Large-vessel vasculitis induced by pegfilgrastim

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ABSTRACT

Granulocyte colony-stimulating factor (G-CSF) is increasingly being used to prevent febrile neutropenia associated with chemotherapy. Large-vessel vasculitis (LVV) has been recognized as a rare side effect of G-CSF treatment. We report a case of G-CSF associated LVV in a patient with breast cancer. While clear pathogenic mechanisms remain unknown, G-CSF may cause vasculitis due to inflammatory cytokines production. This adverse reaction should be recognized in patients with suggestive symptoms following the administration of pegfilgrastim.

A 56-year-old woman with luminal B breast cancer who had undergone surgery and adjuvant chemotherapy, initially with paclitaxel, was started on a doxorubicin plus cyclophosphamide protocol, followed by supportive use of long-acting G-CSF pegfilgrastim. Following the administration of pegfilgrastim, the patient developed intermittent fever and was given empiric antibiotics in the outpatient setting with no improvement. There were no signs of cancer progression, and the contrast-enhanced CT scan highlighted wall thickening of the aortic arch and the proximal segment of the subclavian artery, which was not present in previous imaging studies. The patient was diagnosed with LVV, and a differential diagnosis was performed to rule out paraneoplastic setting, immune-mediated diseases, infection or other drug-induced vasculitis. Treatment with steroids was initiated and tapered with significant improvement and resolution of the radiological signs of aortitis.

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INTRODUCTION

Recombinant human granulocyte-colony stimulating factors (G-CSF), which include filgrastim and PEGylated filgrastim, induce long-acting neutrophil proliferation and maturation. G-CSF have been increasingly established as a primary or secondary prophylaxis to reduce the severity and duration of neutropenia in patients receiving myelosuppressive cytotoxic chemotherapy who are at risk of chemotherapy-induced neutropenic fever and potentially fatal infectious complications[1].

G-CSF decreases all-cause mortality and increases the possibility of maintaining chemotherapy dose, intensity and density, an absolute prerequisite in curable malignancies[2]. Dose-dense chemotherapy is a treatment requiring G-CSF that aims to achieve higher rates of cancer cell death. It has been adopted as an adjuvant therapy in high-risk breast cancer cases with the goal of improving outcomes[3]. The dose-dense doxorubicin and cyclophosphamide (ddAC) for patients with HER-2-negative breast cancer is an example of such cases and is recommended by the National Comprehensive Cancer Network guidelines in the United States of America (USA)[4].

G-CSF acts on the granulocyte lineage, stimulating neutrophil recruitment from the bone marrow to the peripheral blood, thereby promoting differentiation and maturation of these cells. The most commonly described side effects are relatively mild and include fever, bone pain, headache and fatigue[5]. Large-vessel vasculitis (LVV) is a very rare adverse event in patients treated with G-CSF, and the risk factors or relation between arteritis and G-CSF remain unknown. In the USA, G-CSF-associated aortitis has been confirmed only in 15 cases as reported by the Adverse Event Re-

porting System (AERS) of the Food and Drug Administration (FDA)[6]. The Japanese Adverse Drug Event database reported a 0.47% frequency of aortitis in patients treated with G-CSF (16 out of 3409)[7]. To our knowledge, there are no published case reports of pegfilgrastim-associated aortitis in Portugal.

Herein, we report a case of G-CSF-induced aortitis in a patient treated for breast cancer. Although the differential diagnosis of aortitis may be challenging, the present case highlights how finding aortitis during chemotherapy treatment should warrant the recognition of pegfilgrastim as a possible source of inflammation.

CASE REPORT

The authors present a case of a 56-year-old female patient with HER-2 negative luminal B breast cancer who underwent lumpectomy and was receiving adjuvant chemotherapy following a multigene EndoPredict® assessment suggesting high risk of recurrence. Cancer staging had shown no signs of invasive or metastatic disease (pT1cN0M0) with a negative sentinel node biopsy and a normal computerized tomography (CT) scan.

The patient was treated according to the Oncology's chemotherapy protocol, initially with 12 cycles of paclitaxel during three months during which there were no complications, followed by AC dose-dense scheme which included doxorubicin, cyclophosphamide and supportive use of long-acting G-CSF pegfilgrastim. Following the introduction of AC dose-dense scheme, specifically five days after doxorubicin plus cyclophosphamide and three days after pegfilgrastim administration, she developed fever (38.7ºC) and was given empiric antibiotics in the outpatient setting. After five days, given the persistence of fever, she was re-evaluated. A more comprehensive anamnesis showed that in addition to fever, she presented malaise, lipothymia, and left cervical and pleuritic dorsal pain with left arm paraesthesia and claudication. The patient was hemodynamically stable, blood pressure measurements performed in both arms and showed no significant difference (left arm 104/64 mmHg and right arm 106/65 mmHg), there was no pulse asymmetry and her physical exam was unremarkable, with no signs of infection. Laboratory tests showed significant elevation of inflammation markers, namely erythrocyte sedimentation rate (103 mm/h) and C-reactive protein (22.9 mg/dL), without any other abnormalities such as elevation of tumour makers (CEA and CA 15-3) compared to the patient's previous evaluation. For a more detailed evaluation, a contrast-enhanced CT scan was performed and highlighted wall thickening of the aortic arch and the proximal segment of the left subclavian artery, suggesting a localized vasculitis process (Figure 1). No other abnormalities were identified, ruling out lesions in other vascular territories, thromboembolism, signs of tumour recurrence, abnormal lymph nodes or abscesses.

The patient was diagnosed with LVV and was given glucocorticoids, initially with methylprednisolone pulses 1g/day for three days, followed by oral prednisolone 60mg/day.

Further investigation with Doppler ultrasound showed no relevant abnormalities of the temporal, facial and axillary arteries. Primary LVV was considered unlikely, considering the patient's age and lack of previous symptoms suggestive of giant cell arteritis (GCA), such as headache or visual disturbances, or symptoms of polymyalgia rheumatica. A differential diagnosis with secondary aortitis was performed. Complementary exams including anti-nuclear antibodies (ANA) panel, rheumatoid factor, anti-CCP, anti-MPO and anti-PR3 autoantibodies were negative and complement levels were normal. Furthermore, the patient had no manifestations of other immune-mediated diseases, specifically systemic lupus erythematosus, rheumatoid arthritis, spondyloarthropathies, Behçet's disease, IgG4- -related disease or sarcoidosis. No microorganisms such as bacteria or fungi were identified in blood cultures; transthoracic echocardiogram had no vegetations; a negative Interferon Gamma Release Assay (IGRA) excluded tuberculosis; and serologies for *Salmonella*, *Syphilis, Brucella,* varicella zoster virus, hepatitis B and C virus were negative for active infection.

A significant improvement was observed with resolution of symptoms and reduction of inflammatory markers (erythrocyte sedimentation rate 61 mm/h and C-reactive protein 4.8 mg/dL) after five days of glucocorticoids which were then tapered. Considering the acute onset of symptoms following the pegfilgrastim administration, absence of vasculitis signs in CT scans prior to this drug and the rapid response to glucocorticoids, a diagnosis of pegfilgrastim-induced LVV was made. After hospital discharge, the patient was evaluated by the assistant Oncologists and the chemotherapy regimen was adjusted excluding pegfilgrastim. CT scan re-evaluation after four weeks showed complete

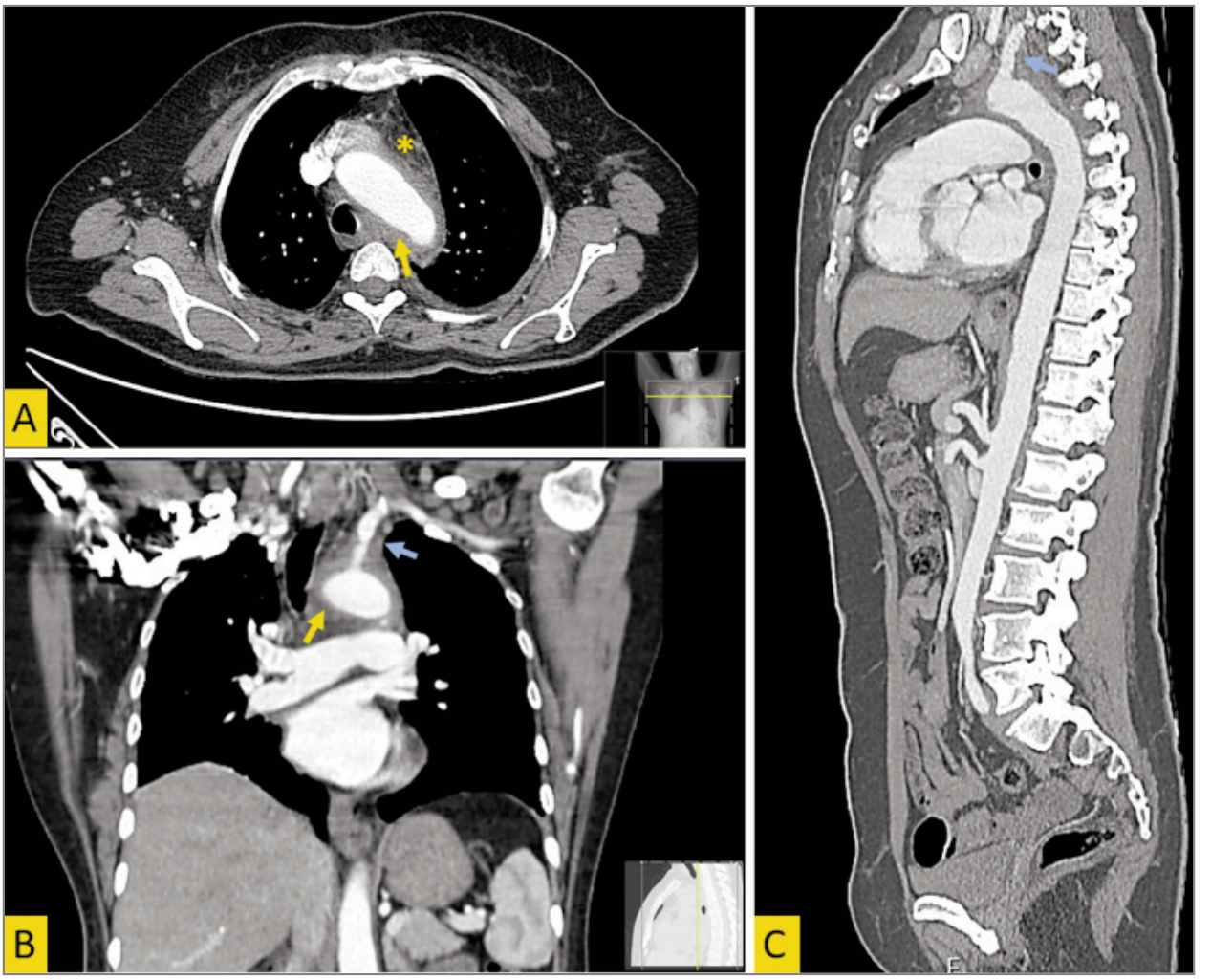

FIGURE 1. Contrast-enhanced computed tomography
(A – axial, B – coronal, and C – sagittal reconstruction planes) shows wall thickening of the aortic arch (yellow arrows) and left subclavian artery (blue arrows) with perivascular fat stranding (yellow asterisk).

resolution of the aortitis signs (Figure 2) and at the time of this manuscript the patient remains without LVV recurrence.

DISCUSSION

Previous reports of G-CSF-induced arteritis show that patients present with high-grade fever, increased C--reactive protein levels and erythrocyte sedimentation rate, which represent non-specific markers of inflammation. When infections or immune-mediated diseases are ruled out, imaging modalities like CT scan, magnetic resonance imaging and positron emission tomography play a major role in attaining a successful diagnosis and should be performed as early as possible when aortitis is suspected. Although the precise mechanism of G-CSF-induced aortitis remains uncertain, it has been demonstrated that CSF-producing cell lines co-produce and activate pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-23, with subsequent pathological activation of Th17 cells, antigen-specific CD4+ T cells and neutrophils, which may be involved in the development of vasculitis[8,9].

The revised International Chapel Hill Consensus Conference nomenclature of vasculitis from 2012 is the

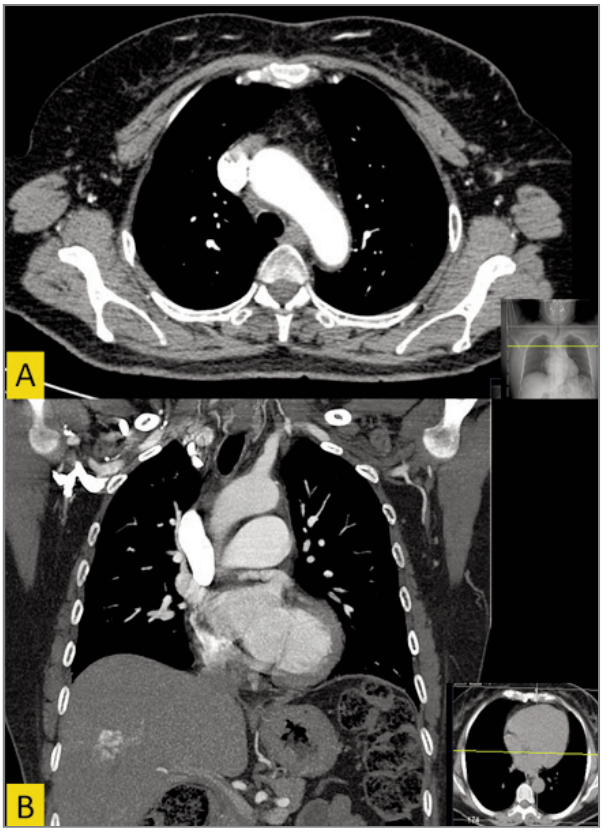

FIGURE 2. Contrast-enhanced computed tomography showing complete resolution of the aortitis signs.
(A – axial and B – coronal reconstruction planes).

most widely used system for describing vasculitis[10]. The etiological diagnosis of aortitis is challenging and should include primary LVV – Takayasu's arteritis (TAK) and GCA – and secondary vasculitis associated with systemic disease. TAK occurs more frequently before the age of 40 years and GCA often occurs after the age of 50 years. However, in this present case the patient did not meet the 1990 American College of Rheumatology classification criteria for neither disease.

Secondary vasculitis may arise due to various causes, including infections, immune-mediated diseases, drug reaction and cancer. The diagnosis of drug-induced vasculitis requires the exclusion of all other potential causes of vasculitis and is frequently not easy to confirm. In our case, infection was ruled out, no symptoms or autoantibodies that would indicate an immune-mediated disease were present and there were no signs of active cancer. Paraneoplastic vasculitis (PNV) represents 2%–5% of all types of vasculitis and occurs in approximately 1 in 80800 solid tumours[11]. The most common site for PNV is the skin, and almost half of all cases appear as a leukocytoclastic vasculitis and are often accompanied with progression of cancer, neither of which were present in this case, making it an unplausible cause for LVV[12]. LVV was unlikely attributed to other drugs, namely doxorubicin and cyclophosphamide which were administered at the time of pegfilgrastim, since none of those have been linked with aortitis[6].

As the appropriate treatment for pegfilgrastim-induced LVV, G-CSF discontinuation can lead to recovery and, notably, glucocorticoid administration has been reported to be effective[13]. In our patient, given the extension of LVV with risk of progression to aortic aneurysm formation and potentially fatal dissection or rupture, glucocorticoids were promptly started having ruled out infectious. The patient also had lipothymia, which could represent a symptom of subclavian steal syndrome from the subclavian artery involvement proximal to the vertebral artery origin. There was an altered vascular haemodynamic phenomenon that resulted in retrograde blood flow in the ipsilateral vertebral artery toward the upper arm, distal to the subclavian artery narrowing, where decreased blood pressure had been established.

Having ruled out other causes for secondary LVV, considering the onset of symptoms following the pegfilgrastim administration, rapid clinical and radiological improvement after glucocorticoid initiation and the fact that vasculitis did not recur after G-CSF therapy was stopped, strongly imply that in our case LVV was caused by pegfilgrastim. Accordingly, the chemotherapy scheme was adjusted with suspension of pegfilgrastim, as re-administration of G-CSF entails a risk of vasculitis recurrence[14].

One of the possible mechanisms by which exogenous administration of G-CSF may induce LVV includes stimulation of the proliferation and differentiation of neutrophil precursors and enhancement of neutrophil chemotaxis[15]. G-CSF may have a priming effect in human neutrophils. Interestingly, viable human neutrophils after priming with granulocyte/macrophage colony-stimulating factor (GM-CSF) and subsequent stimulation of toll-like receptor 4 (TLR4) or complement component 5a (C5a) receptor were able to generate neutrophil extracellular traps (NETs)[16]. C5a via interaction with its cellular receptor on neutrophil surface leads to changes in the neutrophil cell shape and membrane formability that allows the neutrophil not only to transform into a migratory cell and invade

inflammatory sites but also clear pathogens and debris[17]. Mavrilimumab is a fully humanized monoclonal antibody targeting GM-CSF receptor alpha (GM-CSFR) currently ongoing clinical trials as treatment in giant cell arteritis and could have a potential use in drug induced LVV in the future.

In summary, we report a case of arteritis associated with G-CSF, which may be potentially under-recognized due to its rarity. However, it is crucial to correctly identify the presence of aortitis, given its risk of progression to an acute aortic syndrome which can be life-threatening. Clinicians should be increasingly aware of this serious adverse effect for which glucocorticoid administration is effective.

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