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Case Report

Granulocyte Colony-Stimulating Factor and Neutrophilic Aortitis

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Abstract

Objectives: We describe a case of Lipegfilgrastim associated aortitis and review the literature.

Results: There are 18 published cases of G-CSF associated aortitis. It appears to occur predominantly in middle-aged females of Asian ethnicity. This has been described with a range of G-CSF products in both malignancy and in healthy individuals. The commonest presenting symptom was fever and 11/18 cases were associated with leucocytosis. Two patients developed complications of dissection and aneurysm formation. Treatment varied across cases with 8/18 treated with systemic corticosteroids with other cases resolving with cessation of G-CSF alone or with non-steroidal anti-inflammatories.

Discussion: Aortitis is a rare but potentially life threatening complication of G-CSF with potential for complications of dissection and aneurysm. Diagnosis is one of exclusion of other potential causes; most importantly infective etiology in patients who may be immunosuppressed. The underlying pathogenesis of this condition, natural history and optimal treatment currently remain unknown however treatment with corticosteroids appears to be effective.

Methods: A review of the literature to date published in Pubmed was performed with cross-referencing of included articles. Seven relevant publications were included for review in detail and these 18 cases are summarised.

Conclusion: Whilst G-CSF therapy is usually well tolerated, fever and leucocytosis should prompt consideration of G-CSF associated aortitis. Optimal management of this condition includes withdrawal of G-CSF therapy and consideration of systemic corticosteroid use given the potential for development of life-threatening complications. Further research is required to better elucidate the underlying immunopathogenesis, natural history and optimal management of this condition.

ABBREVIATIONS

G-CSF: Granylocyte-Colony Stimulating Factor

INTRODUCTION

Aortitis is a rare condition of inflammation of the aortic wall and is either classified as infective or non-infective [1]. The most commonly recognised non-infectious causes of this disorder are the autoimmune vasculitides such as giant cell arteritis (GCA) or Takayasu's arteritis, however other causes such as IgG4 related sclerosing disease have also been recognised [1,2]. Infective causes are rare, generally occurring in patients with pre-existing aortic disease such as arteriosclerosis or aneurysms, or in those who are immunocompromised. The most frequently reported organisms are bacteria such as salmonella, staphylococci and pneumococci. However other pathogens such as mycobacteria, fungi and viruses have all been reported [2].

Granulocyte colony-stimulating factor (G-CSF) is a recombinant human glycoprotein that promotes proliferation and differentiation of granulocytic committed progenitors. G-CSF is widely used in medical oncology and haematology for the prevention and treatment of neutropenia most commonly following myelosuppressive therapy or for mobilisation of stem cell and progenitor cells from the bone marrow to peripheral blood for transplantation. G-CSF is usually well tolerated with few common side effects including bone pain, myalgia and headache [3]. There are increasing case reports of G-CSF treatment associated with large, medium and small vessel vasculitis [3]. In a cohort of 832 patients with severe chronic neutropenia (SCN) the incidence of vasculitis was 4.1% with the majority being cutaneous leucocytoclastic vasculitis [4]. Ireland's Health products regulatory authority released a warning piece describing the risk of aortitis with G-CSF in June 2018[5]. Several pharmaceutical companies were amongst the first to release a warning for the association between G-CSF and

aortitis in accordance with Health Products Regulatory Authority [5].G-CSF has been associated with new diagnosis of vasculitis such as cutaneous vasculitis as well as with exacerbation of pre-existing autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus [6]. G-CSF use has also been associated with the development of other neutrophil mediated diseases including Sweet's syndrome [3].

At our tertiary centre in Western Australia it is estimated that 382 patients were prescribed at least one dose of G-CSF in one year based on electronic dispensing software history. A number which is likely to increase as there have been the recent changes to our Pharmaceutical benefits scheme (PBS) listing of lipegfilgrastim and pegfilgrastim [7]. Despite G-CSF being generally well tolerated, there are increasing reports of an association between the use of G-CSF and the development of aortitis in the literature. Although this complication appears rare with only 18 other cases reported to date, it is important given the potential for serious complications such as aortic dissection and aneurysm formation. The underlying pathogenesis and natural history of this condition is poorly characterised, however treatment with corticosteroids appears to be effective. We report a case of aortitis associated with lipegfilgrastim which responded to treatment with corticosteroids and review the literature to date.

A comprehensive literature review and cross referencing identified a total of 18 patients with G-CSF associated aortitis [8-14]. The majority (79%) of cases where reported in the last five years. Aortitis has complicated a range of G-CSF products including filgrastim, pegfilgrastim and lenograstim. Of the patients described, the majority (67% 12/18) were reported in Japan and presumably, although not specified, of Asian ethnicity. There appears to be a significant female predominance with 83% (15/18) of the cases being women. The age of patients affected ranged from 47-77 years with the mean age being 63 years (Table 1). This was in keeping with the demographic profile of our patient.

A range of malignancies have been reported in association with this condition. The most frequently reported malignancy was breast cancer (28%) as was seen in our case, but other reported malignancies include ovarian, lung, lymphoma, uterine and prostate cancers. Importantly this condition has also been reported in healthy patients being treated with filgrastim for stem cell mobilisation, indicating that this is unlikely to be purely a paraneoplastic phenomenon [10].

A striking feature in our patient was the profound leukocytosis. This is in keeping with the other cases in the literature in which 14 out of 16 cases reported leucocytosis with the average WCC being 22.9x10^9/L- suggesting that it may be a dose-related effect. Consistent with this Cottle et al., found that the onset of cutaneous vasculitis in patients with SCN coincided with an increase in absolute neutrophil count and resolved once the neutrophils normalised [15]. Interestingly the majority of patients in their cohort were able to continue filgrasitm at a reduced dose [15].

Onset of symptoms ranged from 6 to 365 days with the majority presenting within 10 days. Fever was the most common presenting symptom; noted in 13/19 patients. Pain was also common particularly in the chest, epigastrium, cervical region and back. CT was the most commonly used diagnostic imaging modality with magnetic resonance imaging (MRI) being performed in four cases and PET scan in two. Treatment varied across the cases reported. In all cases G-CSF therapy was ceased and in eleven patients aortitis resolved without the need for further treatment. In seven cases additional corticosteroids were administered and in one case non-steroidal anti-inflammatories were used. All case reports describe resolution of symptoms on cessation of G-CSF and adjunctive therapies as described above. There is only one reported case of rechallenge with G-CSF after aortitis however unfortunately the secondary outcomes were not described [8]. Two patients developed complications from aortitis including aortic dissection [12] and aneurysm formation [10].

CASE PRESENTATION

We report a case of a 51 year old Chinese woman who developed aortitis while receiving adjuvant chemotherapy and trastuzumab for HER2 positive left breast invasive ductal carcinoma supported by lipegfilgrastim. Significant past medical history included; known Hepatitis B carrier on prophylactic Tenofovir 300mg, iron deficiency anaemia and gastro-oesphageal reflux disease. Her breast cancer was treated with a wide local excision followed by adjuvant therapy consisting of three cycles of fluorouracil, epirubicin and cyclophosphamide followed by three cycles of docetaxel and trastuzumab administered every 21 days (FEC-DH). Her first cycle was complicated by asymptomatic neutropenia (neutrophils 0.65 x 10^9/L) and thus lipegfilgrastim was administered on day two of her subsequent cycles of chemotherapy to maintain dose intensity. She received three doses of lipegfilgrastim over a period of seven weeks prior to her presentation without any signs of neutrophilia prior to her third dose. Day 6 after her first cycle of docetaxel and third dose of lipegfilgrastim, she presented with fever and epigastric pain without localising features of infection. She had a marked neutophilia of 39.5 x10^9/L and elevated inflammatory markers. She was treated empirically for non-neutropenic sepsis with piperacillin/tazobactam and vancomycin, however, failed to improve with ongoing high fevers and rising inflammatory markers (Figure 1). A computerised tomography (CT) scan of her chest, abdomen and pelvis revealed circumferential wall thickening of the distal arch and descending thoracic aorta. A subsequent positron emission tomography (PET) scan showed diffuse patchy moderate intensity activity involving the posterior aspect of the aortic arch, descending thoracic aorta and the origin of the left subclavian artery consistent with vasculitis. No activity was seen in the temporal arteries or elsewhere. A CT angiogram confirmed aortitis without any evidence of dissection or aneurysm formation.

The major differential diagnoses included; new presentation of autoimmune large vessel vasculitis (e.g. Takayasu or Giant Cell Arteritis), medication related vasculitis (G-CSF), infective causes of vasculitis (e.g. syphilis, Q fever) in an immunosuppressed patient.

Infective causes for aortitis were excluded with

Table 1: Adapted from Ladiere et al.v [8], Summary of G-CSF associated aoritis cases.

Author, Year	Age (years)	Gender	G-CSF type/ indication (if mentioned)	White cell count X 10^9/L	Time to onset (days)	Diagnostic Imaging	Treatment	Complication
Inderjeeth 2020	51	F	Pegylated G-CSF/chemotherapy induced neutropenia	50.59	6	CT, CTA, PET	Corticosteroids	Nil
Dariea 2004 (9)	55	F	G-CSF/stem cell donor	41.1	6	CT, MRI, USS	Corticosteroid	Nil
Miller 2016 (10)	52	M	Neupoten/ Stem cell donor	10.3	365	CT	Corticosteroid	Left iliac artery aneurysm
Adiga 2009 (11)	54	M	Filgrastim/ Neutropenia	11.4	13	CT and MRI	Corticosteroid	Nil
Sato 2017 (12)	67	F	Pegfilgrastim/ Neutropenia	22.3	8	CT USS and PET	Nil	Stanford B aortic dissection
Ladieri 2013 (8)	Unknown	M	Pegfilgrastim /Neutropenia	Not reported	15	Unknown	Not reported	Nil
Ladieri 2016(8)	49	F	Filgrastim/Neutropenia	8.4	6	CT	NSAID	Nil
Ladieri 2016(8)	72	F	Pegfilgrastim/ Neutropenia	11.7	13	CT	Nil	Nil
Ladieri 2016(8)	76	F	Pegfilgrastim/Neutropenia	21.8	7	CT	Nil	Nil
Ladieri 2016(8)	77	F	Filgrastim/neutropenia	8.7	7	CT	Nil	Nil
Ladieri 2017 (8)	47	F	Lenograstim/Neutropenia	Not reported	8	CT	Corticosteroids	Nil
Ladieri 2017(8)	61	F	Pegfilgrastim/ Neutropenia	18.3	7	CT and MRI	Nil	Nil
Ladieri 2017(8)	62	F	Pegfilgrastim/Neutropenia	16.5	12	CT and MRI	Corticosteroid	Nil
Ladieri 2017(8)	65	F	Pegfilgrastim/Neutropenia	60.4	9	CT	Corticosteroid	Nil
Ladieri 2017(8)	66	M	Pegfilgrastim/Neutropenia	18.6	8	CT	Nil	Nil
Ladieri 2017(8)	69	F	Pegfilgrastim/Neutropenia	19.9	11	CT	Nil	Nil
Parodis 2019 (14)	70	F	Filgrastim /Neutropenia	Not reported	9	CT	Steroid	Nil
Parodis 2019 (14)	60	F	Filgrastim /Neutropenia	Not reported	11	CT	Glucocorticoids	Nil
Kingo 2019 (13)	77	F	6X G-CSF / Neutropenia	8700 UI	15	CT	Nil	Nil
Average	62.78			21.91	28.21			
					Median 9			

G-CSF (granulocyte-colony stimulating factor)
WCC (white cell count) X 10^9/L
CT (Computerised Tomography)
MRI (Magnetic resonance imaging)
PET (Positon emission tomography)
USS (Ultrasound)
NSAID (non-steroidal anti-inflammatory)
M (male)
F (female)

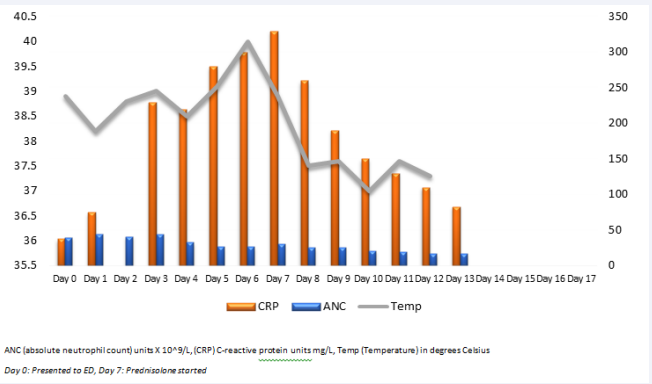

Figure 1 Clinical and biochemical trend
ANC (absolute neutrophil count) units X 109/Litre, CRP (C-reactive protein) units mg/L, Temp (Temperature) in degrees Celsius
Day 0: Presented to ED, Day 7: Prednisolone started

multiple negative blood cultures including cultures for mycobacterium and fungi. Serology for syphilis, Bartonella, Brucella and Q fever was negative. A primary connective tissue disorder was considered unlikely as there were no other features of vasculitis and the patient had received significant immunosuppression in the form of chemotherapy. Autoimmune serology including anti-nuclear antibody (ANA) and anti-neutrophil cytoplasmic antibody (ANCA) were negative. After 6 days antibiotics were ceased because infection was considered unlikely. The patient had persistent fever and neutrophilia of $26.54x10^9$/L (WCC 28.39). With a CT and subsequent PET scan suggestive of vasculitis, and given the potential for lipegfilgrastim associated aortitis progressing to aneurysmal dilatation and dissection, corticosteroids were commenced (50 mg oral prednisolone daily). Within 24 hours of corticosteroid therapy her fevers resolved and inflammatory markers declined (Figure 1). The patient remained on 50mg of prednisolone for one week which was then subsequently weaned over the following month. A repeat PET scan after one month revealed reduction in metabolic activity in the arch and descending aorta and by three months there was complete resolution of aortitis on imaging (Figure 2). She currently remains in remission from her aortitis after over a year of follow-up.

DISCUSSION

Aortitis is a rare complication of G-CSF therapy but it is important that physicians are aware of it. Diagnosis of this condition may be challenging given the non-specific clinical presentation, but early recognition is critical to ensure appropriate treatment in order to prevent serious complications. The differential diagnosis of aortitis in a patient undergoing chemotherapy may be broad and whilst imaging, including CT, MRI and PET scanning are useful for diagnosing and monitoring aortitis they do not reliably discriminate between the underlying aetiologies [1].

A diagnosis of G-CSF associated aortitis is essentially a diagnosis of exclusion. It is critical that infectious causes are excluded in the first instance. The inability to identify an organism and failure to respond to antimicrobial treatment should prompt consideration of this disorder. Differentiating G-CSF associated aortitis from an underlying connective tissue disorder such as giant cell arteritis or Takayasu's arteritis can be difficult. Although the number of cases reported is small, we have found that middle aged Asian women, particularly those with breast cancer, may be at higher risk of developing this complication. It is interesting to note that this demographic is not dissimilar to those patients known to be at risk of developing Takayasu's arteritis and although G-CSF precipitating underlying autoimmune aortitis cannot be entirely excluded there are a number of features that may distinguish them apart [1]. These include; the degree of neutrophilia at diagnosis, absence of relapses on follow-up [16], resolution occurring spontaneously on G-CSF cessation or with short courses of corticosteroids only, the absence of other organ involvement and the demonstrated temporal relationship with G-CSF administration. Sustained remission on cessation of G-CSF over longer term follow-up will provide more confidence in the diagnosis of G-CSF associated aortitis as a separate disease entity.

The underlying pathogenesis of this condition remains unknown although there does appear to be an association between the degree of neutrophilia and aortitis. This may suggest that neutrophils are the effector cell responsible for the inflammatory aortitis. Sato et al., demonstrated in a case of G-CSF associated aortitis that Interleukin 6 (IL-6) levels were raised during active disease and normalised following treatment [12]. However this was the only study to examine cytokine levels. The mechanism proposed is neutrophil promotion of CD4+ T cell survival via IL-6 [10]. The role of G-CSF as an immune regulator of T cells was explored in a paper by Frankze et al [17]. Arterial wall damage from neutrophil mediated phagocytosis and antibody mediated toxicity have also been suggested as possible mechanisms of disease [10,18].

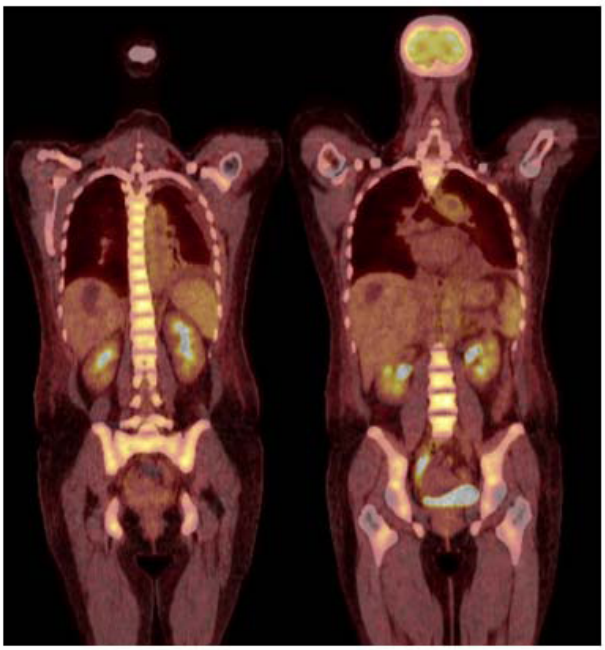

Figure 2 PET images pre-treatment: Circumferential wall thickening of distal arch and descending thoracic aorta.

The optimal treatment of this condition and natural history are also largely unknown. Although corticosteroids have been effective in the cases reported to date, a large number of patients had resolution of disease with cessation of G-CSF alone and therefore the need for corticosteroid treatment is unclear. In our case corticosteroids were used because of the marked neutrophilia, the prolonged half-life of lipegfilgrastim, the persistence of clinical symptoms and potential for complications.

G-CSF associated aortitis is a rare but potentially life-threatening complication of a commonly used treatment. It is important for physicians to consider this complication in patients who develop systemic symptoms post-myelosupressive therapy without a readily identifiable aetiology or failure to respond to treatment for infection. Whilst it is difficult to draw conclusions from the small number of cases reported, it appears that female sex, middle-aged, Asian ethnicity and leucocytosis are all potential risk factors for developing this condition.

Treatment currently involves cessation of G-CSF therapy with or without the addition of corticosteroids. Corticosteroids are effective in controlling symptoms of aortitis however their role in preventing complications such as dissection and aneurysm formation is unknown. Further research is required to elucidate mechanism of G-CSF associated vasculitis and a means to identify patients at risk of complications, to determine optimal management in the future. This is particularly important as usage is likely to increase in Australia with increasing access to therapy and ease of administration of longer acting formulations [7]. We have reported our case to Therapeutic Goods Australia in hope of bringing further attention to Australian prescribers and the risk associated with this previously thought to be safe drug.

REFERENCES

1. H Gornik, Mark AC. Aortitis. Circulation. 2008; 10: 3039-3051.
2. I Töpel, N Zorger, M Steinbauer. Inflammatory diseases of the aorta: Part 1: Non-infectious aortitis. Gefasschirurgie. 2016; 21: 80-86.
3. Anita D'Souza, Ishmael Jaiyesimi, Lance Trainor, Padmaja Venuturumili. Granulocyte Colony-stimulating factor administration: Adverse events. Transfus Med Rev. 2008; 22: 280-290.
4. David C Dale, Tammy E Cottle, Carol J Fier, Audrey Anna Bolyard, Mary Ann Bonilla, Laurence AB, et al. Severe Chronic Neutropenia: Treatment and Follow-Up of Patients in the Severe Chronic Neutropenia. International Registry. Am J Hematol. 2003; 72: 82-93.
5. HPRA. Granulocyte colony-stimulating factors (G-CSFs) (Filgrastim, Lenograstim, Lipegfilgrastim and Pegfilgrastim) - Important Safety Information from Amgen Europe B.V, Chugai Pharma UK, Teva, Apotex Europe B.V, and Accord Healthcare Ltd as approved by the HPRA. 2018.
6. Christof Iking-Konert, Benedikt Ostendorf, Mark Foede, Rebecca Fischer-Betz, Gregor Jung, Maria G Haensch, et al. Granulocyte colony-stimulating factor induces disease flare in patients with antineutrophil cytoplasmic antibody-associated vasculitis. J Rheumatol. 2004; 31: 1655-1658.
7. AGDH. Pharmaceutical Benefits Scheme.
8. Allison Lardieri, Lynda McCulley, Steven Christopher Jones, Daniel Woronow. Granulocyte colony-stimulating factors and aortitis: A rare adverse event. Am J Haematol. 2018; 93: 333-336.
9. C Darie, S Boutalba, P Fichter, J-F Huret, P Jaillot, F Deplus, et al. [Aortitis after G-CSF injections]. Rev Med Interne. 2004; 25: 225-229.
10. Edward B Miller, Roy Grosu, Zvi Landau. Isolated abdominal aortitis following administration of granulocyte colony stimulating factor (G-CSF). Clin Rheumatol. 2016; 35: 1655-1657.
11. G Adiga, S Malik, J Fitzpatrick, S Madajewicz. Isolated abdominal aortitis following administration of granulocyte colony stimulating factor (G-CSF). Clin Drug Investig. 2009; 29: 821-825.
12. Yuki Sato, Shuichiro Kaji, Hiroyuki Ueda, Keisuke Tomii. Thoracic aortitis and aortic dissection following pegfilgrastim administration. Eur J Cardiothorac Surg. 2017; 52: 993-994.
13. Yasuyuki Kinjo, Tomoko Kurita, Taeko Ueda, Seiji Kagami, Yusuke Matsuura, Kiyoshi Y, et al. Acute arteritis after G-CSF administration. Int Cancer Conf J. 2019; 8: 77-80.
14. Ioannis Parodis, Lara Dani, Antonella Notarnicola, Git Martenhed, Pontus Fernström, Alexios Matikas, et al. G-CSF-induced aortitis: Two cases and review of the literature. Autoimmun Rev. 2019; 18: 615-620.
15. Tammy E Cottle, Carol J Fier, Jean Donadieu, Sally E Kinsey. Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. Semin Hematol. 2002; 39: 134-140.
16. Giovanbattista Ippoliti, Marco Paulli, Marco Lucioni, Marinella Lauriola, Andrea Maria D'Armini. Leukocytoclastic Vasculitis as a Complication of Recombinant Granulocyte Colony-Stimulating Factor Therapy in a Heart Transplant Patient. Case Rep Transplant. 2014; 2014: 160407.
17. Anke Franzke, Wenji Piao, Jörg Lauber, Patricia Gatzlaff, Christian Könecke, Wiebke Hansen, et al. G-CSF as immune regulator in T cells expressing the G-CSF receptor: implications for transplantation and autoimmune diseases. Blood. 2003; 102: 734-739.
18. H Zoellner, E L Filonzi, H R Stanton, J E Layton, J A Hamilton. Human arterial smooth muscle cells synthesize granulocyte colony-stimulating factor in response to interleukin-1. Blood. 1992; 80: 2805-2810.

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