

Rash in an Immunocompromised Patient



Figure. Patient's rash on his arm (A) and ear (B).

Javier Munoz, MD

Philip Kuriakose, MD

A 48-YEAR-OLD MAN WITH LOW-RISK ACUTE PROMYELOCYTIC LEUKEMIA (APL) undergoes induction chemotherapy with daily all-*trans* retinoic acid (tretinoin), cytarabine (days 1-7), and daunorubicin (days 1-3). His clinical course is complicated by low-grade fever and a rash on day 15. The rash starts as tender purple papules on the extensor surface of his upper extremities (FIGURE, A) and quickly disseminates to his ears (Figure, B) and shoulders. His vital signs remain stable without hypoxia. Blood culture results are negative, and imaging does not show pulmonary or pericardial effusions. Tretinoin is held on day 21 due to worsening of skin lesions. Subsequently, the rash appears on his lower extremities as well.

What Would You Do Next?

- Consult dermatology department to perform a skin biopsy.
- Consult hematology department to perform a bone marrow biopsy to rule out APL recurrence.
- Discontinue tretinoin indefinitely and ask hematology department to evaluate for allogeneic stem cell transplantation.
- Discontinue tretinoin indefinitely and observe rash for signs of resolution.

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Author Affiliations: Department of Hematology and Oncology, Henry Ford Hospital, Detroit, Michigan.

Corresponding Author: Javier Munoz, MD, Division of Hematology-Oncology, Henry Ford Health System, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (javier.munoz@me.com).

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Diagnosis

Sweet syndrome (acute febrile neutrophilic dermatitis)

What to Do Next

A. Consult dermatology department to perform a skin biopsy.

The key feature in this case is to recognize that the differential diagnosis of a rash in an immunocompromised febrile patient with acute leukemia includes Sweet syndrome. The skin biopsy would be the definitive way to make the diagnosis. Once Sweet syndrome is diagnosed, the appropriate treatment would be to begin oral corticosteroids and restart tretinoin.

Comment

The differential diagnosis of skin lesions in patients with acute leukemia is broad and includes fungal infections, dermal leukemic infiltration, and drug reactions to chemotherapeutic agents, including cytarabine.¹ Sweet syndrome, or acute febrile neutrophilic dermatitis, is characterized by fever, neutrophilia, erythematous skin lesions, and prompt improvement after commencement of systemic corticosteroids.² Tretinoin, chemotherapy, and hypomethylating agents have been associated with Sweet syndrome in the setting of APL and myelodysplastic syndrome.^{3,4} Because Sweet syndrome responds to steroids, it is critical to keep this condition in the differential diagnosis of skin lesions in patients with acute leukemia to facilitate early and aggressive treatment.

Patients can be assessed for relapse depending on their hematologic/morphologic status (ie, a bone marrow biopsy or aspirate showing blasts) or their molecular status (ie, polymerase chain reaction analysis of *PML-RARA*). The presence or absence of skin lesions in a patient with acute leukemia undergoing induction chemotherapy should not be the reason to perform a bone marrow biopsy. Current guidelines recommend assessing mar-

row morphology at blood cell count recovery from start of induction. This prevents premature morphologic or molecular assessment (as in a mandatory day 14 bone marrow evaluation), which may be misleading, because differentiation of the leukemic promyelocytes may require longer than 14 days.

Furthermore, patients usually remain molecularly positive due to persistence of t(15;17) at the end of induction, even when their bone marrow examination shows morphologic remission. Thus assessment of molecular remission should not be made before 4 weeks after induction. If it is uncertain whether complete remission has been achieved, a repeat examination of the bone marrow after an additional 2 to 3 weeks of continuation of tretinoin has been recommended.⁵ Hematopoietic stem cell transplantation (HSCT), either autologous or allogeneic, is an option for patients with APL in first relapse after previous completion of induction and consolidation chemotherapy.⁵ There is no role for HSCT in the upfront management of newly diagnosed low-risk APL.

Several specific supportive care issues arise when treating patients with APL, including disseminated intravascular coagulopathy and the differentiation syndrome, which is characterized by the development of fever, dyspnea, hypotension, pulmonary infiltrates, and fluid retention in the form of pulmonary and pericardial effusions.⁶ It does not usually present with skin lesions. Differentiation syndrome and severe bleeding are the most common causes of death during induction therapy for APL.⁶ Prompt institution of corticosteroids is the cornerstone of the treatment for differentiation syndrome. Consideration for temporarily holding tretinoin should be given only in severe cases of differentiation syndrome, although these agents can safely be restarted when symptoms resolve.⁵ Tretinoin does not need to be indefinitely withheld in patients with

differentiation syndrome because studies have demonstrated that tretinoin can safely be reintroduced in this setting usually without recurrence.

Patient Outcome

In this patient, skin biopsy showed neutrophilic infiltration compatible with Sweet syndrome. Steroids were started with marked clinical improvement. Tretinoin was uneventfully restarted, with a 50% dose reduction, and peripheral fluorescent in situ hybridization after completion of induction chemotherapy showed no evidence of APL. The patient received consolidation therapy with arsenic trioxide, which he tolerated well, with complete disappearance of his skin lesions. The absence of immature leukemic neutrophils on the skin biopsy negates a diagnosis of leukemia cutis, which would also be unlikely because the patient was morphologically and molecularly responding to therapy. Atypical cells sequestered in the skin might develop into mature neutrophils of Sweet syndrome because tretinoin is an inducer of myeloid differentiation.

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