Case report

Pegfilgrastim-induced Sweet’s syndrome: a case report

Mac Machan¹, MD, Brian Matthys², DO, and Garth R. Fraga³, MD

¹Division of Dermatology, University of Kansas Medical Center, Kansas City, KS, ²Sunflower Dermatology and Day Spa, Riverside, MI, and ³Department of Pathology, University of Kansas Medical Center, Kansas City, KS, USA

Correspondence
Mac Machan, MD
Division of Dermatology
University of Kansas Medical Center
3901 Rainbow Blvd
Kansas City, KS 66208
USA
E-mail: mmachan@kumc.edu

Conflicts of interest: None.

doi: 10.1111/j.1365-4632.2012.05744.x

Case report

A 43-year-old Caucasian woman presented with a 7-day history of a painful cutaneous eruption of the trunk and extremities and intermittent fever. Past medical history included hepatitis C, polysubstance abuse, a nonspecific lymphadenopathy, bipolar disorder, and schizoaffective disorder. Her medications were quetiapine and aripiprazole. The patient had recently started pegfilgrastim (Neulasta, Amgen, Inc., Thousand Oaks, CA, USA) for presumed ziprasidone-associated neutropenia. Laboratory testing demonstrated a white blood cell count of 5.5 × 10^9/l (67.7% neutrophils, 26.5% lymphocytes, 1.6% eosinophils, 4.2% monocytes); hemoglobin, 11.8 g/dl; platelets, 177,000/l; alanine aminotransferase, 38 U/l; and aspartate aminotransferase, 20 U/l. Urine toxicology was positive for opiates and cocaine. Physical examination revealed tender, edematous hemorrhagic papules and plaques, some with central crusting and erosion, diffusely involving the face, neck, trunk, and upper and lower extremities (Fig. 1). No lymphadenopathy was detected. A punch biopsy demonstrated diffuse neutrophilic dermatitis with papillary edema and signs of vasculitis, including hemorrhage, leukocytoclasis, collagen necrosis, and peri- and intravascular deposition of fibrin in postcapillary venules (Fig. 2). Grocott methenamine silver and Giemsa preparations did not reveal infectious bacteria or fungi. A diagnosis of pegfilgrastim-induced Sweet’s syndrome (SS) was made. The patient was treated with cessation of pegfilgrastim and intravenous methylprednisolone. She experienced marked improvement within 48 hours.

Discussion

Robert Sweet described a series of patients with an acute febrile neutrophilic dermatosis in 1964.¹ SS is characterized by abrupt onset of fever, peripheral blood neutrophilia, elevated erythrocyte sedimentation rate, and tender red to purple papules and plaques. Women are more frequently affected, with an average age of onset between 30 and 50 years. There is a predilection for the upper extremities, head, and upper trunk, though any part of the skin, mucous membranes, or visceral organs may be involved.² Biopsies reveal a neutrophilic dermatosis with prominent papillary edema.

There are three subtypes of SS: classical, paraneoplastic, and drug-induced.³ Classical SS can be preceded by an upper respiratory tract or gastrointestinal infection, and it is associated with inflammatory bowel disease or pregnancy. Paraneoplastic SS is most often associated with acute myelogenous leukemia and has been described in a variety of solid neoplasms and other hematopoietic neoplasms. Drug-induced SS (DISS) was first reported in 1986 in association with trimethoprim–sulfamethoxazole.⁴ It has been described in association with antibiotics, antiepileptics, antiretrovirals, antineoplastics, antipsychotics,
antithyroid hormone medication, contraceptives, diuretics, nonsteroidal anti-inflammatory drugs, and retinoids, but the majority of cases are due to the granulocyte-colony stimulating factor filgrastim. Pegfilgrastim is a pegylated version of filgrastim. Polyethylene glycol is covalently bonded to filgrastim producing a larger molecule that is resistant to renal clearance. It has a half-life of up to 80 hours and allows once-daily dosing (versus multiple daily doses with filgrastim). Arthralgias and myalgias are the most common side effects. To the best of our knowledge, there is only a single previous case report of pegfilgrastim-induced SS. In 1996, Walker and Cohen proposed the following diagnostic criteria for DISS: (i) abrupt onset of painful erythematous plaques or nodules; (ii) a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis; (iii) pyrexia >38 °C; (iv) temporal relationship between drug ingestion and clinical presentation; and (v) resolution of lesions after drug withdrawal or after treatment with systemic corticosteroids. Neutrophilia is less common in DISS, as was the case in our patient. Our case meets Walker and Cohen’s criteria for DISS except that it demonstrated histopathologic signs of vasculitis. Biopsy evidence of vasculitis is an historical exclusionary criterion for SS. However, recent studies suggest SS may show vasculitis on biopsy. Two independent series of 29 and 31 cases identified vasculitis in the majority of SS cases and postulated that SS may represent a form of vasculitis. Our case demonstrates that vasculitis may be seen in DISS, and we suggest that Walker and Cohen’s criteria be modified to allow for signs of vasculitis in biopsies of neutrophilic dermatitis.

The pathogenesis of SS is unclear and likely multifactorial. The association with infection, inflammatory bowel disease, malignancy, autoimmune disease, and medications suggests a hypersensitivity reaction to bacterial, viral, medication, or neoplastic antigens. Recently, several authors have hypothesized that SS is a result of local or systemic dysregulation of cytokine secretion, with interleukin-1, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interferon-γ as candidate cytokines. Alternatively, SS may result from externally administered granulocyte colony-stimulating factor or neoplastic-derived cytokines.
The differential diagnosis of SS includes reactive erythemas (pyoderma gangrenosum, erythema nodosum, and erythema multifforme) and infections (cellulitis, erysipelas, and herpes simplex virus infection). Neoplastic conditions (leukemia/lymphoma cutis and cutaneous metastases), vasculitides, and systemic diseases (bowel bypass syndrome and inflammatory bowel disease) must also be considered. Tissue biopsy is essential to diagnosis and demonstrates a neutrophilic dermatosis. The pathologic changes of SS may mimic an abscess or cellulitis, and tissue culture for bacteria, fungi, and mycobacteria should be considered. Prominent papillary edema, diffuse distribution of mature neutrophils, and leukocytoclasis favor SS over other neutrophilic dermatoses.

Classical SS is a benign condition in which the skin lesions eventually involute without scarring; however, without therapeutic intervention, the lesions may last for months. Systemic corticosteroids are the primary and most effective treatment for SS. In localized SS, topical or intralesional corticosteroids can be efficacious. Dapsone, potassium iodide, and colchicine are alternate first-line treatments. Cyclosporine has been used in patients who fail first-line therapies. In DISS, improvement and clearing of the dermatosis often occurs following discontinuation of the offending medication.

**Conclusion**

SS manifests with tender, nonpruritic, red to purple papules and plaques accompanied by fever and frequently neutrophilia. Biopsy demonstrates marked papillary edema and a diffuse neutrophilic infiltrate with leukocytoclasis. The pathogenesis of SS is not well understood, but is likely multifactorial with cytokine dysregulation, directly or indirectly, playing a large role. DISS was initially described in 1986 in association with trimethoprim-sulfamethoxazole but most commonly occurs in patients receiving granulocyte colony-stimulating factors. We report the second case of DISS secondary to pegfilgrastim. Though signs of vasculitis have been historically considered an exclusionary criterion to the diagnosis, recent studies have demonstrated vasculitis in the majority of cases of SS. We propose that the criteria for DISS be modified to allow for signs of vasculitis when biopsies demonstrate a neutrophilic dermatosis.

**References**