

Atypical Bullous Sweet Syndrome

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ABSTRACT

Sweet syndrome (acute febrile neutrophilic dermatosis) is characterized by fever, leukocytosis, and tender erythematous skin lesions with neutrophilic infiltrate. Although associated with granulocyte colony-stimulating factor (G-CSF) use, its occurrence with pegfilgrastim—the pegylated form—is rare, with fewer than five reported cases. Sweet syndrome has also been rarely linked to FLT3 inhibitors such as quizartinib. We report a 71-year-old male with acute myeloid leukemia who developed bullous Sweet syndrome following concurrent exposure to pegfilgrastim and quizartinib.

KEYWORDS: Atypical Sweet Syndrome; Pegfilgrastim; Quizartinib

INTRODUCTION

Sweet syndrome (SS) is a rare disorder characterized by tender erythematous nodules or plaques, fever, arthralgia, and systemic symptoms, diagnosed by clinical presentation and histological evidence of neutrophilic infiltrate on skin biopsy.¹ It is most commonly idiopathic, but is also associated with myeloproliferative disorders, autoimmune diseases, infections, and medications, including G-CSF, antihypertensives, antibiotics, antipsychotics, and NSAIDs.¹ Pegfilgrastim-associated SS has been reported in fewer than five cases,² and FLT3 inhibitors such as quizartinib have been implicated in rare cases as well.³ We report a 71-year-old male with acute myeloid leukemia (AML) who developed atypical bullous SS after receiving both pegfilgrastim and quizartinib.

CASE PRESENTATION

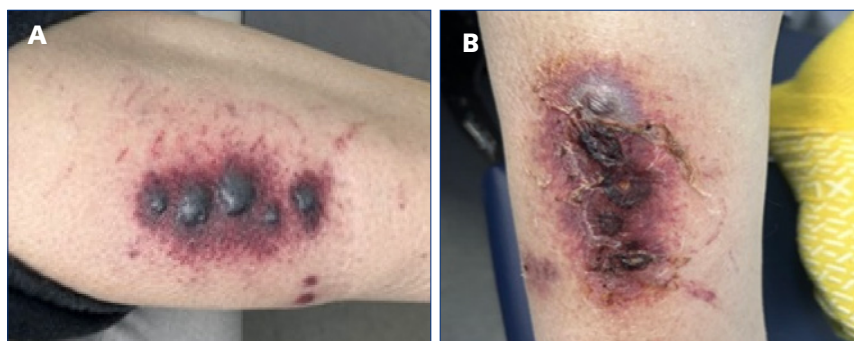
A 71-year-old male with a history of stage III sigmoid adenocarcinoma (treated with colectomy and 12 cycles of adjuvant chemotherapy) was diagnosed 13 months later with AML. Next-generation sequencing was positive for FLT3-ITD, IDH2, NPM1, and SRSF2. He received 7+3 induction with cytarabine and daunorubicin, followed by high-dose cytarabine consolidation with

intrathecal methotrexate and quizartinib 35.4 mg daily. On day 4 of consolidation, he received pegfilgrastim 6 mg subcutaneously without immediate adverse effects. Notably, he had previously tolerated 10 doses of pegfilgrastim during adjuvant chemotherapy for his colon cancer without incident. Six days after pegfilgrastim and four days after starting quizartinib, he presented following a fall and was found to have a blistering rash of several days' duration. He was otherwise asymptomatic. Vital signs showed a low-grade fever of 99.7°, blood pressure 137/98 mmHg, heart rate 110 bpm, and respiratory rate 16/min with normal oxygen saturation. Examination revealed purple-red erythematous necrotic lesions on the left ear, right shin, right dorsum of the hand, chest, and abdomen [Figure 1A]. Labs were notable for WBC $0.1 \times 10^3/\mu\text{L}$, Hgb 9.3 g/dL, and platelets $6 \times 10^3/\mu\text{L}$; the comprehensive metabolic panel was unremarkable. Skin biopsy from the right hand demonstrated papillary dermal edema with superficial lymphohistiocytic inflammation and scattered neutrophils, consistent with resolving SS. A prednisone taper was initiated at 50 mg daily, reduced by 10 mg every three days, with subsequent clinical improvement [Figure 1B].

DISCUSSION

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is a rare inflammatory disorder characterized by fever, neutrophilic leukocytosis, and painful erythematous plaques or nodules typically on the face, neck, and upper

Figure 1. [A] Initial examination revealed purple-red erythematous necrotic lesions on the left ear, right shin, right dorsum of the hand, chest, and abdomen. **[B]** Examination following the initiation of prednisone taper significantly improved the rash.



extremities.^{1,4} It is most commonly idiopathic, but may be secondary to infections, malignancies, autoimmune diseases, and drugs, including G-CSF, FLT3 inhibitors, antihypertensives, antibiotics, antipsychotics, and NSAIDs.^{1,5} Drug-induced SS typically presents abruptly within days to weeks of exposure. Sweet syndrome predominates in women (4:1), and most commonly occurs between ages 30 and 60.¹

The pathophysiology of SS remains incompletely understood; proposed mechanisms include hypersensitivity to infectious or tumor antigens leading to neutrophil activation, and cytokine dysregulation.^{1,5} Diagnosis requires histopathologic confirmation. Classic findings include dense neutrophilic infiltrate in the reticular dermis, with papillary dermal edema, leukocytoclastic nuclear debris, swollen endothelial cells, and dilated vessels also frequently present.^{1,5}

Clinically, SS presents with tender skin lesions—appearing red or purple-red as papules, nodules, or plaques—typically on the upper extremities, face, and neck, accompanied by fever (which may be absent), and constitutional symptoms, including myalgia, arthralgia, headache, and malaise.^{1,4,5} Recognized clinical variants include bullous, cellulitis-like, and necrotizing SS.⁶ Bullous SS, which may present with tense or flaccid blisters, is uncommon with unknown incidence⁶—the presentation seen in our patient.

Management of drug-induced SS involves discontinuation of the offending agent and systemic corticosteroids, the mainstay of treatment.¹ A 2-4 week prednisone taper starting at 40-60 mg daily is typically effective; dapsone, doxycycline, colchicine, methotrexate, and cyclosporine are alternatives for refractory or relapsing cases.¹

G-CSF agents are widely used to mitigate chemotherapy-induced neutropenia. Pegfilgrastim, the pegylated form of filgrastim, offers the convenience of a single dose per cycle due to its prolonged half-life. While filgrastim-associated SS is relatively well documented, pegfilgrastim-induced SS has been reported in fewer than five cases.^{2,7} Our patient was also initiated on quizartinib, a FLT3 inhibitor, four days prior to presentation. Fewer than 10 cases of FLT3 inhibitor-induced SS have been reported in the literature.³

The temporal proximity of both agents—pegfilgrastim administered six days before admission and quizartinib initiated four days prior—makes it difficult to attribute causality to either drug alone. A synergistic effect cannot be excluded. The bullous morphology further distinguished this from a typical SS presentation.

CONCLUSION

We report a rare case of bullous SS likely triggered by pegfilgrastim and/or quizartinib in a patient with AML, highlighting the importance of clinical vigilance for this adverse effect in patients receiving these agents. Further research is warranted to investigate whether concurrent use of multiple SS-triggering agents confers a synergistic risk.

References

1. Vashisht P, Goyal A, Hearth Holmes MP. Sweet Syndrome. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; September 12, 2022.
2. Clarey D, DiMaio D, Trowbridge R. Deep Sweet Syndrome Secondary to Pegfilgrastim. *J Drugs Dermatol*. 2022;21(4):422-424. doi:10.36849/JDD.4794
3. Yang L, Zhang R, Ma H. Sweet syndrome induced by FLT3 inhibitors: case report and literature review. *Hematology*. 2024;29(1):2337230. doi:10.1080/16078454.2024.2337230
4. Rochet NM, Chavan RN, Cappel MA, Wada DA, Gibson LE. Sweet syndrome: clinical presentation, associations, and response to treatment in 77 patients. *J Am Acad Dermatol*. 2013; 69(4):557-564. doi:10.1016/j.jaad.2013.06.023
5. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis*. 2007;2:34. Published 2007 Jul 26. doi:10.1186/1750-1172-2-34
6. Joshi TP, Friske SK, Hsiou DA, Duvic M. New Practical Aspects of Sweet Syndrome. *Am J Clin Dermatol*. 2022;23(3):301-318. doi:10.1007/s40257-022-00673-4
7. White JM, Mufti GJ, Salisbury JR, du Vivier AW. Cutaneous manifestations of granulocyte colony-stimulating factor. *Clin Exp Dermatol*. 2006;31(2):206-207. doi:10.1111/j.1365-2230.2005.01996.x

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Disclosures

The authors have no disclosures.

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