar to LVV.

Studied parameters

We gathered the standardized information, when available, from all patient cases. The data consisted of age at diagnosis, sex, the administered G-CSF or chemotherapy, affected blood vessels, symptoms associated with LVV, the time interval from drug administration to symptoms, diagnostic testing methods, imaging findings, diagnosis as described by the authors, treatment used for LVV, chemotherapeutic treatment strategy and

whether cancer was considered macroscopic at the time of G-CSF or chemotherapy.

Results

Our case series of six patients

Six female patients from Turku and Helsinki University Hospitals between 2016 and 2018 represent our own cases. All patients had breast cancer, and they received both G-CSF and docetaxel. The timeline of the drug use and symptom development of these patients is presented in Fig. 1, which shows all the chemotherapy and G-CSF administrations before the onset of LVV.

Patients developed LVV symptoms (such as fever, chest and neck pain, general malaise) within 8 days after the last G-CSF treatment and 9 days after the administration of the last dose of chemotherapy, which was docetaxel in 5/6 and 5-fluorouracil, epirubicin and CYC in 1/6 patients, respectively (Fig. 1). The onset and clinical characteristics of their symptoms and the imaging findings were remarkably similar (Table 1).

Upon US, there was diffuse and hypoechoic wall thickening in affected vessels (Fig. 2). CT showed a perivascular mass and diffuse thickening of the vessel walls (Figs 2 and 3). Upon MRI, there was increased signal intensity, indicating oedema around the vessels, on T2-weighted fat saturation/short tau inversion recovery images and perivascular contrast enhancement in the same areas on T1-weighted images (Figs 2 and 3).

Literature review search results

The search strategy from the two literature searches resulted in a total of 1624 records, which were screened, and of those, 48 articles (51 case reports) were evaluated in detail. Fourteen patients were excluded because they did not receive either cancer treatment medicine or G-CSF before LVV. Six patient cases were excluded owing to the use of cancer immunotherapy treatments, which have a known association with immunological side-effects [11]. Four cases had no inflammation in the large vessels. Five cases were excluded owing to insufficient information regarding cancer treatment. Four cases were excluded for the following reasons: mechanical trauma to the aorta; an 18 year delay between drug administration and symptoms; the patient had LVV before treatment; and information was limited to assess ADR. Eighteen patients met our criteria and were included in the study (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online). Altogether, 24 cases were included in the study when literature search results and our case series were combined (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Clinical characteristics and vasculitis distribution in all patients ($n = 24$)

The mean age was 59 years (range = 40–77 years), and 18/24 (75%) were female. The most prevalent cancer types were breast cancer (10/24, 42%), haematological malignancies (7/24, 29%) and lung cancer (3/24, 13%). The most common clinical symptoms were fever (21/24, 88%), neck pain (12/24, 50%) and chest pain (10/24, 42%). Based on imaging, 17/24 (71%) had vascular inflammation in their thoracic aorta and their supra-aortic vessels and 5/24 (21%) reportedly only in their carotid area.

Drug history in relationship to vasculitis manifestation in all patients ($n = 24$)

The time delay from the last drug administration to LVV symptoms was on average 5 days (range = 1–8 days) with G-CSF and on average 9 days (range = 1–21 days) with chemotherapy.

In 16/24 cases, data from G-CSF administration were provided: five patients had filgrastim, four had pegfilgrastim, three patients had lipegfilgrastim, two had an unspecified product, one had lenograstim and one patient had been treated with both filgrastim and pegfilgrastim. Within the past 12 months, 23/24 patients had received chemotherapy, mostly a combination chemotherapy (14/23, 61%). Docetaxel was the most prevalent single chemotherapy drug, because 11/23 (48%) patients had used it. For anticancer monotherapy, four had received docetaxel, one patient received gemcitabine and one decitabine.

The exact temporal data for G-CSF administration were provided for 13/16 patients and the exact temporal data for chemotherapy administration for 16/23 patients, including all breast cancer patients. In other cases, time data were less detailed (e.g. during the first cycle of chemotherapy), and information was not used for statistics.

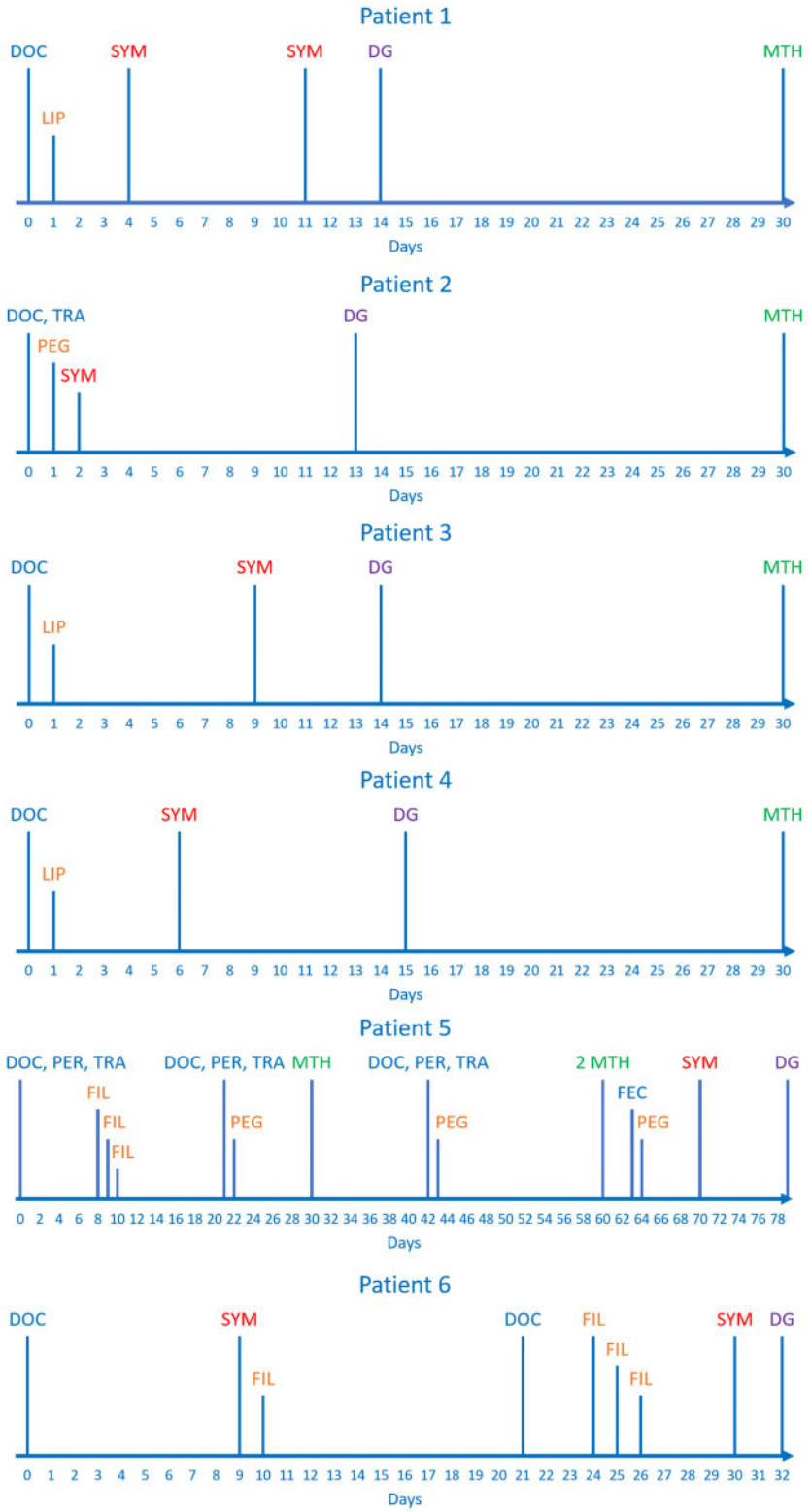
Chemotherapy and G-CSF were reportedly given in conjunction to 15 patients (nine literature cases and our six cases). In seven published cases, the authors assumed that G-CSF was the primary cause of LVV although patients also received chemotherapy [12–17]. In one report [7], LVV was considered to be a result of either chemotherapy or G-CSF. One article considered only chemotherapy to be associated with LVV, although the patient also received G-CSF [18]. In eight cases, there were no data about the use of G-CSF. In those reports, chemotherapy was considered to cause an adverse drug reaction in four cases [8, 19–21]. The other four patients [22–25] had haematological malignancies, and the possibility of ADR was not discussed; instead, in two reports [24, 25], the authors considered LVV as a paraneoplastic phenomenon.

Discussion

Own patient cases and similar cases from the literature search

This detailed case series is, to our knowledge, the largest and, together with the systematic literature review, emphasizes the connection between LVV, G-CSF and, possibly, docetaxel. Our six patients developed

Fig. 1 Timelines of the presented cases 1–6



Abbreviations: DG: diagnosis; DOC: docetaxel; FEC: 5-fluorouracil, epirubicin and CYC; FIL: filgrastim; LIP: lipegfilgrastim; MTH: a month mark; PEG: pegfilgrastim; PER: pertuzumab; SYM: symptoms; TRA: trastuzumab.

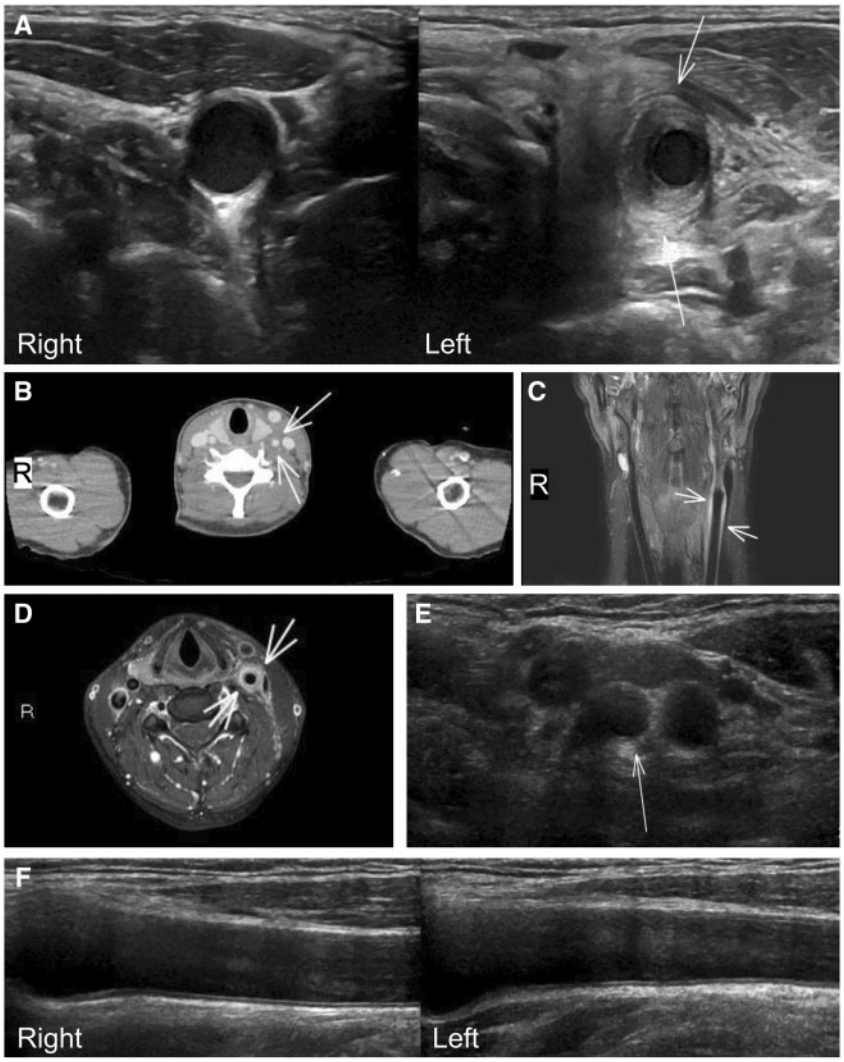
Table 1 Detailed summary of all used chemotherapy and granulocyte colony-stimulating factor agents in relationship to first large-vessel vasculitis symptoms in our patient series

Patient no.	Age (years) and sex	Cancer	Cancer size and treatment strategy	Cancer treatment	G-CSF	LVV symptoms	Drug name: first/last dose (days)[a]	Vessel(s)	Method of diagnosis	Vasculitis treatment	Year and country
1	40 Female	Ductal breast carcinoma	Microscopic Adjuvant therapy	Docetaxel	Lipegfilgrastim	Fever, sore throat and chest pain Second episode: general malaise, throat and neck pain	Docetaxel: 4/4 Lipegfilgrastim: 3/3 Second episode: Docetaxel: 11/11 Lipegfilgrastim: 10/10	Carotid artery	US, CT and MRI	GC	2017 Finland
2	53 Female	Ductal breast carcinoma	Microscopic Adjuvant therapy	Docetaxel and trastuzumab	Pegfilgrastim	Fever, sore throat, earache, dyspnoea and chest pain	Docetaxel: 2/2 Pegfilgrastim: 1/1	Aorta	CT and MRI	GC	2016 Finland
3	56 Female	Lobular breast carcinoma	Microscopic Adjuvant therapy	Docetaxel	Lipegfilgrastim	Fever; neck pain with tender mass; jaw pain and general malaise	Docetaxel: 9/9 Lipegfilgrastim: 8/8	Carotid artery and thoracic aorta	MRI	GC	2018 Finland
4	70 Female	Apocrine breast carcinoma	Microscopic Adjuvant therapy	Docetaxel	Lipegfilgrastim	Fever	Docetaxel: 6/6 Lipegfilgrastim: 5/5	Aorta and supra-aortic vessels	CT	Antibiotic	2018 Finland
5	62 Female	Ductal breast carcinoma	Microscopic Adjuvant therapy	Pertuzumab, trastuzumab and docetaxel for three cycles FEC	Filgrastim for three doses Pegfilgrastim for three doses	Fever	Pertuzumab, trastuzumab and docetaxel: 70/28 FEC: 7/7 Filgrastim: 62/60 Pegfilgrastim: 48/6	Aorta	CT and PET-CT	GC	2018 Finland
6	52 Female	Lobular breast carcinoma	Microscopic Adjuvant therapy	Docetaxel for two cycles	Filgrastim for four doses	Fever and chest pain, two episodes	Docetaxel: 9/9 Docetaxel: 30/9 Filgrastim: 20/4	Aorta	CT	GC	2018 Finland

[a]The first number shows the number of days from the first administration of the drug in question to the onset of the first LVV symptoms. The last number shows the number of days since the last administration of the drug.

Abbreviations: FEC: 5-fluorouracil, epirubicin and CYC; GC: glucocorticoid treatment; G-CSF: granulocyte colony-stimulating factor; LVV: large-vessel vasculitis.

Fig. 2 Different imaging techniques showing vascular inflammation in the carotid area in Patient 1

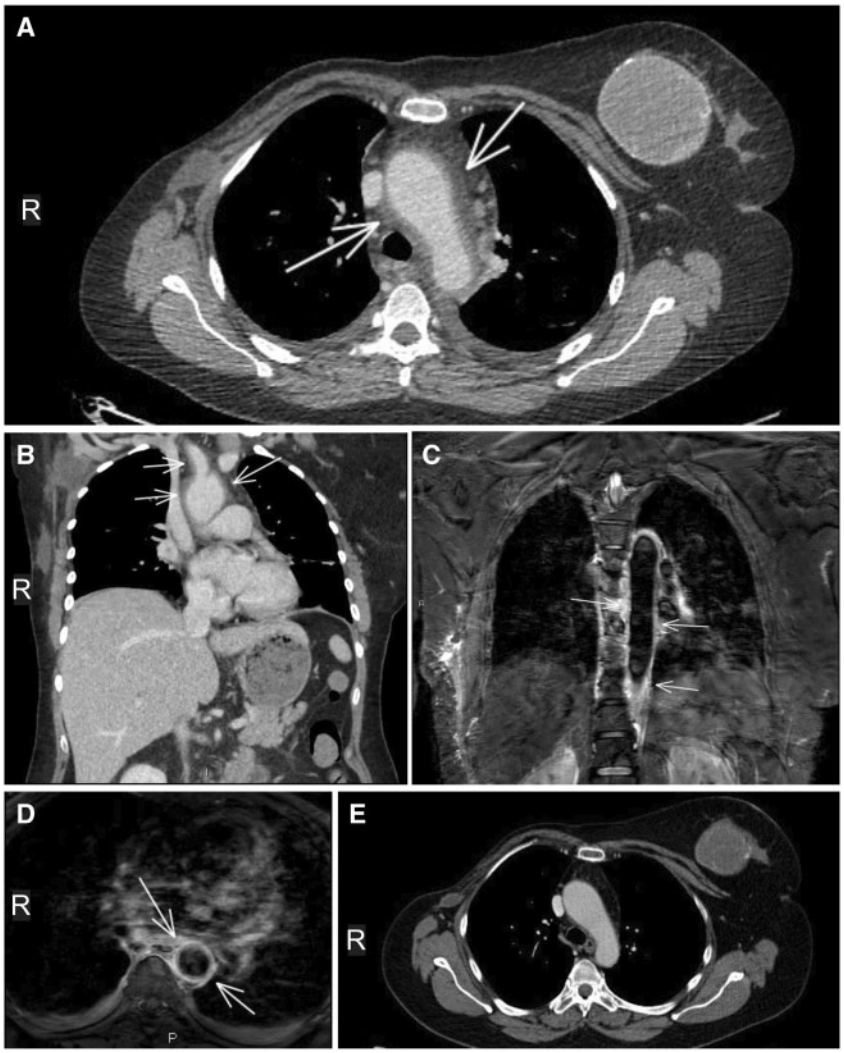


(**A**) US images of both common carotid arteries (CCA) showing normal right CCA and abnormal left CCA with a hypoechoic and thickened wall. (**B**) CT on the same day shows a perivascular mass around the left CCA. (**C**, **D**) Next day, with MRI: T2-weighted Dixon image (**C**) shows perivascular increased signal intensity around the left CCA, and the same areas are enhanced on a T1-weighted, fat-saturated, post-contrast image (**D**). (**E**, **F**) Five weeks afterwards, with a control US, the wall of the left CCA was normal.

symptoms within 9 days after administration of the last G-CSF and chemotherapy, which was docetaxel in 5/6 patients. Discontinuation or change of therapy and, in some cases, glucocorticoid (GC) treatment resulted in drastic improvement of symptoms. In our series, docetaxel was discontinued in four patients, and in two patients the dosage was reduced to avoid the need for G-CSF. Management decisions, including GC therapy, were made by the clinicians. We did not find a connection with co-morbidities, such as other autoimmune diseases. None of the patients had a relapse in LVV during their follow-up examinations. When compared with the clinical presentation of the idiopathic LVV, our cases recovered faster with less medication.

Four cases similar to ours were found in the literature review [8, 13, 17]. All four patients suffered from breast cancer and received chemotherapy with docetaxel and trastuzumab. Patients developed symptoms within 15 days (average = 8 days) after the last cycle of chemotherapy and within 7 days after their last G-CSF treatment (one author [8] did not provide information about the G-CSF). All patients had a high fever and a CRP >200 mg/l. Imaging studies showed perivascular inflammation and wall thickening, especially around the aorta and the supra-aortic arteries. Although clinical pictures and findings were similar, the authors had different interpretations of ARD aetiology, because Chino *et al*. [13] and Parodis *et al*. [17] considered G-CSF to be the

Fig. 3 Aortitis in Patient 2



(**A**, **B**) CT shows diffuse wall thickening in the thoracic aorta and in the arteries ascending from the aortic arch. (**C**, **D**) Six days later, MRI shows that there is increased signal intensity around the thoracic aorta on the short tau inversion recovery image (**C**) and contrast enhancement in the same areas on T1 weighted, post-contrast Dixon images (**D**). (**E**) Three months afterwards, with a control CT showing that the wall of the thoracic aorta has recovered.

causative agent, whereas Azar *et al*. [8] concluded that chemotherapy was suspected to be the causative agent.

After the recovery from LVV, several patients continued to receive trastuzumab without signs of vasculitis.

Connection between G-CSF and LVV

Two drug adverse reaction database-related studies concerning G-CSF-induced aortitis have recently been published [9, 10]. In October 2018, Lardieri *et al*. [9] published a report of 15 patients, supporting the causal association between aortitis and G-CSF. Thirteen patients received concomitant chemotherapy for underlying cancer. However, the authors thought that aortitis was unlikely to be attributed to drugs other than G-CSF or malignancy. Four of those cases were previously published [12, 16, 26, 27] and the others were previously unreported. In February 2019, Oshima *et al*. [10] reported results from a Japanese database identifying 25 cases of aortitis in patients with malignancies, of which 16 cases had a possible association with G-CSF [10]. The authors concluded that G-CSF was associated with a sign for an increased risk for aortitis.

In our literature search, 10 published cases had received G-CSF before the onset of LVV. Six authors considered LVV possibly to be connected to G-CSF [7, 12–16]. In one study, the authors considered LVV as a paraneoplastic phenomenon in the setting of myelodysplastic syndrome [25], and in another study, the authors associated LVV with gemcitabine therapy [18]. Paraneoplastic syndrome is very rare in breast cancers,

and we could not find any cases where breast cancer itself caused vasculitis in large vessels. The paraneoplastic phenomenon associated with breast cancer seems to involve the nervous system and other non-vascular based systems [28].

Interestingly, in both database studies of suspected G-CSF-induced aortitis [9, 10], there was a large increase in reports after 2016. The same phenomenon was observed in our systematic literature review (Supplementary Table S1, available at *Rheumatology Advances in Practice* online), because only two cases were published before 2010. This raises important questions about whether G-CSF- and chemotherapy-induced LVV is a new phenomenon or the possibility that this entity has remained elusive owing to a lack of awareness and underdiagnosis. Long-acting pegylated G-CSF is relatively new to the market. Pegfilgrastim was associated with aortitis in 9/15 cases by Lardieri *et al*. [9] and in 11/16 cases by Oshima *et al*. [10]. However, there were several patients who developed aortitis after treatment with filgrastim and a few after lenograstim. We also found three published cases where patients without malignancy developed LVV after administration of G-CSF [26, 27, 29].

Based on the information gathered from our case series and from our systematic literature search, it seems possible that G-CSF may cause LVV as an ADR alone or together with chemotherapy. LVV does not seem to be specific to any G-CSF.

Connection between chemotherapy and LVV

In the literature review cases, 17/18 patients received chemotherapy before LVV. Ramsay *et al*. [20] and Bendix *et al*. [21] have reported a gemcitabine-associated LVV. In those cases, gemcitabine was used in combination with docetaxel, and there were no data about the use of G-CSF. According to our patient cases, docetaxel and/or G-CSF could have been the drug inducing vasculitis. In addition to the two cases mentioned above, in four cases [7, 8, 18, 19] chemotherapy was assumed to be at least a contributing factor in causing the LVV, and the drugs associated with the symptoms were docetaxel and gemcitabine.

Oshima *et al*. [10] recently published an observational study of 102 014 cancer patients documented in the JADER database, of whom 98 630 were not treated with G-CSF, and nine of those patients developed aortitis. Out of all the patients, 5234 received carboplatin, 8220 bevacizumab and 7345 paclitaxel, and in each group there emerged eight, four and eight cases of aortitis, respectively. Docetaxel and paclitaxel are both taxanes. In our data, docetaxel was the most used chemotherapy drug (Supplementary Table S1, available at *Rheumatology Advances in Practice* online); therefore, the possible connection of LVV to taxanes is worth considering. In our material, five patients (Supplementary Table S1, available at *Rheumatology Advances in Practice* online) were treated with carboplatin, and most patients received carboplatin during longer periods without adverse events.

Imaging findings of LVV and carotidynia

In most patients, the findings of vasculitis were in the aorta and supra-aortic vessels. Interestingly, in our material, 5/22 patients had symptoms and, reportedly, findings only in the carotid vessels suitable for carotidynia [30–32]. Our own six patients had very similar perivascular changes compared with each other. Also, the findings were in agreement with the 18 cases found in the literature (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). US imaging shows a circular wall thickening of the affected vessel [7, 21, 33]. Cross-sectional imaging (CT and MRI) shows perivascular, enhancing tissue around the vessel [7, 21, 30, 33, 34]. Diagnostic imaging is crucial when making a diagnosis of LVV and carotidynia. Imaging studies are also needed to exclude other vascular conditions causing neck or chest pain, such as dissection, thrombosis, atherosclerosis, fibromuscular dysplasia, migraine and aneurysm formation. Confirmed carotidynia should improve by itself, without the need for GC treatment [31]. However, differential diagnostics with vasculitis are challenging, and clinicians are forced to treat patients with presenting symptoms. In many cases, the exact diagnosis remains elusive.

Pathobiological aspects

The pathobiology of LVV in association with docetaxel might involve mechanisms related to the mode of action of docetaxel, which could be potentiated by G-CSF. Through its effects on microtubule reorganization [35], docetaxel could interfere with several cellular functions, including complement receptor-mediated endocytosis [36] and granule exocytosis [37]. This could predispose individuals to vasculitis by mechanisms related to the clearance of immune complexes, the cytotoxic functions of CD8 T cells and through macrophage activation.

An interesting consideration is the possible interference in immune complex clearance by docetaxel [36] and activation of neutrophils on endothelial surfaces. Immune complexes are ligands of neutrophil phagocytic receptors. When precipitated on surfaces such as vessel walls in the vasa vasorum, engagement of neutrophil receptors by these ligands could induce neutrophils to secrete their lysosomal enzymes and free oxygen radicals on the surface of endothelial cells [38]. By promoting neutrophils, G-CSF could perhaps act in synergy with docetaxel to promote vascular inflammation and injury.

Strengths and limitations

This study has limitations. It was retrospective; hence, all detailed data were not available for literature cases. Some literature cases do not include detailed description of the extent to which the vascular territories were evaluated apart from the diagnostic finding. Also,

comprehensive biological markers and tissue samples were not available. The effect of paraneoplastic syndrome as part of the aetiology of LVV cannot be excluded completely.

A strength of the study was the systematic literature review, and our patient cases were current, with excellent patient records and imaging studies. In our patient series, 5/6 patients had all large-vessel territories evaluated.

Future considerations

It is important to keep the possibility of drug-induced LVV in mind when treating patients with G-CSF and chemotherapy. LVV is a serious condition that requires prompt diagnosis, and it may result in complications such as arterial wall dissection. Based on currently available data, there is high suspicion of a connection between G-CSF, docetaxel and LVV. However, based on the published data, this causality is not certain, and further studies are needed.

Conclusions

LVV is a possible serious rare adverse event associated with G-CSF and chemotherapy. Symptoms, such as fever and chest pain, can develop within 2 weeks after the last drug administration. We assume that LVV is often underdiagnosed. Diagnostic imaging (i.e. US, CT and MRI) plays a major role in making a successful diagnosis of LVV. Accurate management of LVV requires early identification and discontinuation of the drug. This potentially severe ADR should be taken into consideration when treating oncological patients with G-CSF. When diagnosed and treated properly, the patients' recovery time is usually short.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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