Case Report

Leukocytoclastic Vasculitis in Patients with Severe Congenital Neutropenia

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Summary

Leukocytoclastic vasculitis is a rare complication of the use of granulocyte colony-stimulating factor (G-CSF). We present two cases of severe congenital neutropenia (SCN) associated with GCSF use. It is reported that skin rashes and biopsy findings of leukocytoclastic vasculitis following the use of G-CSF.

Key words: leukocytoclastic vasculitis, severe congenital neutropenia, G-CSF, neutrophilic dermatoses.

Severe congenital neutropenia (SCN) includes a variety of hematological disorders characterized by severe neutropenia, with absolute neutrophil counts (ANC) $<0.5 \times 10(9)\,l^{-1}$, and associated with severe systemic bacterial infections from early infancy. The bone marrow usually shows a reduced number of mature myeloid cells with an arrest in myelopoiesis at the promyelocyte or myelocyte stage [1]. Genetic analyses in patients with SCN indicated that 35–69% of the cases were attributable to heterozygous mutations in the gene-encoding neutrophil elastase (ELA2) [2]. Recently, homozygous germline mutations in the *HAX-1* gene were identified in a subset of patients with SCN. Ongoing linkage studies suggest that more and, as yet unidentified, genes may be involved in the pathophysiology of severe congenital neutropenia. Approximately 90–95% of SCN patients respond to granulocyte colony-stimulating factor (G-CSF) therapy with increasing ANC, reduced infection rates and improved quality of life [3]. Adverse events of G-CSF treatment included bone pain, splenomegaly, hepatomegaly, thrombocytopenia, osteopenia/osteoporosis, vasculitis, glomerulonephritis, leukemic transformation and mortality have been reported [1].

We present two cases of SCN associated with G-CSF use which caused cutaneous vasculitis.

Case 1

We describe a 13-years-old Turkish girl with severe congenital neutropenia, who was admitted to our outpatient clinic with cellulitis and osteomyelitis on her right lower leg. She suffered from oral moniliazis, aphthous stomatitis and recurrent respiratory tract infections since her infancy period. She had a left upper lung lobectomy operation at the age of 4 years because of pulmonary abscess. Her laboratory investigations showed us white blood cell (WBC) count 2.74×103, absolute neutrophil count (ANC) $195/mm^3$, hemoglobin $12.5\,g\,dl^{-1}$ and platelet count of $135\,000\,mm^{-3}$. Bone marrow aspiration was performed and revealed normal megakaryocytes and erythroid precursors. Myeloid development, however, was altered, exhibiting maturation arrest at the promyelocyte stage. Mutation analysis tests for ELA-2, Hax-1 and G-CSF receptor were negative. She was put on regular subcutaneous Lenograstim injections ($5\,mcg\,kg^{-1}\,day^{-1}$). At 1 month of the therapy, the patient was admitted to our department with skin lesions. Physical examination revealed non-itchy skin lesions on both arms, legs (Fig. 1) and over the trunk. Laboratory tests for platelet count, activated partial thromboplastin time (aPPT), antinuclear antibody (ANA), ANCA, anticardiolipin IgG and IgM were normal. Skin punch biopsy from her left cruris revealed leukocytoclastic vasculitis. Having assumed that these symptoms can be the side effect of Lenograstim, we decided to replace it on Filgrastim ($5\,mcg\,kg^{-1}\,day^{-1}$) following 1 week cessation of G-CSF therapy. This medicine was well tolerated and her lesions improved gradually in 2 weeks.

Case 2

A 5-year-old girl initially presented with otitis media and recurrent periodontitis. She was first hospitalized with pneumonia at the age of 3 years at local

doi:10.1093/tropej/fmp140 Advance Access published on 25 January 2010

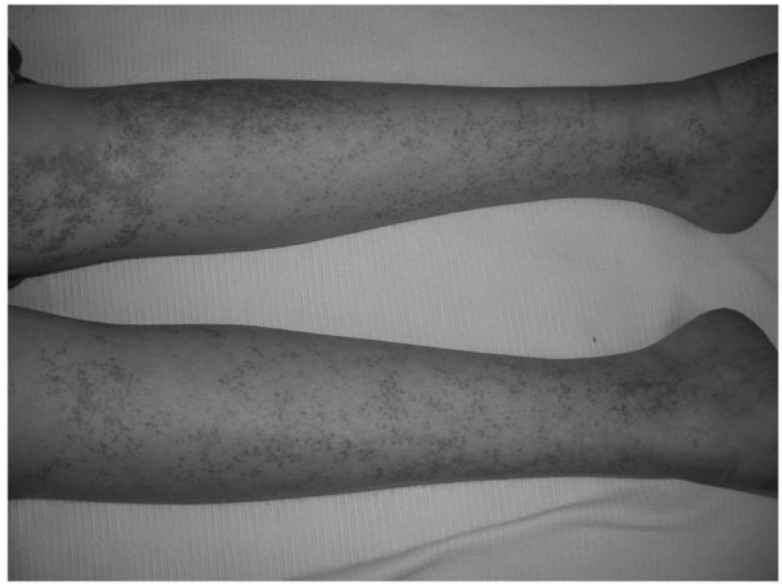

FIG. 1. Cutaneous vasculitis following Lenograstim treatment.

hospital. During the years that followed, she suffered from repeated otitis media, tonsillitis, skin abscesses and, on one occasion, a septic infection. The peripheral WBC count was $5.3 \times 10^9 l^{-1}$ with no neutrophils, hemoglobin $10.1\,g\,dl^{-1}$, hematocrit 30% and a platelet count of $185\,000\,mm^{-3}$. Bone marrow aspiration revealed maturation arrest of myelopoiesis at the promyelocyte stage which was compatible with the diagnosis of Kostmann syndrome. Bone marrow aspirate showed maturation arrest of myelopoiesis at the promyelocyte stage which was compatible with the diagnosis of Kostmann syndrome. A homozygous single-nucleotide insertion leading to a premature stop codon (W44X) was identified in the *HAX-1* gene in our patient (by Klein C., Hannover Medical School, Hannover, Germany). The G-CSF (Lenograstim) dose necessary to normalize the granulocyte numbers was $8\,mcg\,kg^{-1}\,day^{-1}$ subcutaneously.

Four days after commencing Lenograstim, she developed a number of purple rashes on the upper and lower extremities. The rash subsided for about 2–3 days after G-CSF had been discontinued. A biopsy of the skin lesions (Fig. 2) revealed lymphocytic vasculitis with extensive involvement of blood vessels by fibrin thrombi and neutrophils, consistent with leukocytoclastic vasculitis. Since the WBC count remained low, the patient was started on Filgrastim ($5\,mcg\,kg^{-1}\,day^{-1}$).

Discussion

The availability of hematopoietic growth factors has dramatically changed the prognosis of congenital neutropenia. Before recombinant human G-CSF became available, most of the patients succumbed to infections early in life. Today, most patients with congenital neutropenia survive into adulthood when treated with recombinant human G-CSF. Cutaneous vasculitis should be recognized as an adverse reaction to G-CSF with low morbidity. The safety and efficacy of long-term administration of G-CSF to patients with congenital neutropenia has been established. Of 54 patients with congenital and cyclical neutropenia treated by Bonilla *et al*. [4], two experienced self-limiting vasculitis. Long-term data from The Severe Chronic Neutropenia International Registry indicated some form of vasculitis occurred in 4.1% of patients, with a slightly higher rate among patients with idiopathic neutropenia (5.9%) compared with patients with congenital neutropenia (3.1%) [1]. In our immunodeficiency center, we follow-up 10 patients with SCN who were all given Lenograstim. When cutaneous vasculitis was developed in two of them, G-CSF had been discontinued for a week and subsequently Lenograstim was replaced by Filgrastim. None of our patients used other medications except G-CSF, and the timing of the eruption is highly suggestive that G-CSF was the causative agent. According to literature, there is no difference on the risk of development of vasculitis whether Lenograstim or Filgrastim is started.

Three G-CSFs are available for clinical use, including Filgrastim, Lenograstim and pegfilgrastim. From the chemical point of view, Filgrastim and Lenograstim are not identical. Their amino acid sequence is different and Lenograstim is glycosylated,

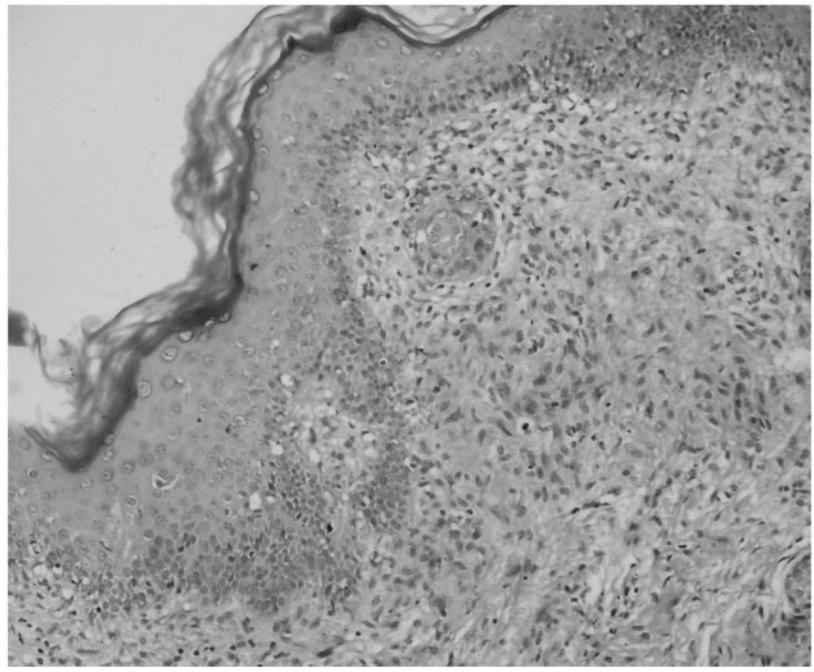

FIG. 2. Leukocytoclastic vasculitis. There is a perivascular and mural infiltrate of neutrophils, a few eosinophils with leukocytoclasis and erythrocyte and fibrin extravasation. (Hematoksilen Eosin x40).

whereas the other is not. Filgrastim (nonglycosylated methionyl G-CSF) is produced in culture by bacteria, whereas Granocyte (glycosylated G-CSF) is produced in culture by mammalian cells. Filgrastim does not have a structure that is exactly identical to the natural molecule. It has an additional amino acid and is not glycosylated (addition of a saccharide residue following the assembly of amino acids), whereas Granocyte is glycosylated making it a true glycoprotein, identical to the endogenous human molecule [5]. Because of this difference, Filgastrim might lead to development of cutaneous vasculitis in two patients.

Up-regulation of neutrophilic function and secondary release of cytokines appear to be involved in the pathogenesis. A variety of other vasculitides and dermatoses associated with leukocyte colony-stimulating factors have been described. These include necrotizing vasculitis, Sweet's syndrome and pyoderma gangrenosum. The mechanisms of neutrophilic dermatoses are largely unknown, although various hypotheses have been considered, mainly the possibility of intrinsic or extrinsic abnormalities of neutrophils, e.g. the presence of circulating activating factors such as immunocomplexes, T-cell activation or altered functions of neutrophils [6].

Release of partially immature neutrophils from bone marrow and indirect activation of these cells by G-CSF were proposed as possible reasons for the alterations in the surface marker expression and chemotaxis. This may also explain some of the side effects such as vasculitis seen with administration of G-CSF. Leukocytoclastic vasculitis can be managed by reduction of dose or discontinuation of G-CSF therapy with or without high-dose prednisone treatment. We observed rapid clinical improvement when G-CSF had been discontinued in our patients without need for any further treatment.

Despite successful supportive treatment using recombinant human G-CSF, definitive and curative treatment of SCN is only possible by means of allogeneic bone marrow transplantation.

Conclusion

Cutaneous vasculitis is a rare adverse reaction of G-CSF treatment with low morbidity. When the association between G-CSF and leukocytoclastic vasculitis is recognized, the drug promptly withdrawn, the rash may resolve completely without need for any further treatment. In severe cases, high-dose prednisone treatment is required.

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