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 May 2015 she received four cycles of rituximab 375 mg/m² and methotrexate 8000 mg/m² 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/m² i.v. at day 0, cytarabine 3000 mg/m² i.v. at day 1 and 2, thiotepa 40 mg/m² i.v. at day 2, and G-CSF 5 µg/kg s.c. starting at day 5) for PBSC collection and 14.71 × 10⁹ 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 aortitis prophylaxis was initiated. The lymphoma-specific chemotherapy was continued with a second course of rituximab, cytarabine and thiotepa on schedule for 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 vasoorum, such as...
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


