Lisenko et al., J Clin Case Rep 2016, 6:5
DOI: 10.4172/2165-7920.1000788

Journal of Clinical Case Reports

Case Report Open Access

Giant Cell Arteritis Related to Granulocyte-Colony-Stimulating Factor Administration

Katharina Lisenko[1]*, Norbert Blank[1], Patrick Wuchter[1], Tim Weber[2], Martin Cremer[1], Mark Kriegsmann[3], Anthony D Ho[1] and Mathias Witzens-Harig[1]

[1]*Department of Hematology, Oncology and Rheumatology, University Heidelberg, Heidelberg, Germany*
[2]*Department of Radiology, University Heidelberg, Heidelberg, Germany*
[3]*Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany*

Abstract

Objective: Granulocyte-colony-stimulating factor (G-CSF) is routinely used to mobilize stem cells for peripheral blood stem cell (PBSC) collection by leukapheresis. Although generally considered safe and effective, G-CSF has been reported to cause severe side-effects in rare cases.

Methods and Results: We report a case of a 65-year-old woman with diffuse large B-cell lymphoma, who received G-CSF for PBSC mobilization for ten days and developed fever of unknown origin. She was diagnosed with giant cell arteritis (GCA) related to G-CSF with aortic involvement based on typical findings obtained by contrast-enhanced computed tomography and treated with high-dose prednisone.

Conclusion: GCA might have to be considered as a rare but severe side effect of G-CSF administration. Imaging studies may help to identify large vessel vasculitis in cases that cannot be confirmed by tissue biopsy.

Keywords: G-CSF; Side effect; Giant cell arteritis; Aortitis; PBSC mobilization

Introduction

Granulocyte-colony-stimulating factor (G-CSF) treatment is routinely used for peripheral blood stem cell (PBSC) mobilization in patients with hematologic malignancies for collection of an autologous blood stem cell graft, as well as in healthy donors for collection of an allograft [1-3]. G-CSF stimulation of neutrophils also reduces the duration and severity of chemotherapy-induced myelosuppression and allows timely continuation of cytotoxic therapy without dose adjustment [4]. Administration of G-CSF is generally considered safe and effective. Common minor adverse effects include flu-like symptoms, bone and muscle pain, fatigue, nausea and headache that are usually self-limiting. Severe adverse effects like pyogenic infection, acute gouty arthritis, capillary leak syndrome, pyoderma gangrenosum, splenic rupture, acute respiratory distress syndrome or glomerulonephritis are rare [5-11]. Here, we report a case of giant cell arteritis (GCA) related to G-CSF treatment in a 65-year-old woman with diffuse large B-cell lymphoma (DLBCL), who received G-CSF for PBSC mobilization.

Case Report

A 65-year-old caucasian woman was diagnosed with stage IVA DLBCL with involvement of cervical and submandibular lymph nodes as well as the central nervous system in March 2015. Her medical history included von Willebrand disease, arterial hypertension and a history of oropharynx carcinoma. From March until Mai 2015 she received four cycles of rituximab 375 mg/m^2 and methotrexate 8000 mg/m^2 i.v. every ten days according to a well-established German treatment protocol for primary CNS lymphoma (12). Upon response to induction therapy, the patient proceeded with mobilization chemotherapy (rituximab 375 mg/m^2 i.v. at day 0, cytarabine 3000 mg/m^2 i.v. at day 1 and 2, thiotepa 40 mg/m^2 i.v. at day 2, and G-CSF 5 µg/kg s.c. starting at day 5) for PBSC collection and 14.71 × 10^6 CD34+ cells/kg were collected by leukapheresis after 10 days of G-CSF stimulation. At the day of PBSC collection the patient developed fever up to 39°C. There were no remarkable findings or evidence of infection on physical examination. Laboratory results revealed leukocytosis (54 × 109/L), increased C-reactive protein (CRP, 256 mg/L) and alkaline phosphatase (AP, 222 U/l). An empirical intravenous antibiotic therapy with tazobactam/piperacillin was initiated and escalated to linezolid and meropenem in view of positive urine cultures for vancomycin-resistant Enterococcus faecium. Routine blood cultures were negative. Since this combination of intravenous antibiotics did not control the fever, antibiotic therapy was discontinued. A subsequent computed tomography (CT) scan did not show a focus of infection but revealed contrast-enhanced wall thickening of the aortic arch, supra-aortic branches and abdominal aorta compatible with vasculitis (Figure 1A-1C). In a CT scan performed four months earlier there was no evidence of inflammatory vessel wall thickening (Figure 1D). The patient was diagnosed with aortic involvement in GCA. She received a seven-day course of treatment consisting of 60 mg orally administered prednisone per day. Patient's body temperature and CRP levels decreased quickly to normal ranges. Over the course of five weeks prednisone was reduced to a daily maintenance dose of 10 mg and an osteoporosis prophylaxis was initiated. The lymphoma-specific chemotherapy was continued with a second course of rituximab, cytarabine and thiotepa on schedule and high-dose carmustine/thiotepa followed by autologous stem cell transplantation. A cranial CT scan six month after autologous stem cell transplantation did not reveal any evidence of lymphoma relapse.

Discussion

We report a severe side-effect of G-CSF, GCA, which to the best of our knowledge has not been published so far. GCA is an inflammatory vasculopathy that mostly affects the elderly, with peak incidences at the age of 70 to 80 years. It is more frequently found in women than in men with a ratio of 2:1 [12,13]. Typically medium and large arteries with well-developed wall layers and adventitial vasa vasorum, such

***Corresponding author:** Katharina Lisenko, Department of Hematology, Oncology and Rheumatology, University Heidelberg, Heidelberg, Germany, Tel: +4962215637238; E-mail: katharina.lisenko@med.uni-heidelberg.de

Received March 14, 2016; **Accepted** May 07, 2016; **Published** May 13, 2016

Citation: Lisenko L, Blank N, Wuchter P, Weber T, Cremer M, et al. (2016) Giant Cell Arteritis Related to Granulocyte-Colony-Stimulating Factor Administration. J Clin Case Rep 6: 788. doi:10.4172/2165-7920.1000788

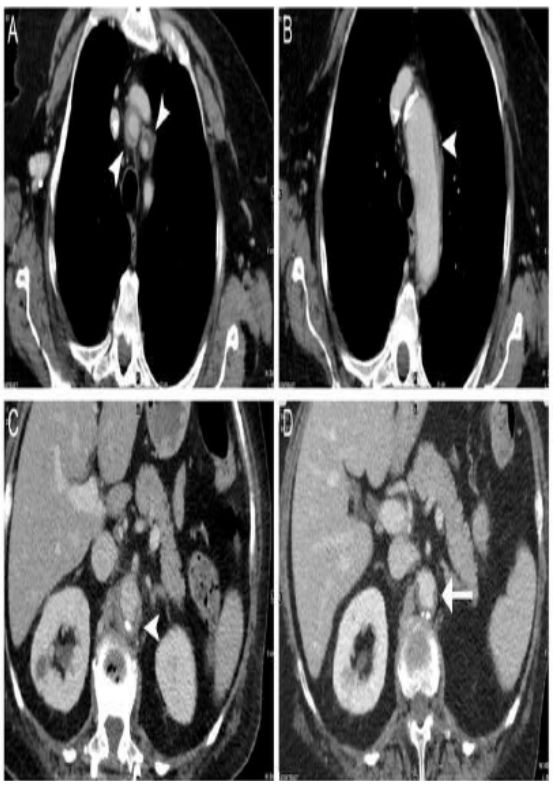

Figure 1: Contrast-enhanced computed tomography during portal venous phase. A marked thickening of vessel walls with contrast enhancement predominantly affecting media and adventitia is compatible with large vessel vasculitis. Affected vessels include the brachiocephalic trunk and the left carotid artery (arrowheads in A), the aortic arch (arrowhead in B) and the visceral segment of the abdominal aorta (arrowhead in C). In a prior scan performed 4 months earlier there was evidence of atherosclerosis, but inflammatory vessel wall thickening was not present (arrow in D).

as external carotid branches, the ophthalmic, vertebral, and axillary arteries are involved [14]. Aortitis has been estimated to occur in up to 18% of patients, but its incidence in GCA might be higher because aortitis can be clinically silent in up to 77% of cases and complications as aortic aneurysm or dissection occur late in the history of the disease [15,16].

In the present case a 65-year-old woman was diagnosed with GCA and aortitis based on contrast-enhanced wall thickening on contrast-enhanced CT. We did not obtain a histological confirmation of this diagnosis, since there was no evidence for involvement of any small blood vessels that would have been accessible for a biopsy. As contrast-enhanced CT can evaluate both the blood vessel wall for thickening as well as the lumen it may be helpful in the early diagnosis in patients with suspected GCA that has not been confirmed on biopsy, particularly if significant vascular stenoses are absent [16-18]. Similarly, in a case of a 79 year-old woman with fever of unknown origin and negative temporal artery biopsies in whom diagnosis of GCA was delayed, a CT angiogram was helpful to identify aortic vasculitis [19]. Furthermore, elevated CRP, which has a sensitivity of 86% for GCA, and elevated AP, which is common in up to 25% of GCA patients, were found on laboratory examination [20,21]. Leukocytosis should be considered as an effect of G-CSF administration upon PBSC collection. Whereas leukocytoclastic vasculitis can be a well-known adverse effect of G-CSF, as documented in several reports of cutaneous and also very few cases of renal vasculitis [22], to the best of our knowledge no cases of GCA after G-CSF use have been reported so far. Leukocytoclastic vasculitis refers to several subtypes of a small-vessel vasculitis that are histologically characterized by a neutrophil inflammation with fibrinoid necrosis and fragmented neutrophil nuclei [23]. In patients who developed cutaneous leukocytoclastic after G-CSF administration, vasculitis usually followed the increase of absolute neutrophil count and subsided after the decrease of neutrophils, suggesting that neutrophils, in line with histological findings, may play a pathogenic role [22]. In large-vessel vasculitis, as GCA, dendritic cells residing in the vessel wall are considered to initiate the inflammatory cascade and to recruit T-cells and macrophages to form granulomatous infiltrates [17,24].

Little is known about the role of neutrophils in GCA. Nadkarni et al. investigated the neutrophil reactivity in GCA patients and found an escaped proinflammatory neutrophil phenotype upon glucocorticoid dosage reduction during the course of the therapy [25]. These results indicate potential involvement of neutrophils in GCA and might provide a pathogenic link between GCA and neutrophil stimulation by G-CSF in this case. Despite these findings the pathogenic link between G-CSF and pathogenesis of vasculitis remains unclear. In summary, this case illustrates several important clinical points. Primarily, it shows that GCA might be a severe side effect of G-CSF administration. Moreover, imaging studies such as contrast-enhanced CT may help to identify large vessel vasculitis in cases that cannot be confirmed by tissue biopsy.

References

1. Ozkan MC, Sahin F, Saydam G (2015) Peripheral blood stem cell mobilization from healthy donors. Transfusion and apheresis science: official journal of the World Apheresis Association: official journal of the European Society for Haemapheresis..
2. Kindwall-Keller T (2014) Peripheral stem cell collection: from leukocyte growth factor to removal of catheter. J Clin Apher 29: 199-205.
3. Reddy RL (2005) Mobilization and collection of peripheral blood progenitor cells for transplantation. Transfusion and apheresis science: official journal of the European Society for Haemapheresis 32: 63-72.
4. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, et al. (2006) EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 42: 2433-2453.
5. Hilbe W, Nussbaumer W, Bonatti H, Thaler J, Niederwieser D, et al. (2000) Unusual adverse events following peripheral blood stem cell (PBSC) mobilisation using granulocyte colony stimulating factor (G-CSF) in healthy donors. Bone marrow transplantation 26: 811-813.
6. Anderlini P, Donato M, Chan KW, Huh YO, Gee AP, et al. (1999) Allogeneic blood progenitor cell collection in normal donors after mobilization with filgrastim: the M.D. Anderson Cancer Center experience. Transfusion 39: 555-560.
7. Spitzer T, McAfee S, Poliquin C, Colby C (1998) Acute gouty arthritis following recombinant human granulocyte colony-stimulating factor therapy in an allogeneic blood stem cell donor. Bone marrow transplantation 21: 966-967.
8. Spiekermann K, Roesler J, Emmendoerffer A, Elsner J, Welte K (1997) Functional features of neutrophils induced by G-CSF and GM-CSF treatment: differential effects and clinical implications. Leukemia 11: 466-478.
9. Oeda E, Shinohara K, Kamei S, Nomiyama J, Inoue H (1994) Capillary leak syndrome likely the result of granulocyte colony-stimulating factor after high-dose chemotherapy. Internal medicine 33: 115-119.
10. Johnson ML, Grimwood RE (1994) Leukocyte colony-stimulating factors. A review of associated neutrophilic dermatoses and vasculitides. Arch Dermatol 130: 77-81.
11. Ross HJ, Moy LA, Kaplan R, Figlin RA (1991) Bullous pyoderma gangrenosum after granulocyte colony-stimulating factor treatment. Cancer 68: 441-443.
12. Finke J (2009) Primary Non Hodgkin Lymphoma of the Central Nervous
13. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, et al. (2009) Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 61: 1454-1461.
14. Weyand CM, Liao YJ, Goronzy JJ (2012) The immunopathology of giant

cell arteritis: diagnostic and therapeutic implications. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 32: 259-265.

15. Martínez-Valle F, Solans-Laqué R, Bosch-Gil J, Vilardell-Tarrés M (2010) Aortic involvement in giant cell arteritis. Autoimmun Rev 9: 521-524.
16. Marie I, Proux A, Duhaut P, Primard E, Lahaxe L, et al. (2009) Long-term follow-up of aortic involvement in giant cell arteritis: a series of 48 patients. Medicine (Baltimore) 88: 182-192.
17. Weyand CM, Goronzy JJ (2014) Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med 371: 1653.
18. Pipitone N, Versari A, Salvarani C (2008) Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update. Rheumatology (Oxford) 47: 403-408.
19. Schafer VS, Warrington KJ, Williamson EE, Kermani TA (2009) Delayed diagnosis of biopsy-negative giant cell arteritis presenting as fever of unknown origin. J Gen Intern Med 24: 532-536.
20. Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, et al. (2012) Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. Seminars in arthritis and rheumatism. 41: 866-871.
21. Gonzalez-Gay MA, Lopez-Diaz MJ, Barros S, Garcia-Porrua C, Sanchez-Andrade A, et al. (2005) Giant cell arteritis: laboratory tests at the time of diagnosis in a series of 240 patients. Medicine (Baltimore) 84: 277-290.
22. Jain KK (1994) Cutaneous vasculitis associated with granulocyte colony-stimulating factor. J Am Acad Dermatol 31: 213-215.
23. Lotti T, Ghersetich I, Comacchi C, Jorizzo JL (1998) Cutaneous small-vessel vasculitis. J Am Acad Dermatol 39: 667-687.
24. Weyand CM, Goronzy JJ (2013) Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol 9: 731-740.
25. Nadkarni S, Dalli J, Hollywood J, Mason JC, Dasgupta B, et al. (2014) Investigational analysis reveals a potential role for neutrophils in giant-cell arteritis disease progression. Circulation research 114: 242-248.