Sweet Syndrome With Pulmonary Involvement Preceding the Development of Myelodysplastic Syndrome

David Y. Chen, MD, PhD; Arthur Z. Eisen, MD

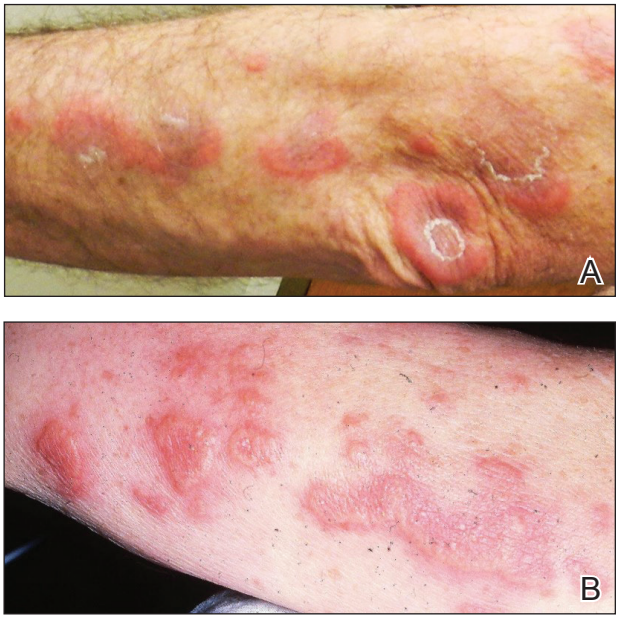
PRACTICE **POINTS**

- Sweet syndrome is characterized by the clinical constellation of fever, a skin eruption of tender erythematous papules or plaques, and response to corticosteroids.
- Skin biopsy characteristically demonstrates marked papillary dermal edema with a dense infiltrate of mature neutrophils without leukocytoclasia.
- Sweet syndrome often is idiopathic, though it has been associated with infection, autoimmunity, medication, and malignancy.

To the Editor:

A 59-year-old man was referred to our clinic for a rash, fever, and night sweats following treatment for metastatic seminoma with cisplatin and etoposide. Physical examination revealed indurated erythematous papules and plaques on the trunk and upper and lower extremities, some with annular or arcuate configuration with trailing scale (Figure, A). A skin biopsy demonstrated mild papillary dermal edema with a mixed infiltrate of mononuclear cells, neutrophils, eosinophils, mast cells, lymphocytes, and karyorrhectic debris without evidence of leukocytoclastic vasculitis. The histopathologic differential diagnosis included a histiocytoid variant of Sweet syndrome (SS), and our patient's rapid clinical response to corticosteroids supported this diagnosis.

With a relapsing and remitting course over 3 years, the rash eventually evolved into more edematous papules and plaques (Figure, B), and a repeat biopsy 3 years later



A, Indurated erythematous papules and plaques on the arm, some with an annular or arcuate configuration with trailing scale. B, The rash evolved into more edematous papules and plaques over the course of 3 years.

From the Division of Dermatology, Washington University School of Medicine, St. Louis, Missouri.
The authors report no conflict of interest.
Coauthor Arthur Z. Eisen, MD, died November 12, 2017.
Correspondence: David Y. Chen, MD, PhD, Division of Dermatology, Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8123, St. Louis, MO 63110 (davidchen@wustl.edu).
doi:10.12788/cutis.0547

was consistent with classic SS. Although the patient's condition improved with prednisone, attempts to taper prednisone invariably resulted in relapse. Multiple steroid-sparing agents were trialed over the course of 3 years including dapsone and mycophenolate mofetil, both of which resulted in hypersensitivity drug eruptions. Colchicine and methotrexate were ineffective. Thalidomide strongly was considered but ultimately was avoided due to substantial existing neuropathy associated with his prior chemotherapy for metastatic seminoma.

Four years after the initial diagnosis of SS, our patient presented with dyspnea and weight loss. Computed tomography revealed a nearly confluent miliary pattern of nodularity in the lungs. A wedge biopsy demonstrated pneumonitis with intra-alveolar fibrin and neutrophils with a notable absence of granulomatous inflammation. Fungal and acid-fast bacilli staining as well as tissue cultures were negative. He had a history of *Mycobacterium kansasii* pulmonary infection treated 18 months prior; however, in this instance, the histopathology, negative microbial cultures, and rapid steroid responsiveness were consistent with pulmonary involvement of SS. Over the ensuing 2 years, the patient developed worsening of his chronic anemia. He was diagnosed with myelodysplastic syndrome (MDS) by bone marrow biopsy, despite having a normal bone marrow biopsy more than 3 years prior to evaluate his anemia. At this time, thalidomide was initiated at 50 mg daily leading to notable improvement in his SS symptoms; however, he developed worsening neuropathy resulting in the discontinuation of this treatment 2 months later. An investigational combination of vosaroxin and azacytidine was used to treat his MDS, resulting in normalization of blood counts and remission from SS.

Sweet syndrome may occur in the setting of undiagnosed cancer or may signal the return of a previously treated malignancy. The first description of SS associated with solid tumors was in a patient with testicular cancer,[1] which prompted continuous surveillance for recurrent seminoma in our patient, though none was found. Hematologic malignancies, as well as MDS, often are associated with SS.[2] In our patient, multiple atypical features linked the development of SS to the ultimate presentation of MDS. The initial finding of a histiocytoid variant has been described in a case series of 9 patients with chronic relapsing SS who eventually developed MDS with latency of up to 7 years. The histopathology in these cases evolved over time to that of classic neutrophilic SS.[3] Pulmonary involvement of SS is another interesting aspect of our case. In one analysis, 18 of 34 (53%) cases with pulmonary involvement featured hematologic pathology, including myelodysplasia and acute leukemia.[4]

In our patient, SS preceded the clinical manifestation of MDS by 6 years. A similar phenomenon has been described in a patient with SS that preceded myelodysplasia by 30 months and was recalcitrant to numerous steroid-sparing therapies except thalidomide, despite the persistence of myelodysplasia. Tapering thalidomide, however, resulted in recurrence of SS lesions in that patient.[5] In another case, resolution of myelodysplasia from azacytidine treatment was associated with remission from SS.[6]

Our case represents a confluence of atypical features that seem to define myelodysplasia-associated SS, including the initial presentation with a clinically atypical histiocytoid variant, chronic relapsing and remitting course, and extracutaneous involvement of the lungs. These findings should prompt surveillance for hematologic malignancy or myelodysplasia. Serial bone marrow biopsies were required to evaluate persistent anemia before the histopathologic findings of MDS became apparent in our patient. Thalidomide was an effective treatment for the cutaneous manifestations in our patient and should be considered as a steroid-sparing agent in the treatment of recalcitrant SS. Despite the discontinuation of thalidomide therapy, effective control of our patient's myelodysplasia with chemotherapy has kept him in remission from SS for more than 7 years of follow-up, suggesting a causal relationship between these disorders.

REFERENCES

1. Shapiro L, Baraf CS, Richheimer LL. Sweet's syndrome (acute febrile neutrophilic dermatosis): report of a case. *Arch Dermatol*. 1971;103:81-84.
2. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis*. 2007;2:34.
3. Vignon-Pennamen MD, Juillard C, Rybojad M, et al. Chronic recurrent lymphocytic Sweet syndrome as a predictive marker of myelodysplasia. *Arch Dermatol*. 2006;142:1170-1176.
4. Fernandez-Bussy S, Labarca G, Cabello F, et al. Sweet's syndrome with pulmonary involvement: case report and literature review. *Respir Med Case Rep*. 2012;6:16-19.
5. Browning CE, Dixon DE, Malone JC, et al. Thalidomide in the treatment of recalcitrant Sweet's syndrome associated with myelodysplasia. *J Am Acad Dermatol*. 2005;53(2 suppl 1):S135-S138.
6. Martinelli S, Rigolin GM, Leo G, et al. Complete remission Sweet's syndrome after azacytidine treatment for concomitant myelodysplastic syndrome. *Int J Hematol*. 2014;99:663-667.