Sweet Syndrome Associated With Hydralazine-Induced Lupus Erythematosus

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Sweet syndrome (SS) is a distinctive but poorly understood clinical syndrome, which likely represents an immunologic reaction pattern to a wide range of underlying or preceding conditions, including viral illnesses, inflammatory bowel disease, and malignancies. We report the case of a patient who presented with an acute eruption that was clinically and histologically consistent with SS. The patient also met diagnostic criteria for systemic lupus erythematosus with serositis, stomatitis, positive antinuclear antibody (ANA), and positive anti–double-stranded DNA antibodies. Additionally, positive antihistone antibodies and exposure to hydralazine supported the specific diagnosis of drug-induced lupus erythematosus, and we concluded that his SS was a manifestation of hydralazine-induced lupus. We also briefly review the precedence for this unusual dual diagnosis in the literature.

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Case Report

A 53-year-old man with cirrhosis caused by hepatitis C was referred to the Emory University, Atlanta, Georgia, dermatology inpatient consultation service with the acute onset of painful purpuric papules and plaques on his trunk (Figure 1A) and upper extremities as well as edematous erythematous periorbital papules. The patient had been admitted to the hospital 2 days prior to presentation with episodic sharp severe chest pain of several weeks' duration, which improved upon leaning forward. Imaging studies revealed pleural and pericardial effusions. Of note, he was afflicted with general malaise, nausea, and vomiting over the preceding few weeks. He had no recent fevers. Laboratory evaluation revealed a white blood cell count of 5500/μL (reference range, 3600–11,100/μL) with 80% segmented neutrophils (reference range, 44%–70%). He had microscopic hematuria as well as an elevated erythrocyte sedimentation rate of 75 mm/h (reference range, 0–20 mm/h) and C-reactive protein at 95 mg/L (reference range, <8 mg/L). C3 and C4 levels were low. Serologic analysis was notable for a positive antinuclear antibody (ANA) with a titer of 1:1280 (ANA had been negative 5 months prior), weakly positive anti–double-stranded DNA at 31 IU/mL (reference range, <29 IU/mL), and positive antihistone antibodies at 1.8 U (reference range, <0.9 U). The patient had been on multiple medications prior to admission, including furosemide and hydralazine (25 mg 3 times daily for several months) to manage portal hypertension and ascites. He had no recent notable changes in his medications or dosages. Although some of his symptoms and laboratory abnormalities might be attributable to chronic viral infection, the patient had undergone treatment of hepatitis C virus 1 year earlier with complete viral clearance.

Over the next 48 hours, the periorbital papules expanded into large crusted purpuric plaques (Figure 1B) and bullae developed in some of his preexisting lesions (Figure 1C). Multiple oral aphthous ulcers were noted. Two biopsies of involved skin showed mild dermal edema and a sheetlike neutrophil-predominant infiltrate in the superficial and mid dermis (Figure 2). The clinical and histologic findings were suggestive of Sweet syndrome (SS) and treatment with corticosteroids was initiated; hydralazine was discontinued. His mucocutaneous eruption demonstrated marked clinical improvement within

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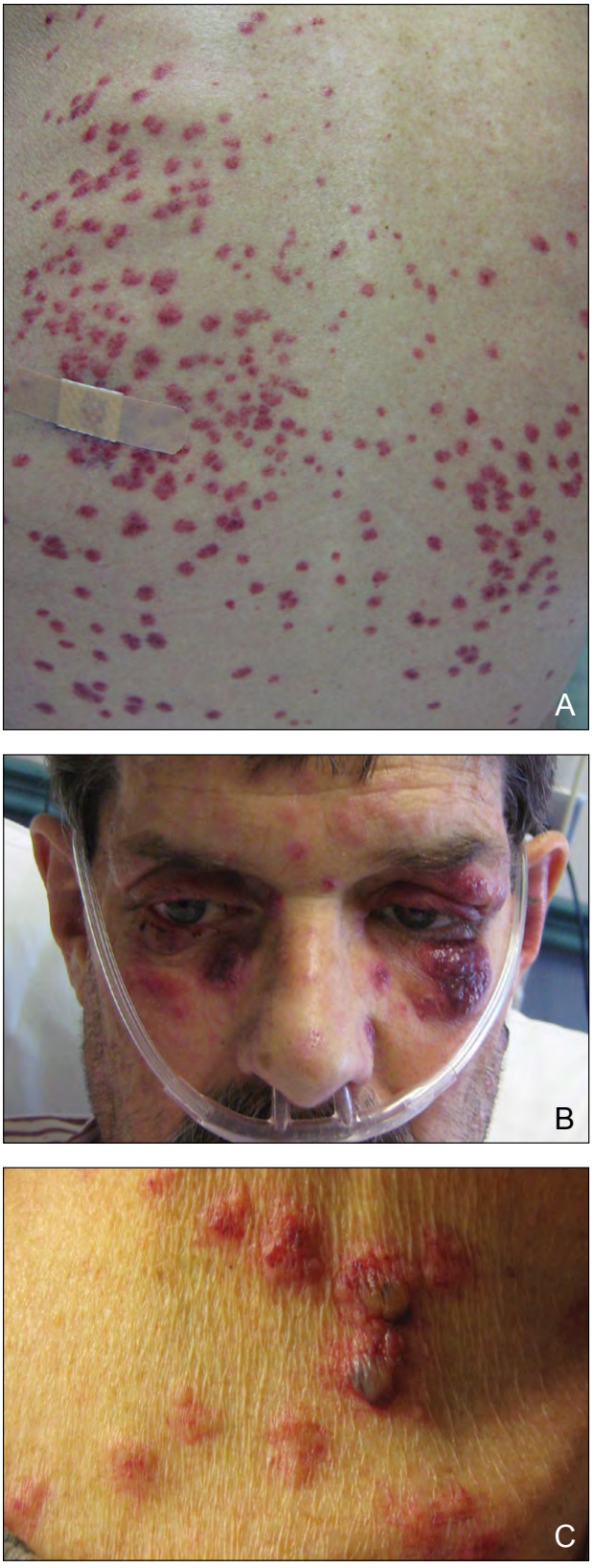

Figure 1. The patient initially presented with erythematous and purpuric papules on his trunk (A) and face that progressed to boggy, purpuric, crusted plaques (B). Bullae developed in some lesions (C).

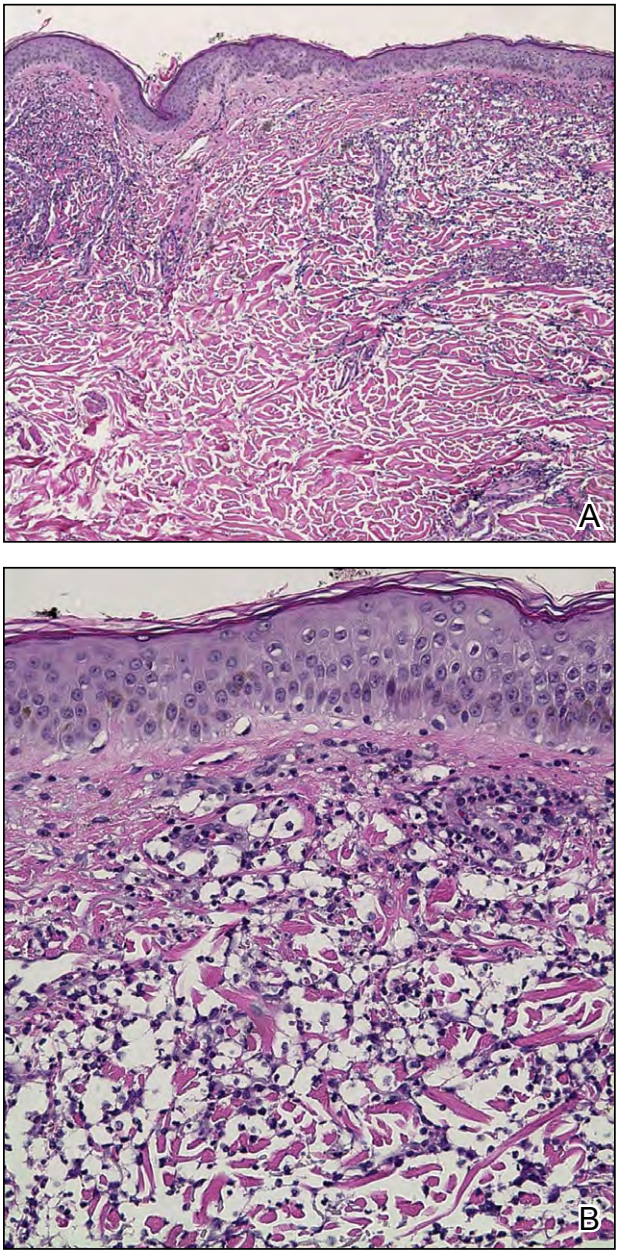

Figure 2. A dense neutrophilic infiltrate was appreciable with splaying of the dermal collagen due to edema (A and B)(H&E; original magnifications ×4 and ×10, respectively). No vacuolar interface dermatitis, vasculitis, or mucin deposition was present.

48 hours and resolved within a few weeks of continuous corticosteroids. Similarly, his pleuritic chest pain and constitutional symptoms remitted.

Comment

Sweet syndrome, named after Dr. Robert Sweet who first reported it in 1964,[1] bears the alternative descriptive moniker acute febrile neutrophilic dermatosis,

which accurately encapsulates the key features of the disease. Patients present with an eruption of discrete, painful, erythematous papules and plaques that rapidly evolve into edematous, pseudovesicular, or occasionally frankly bullous lesions that can occur anywhere but favor the face (especially the periorbital region), upper trunk, and proximal extremities. Sweet syndrome is exquisitely sensitive to systemic steroids, so much so that steroid responsiveness is an accepted diagnostic criterion. Sweet syndrome can be classified into 3 major clinical forms: (1) classical SS, which typically is associated with a preceding upper respiratory or gastrointestinal tract illness, inflammatory bowel disease, or pregnancy; (2) malignancy associated, most commonly a hematologic malignancy, especially acute myeloid leukemia; and (3) drug induced.[2] Sweet syndrome has been described in numerous other unusual clinical contexts, including autoimmune diseases, immunodeficiency disorders, and vaccination induced, to name a few.

Our patient met diagnostic criteria for classical SS with both of the major criteria—acute eruption of painful erythematous papules and neutrophilic dermatosis on histology—and 2 of 4 minor criteria—steroid responsiveness and characteristic laboratory abnormalities (elevated erythrocyte sedimentation rate, C-reactive protein, and neutrophilia).[3] However, he did not have an obvious precipitating cause. Furthermore, his overall clinical presentation was confusing because of positive serologies associated with new-onset serositis, stomatitis, microscopic hematuria, and hypocomplementemia. Additionally, direct immunofluorescence of perilesional photoprotected skin revealed linear IgM and C3 deposition at the basement membrane zone (positive lupus band test)(Figure 3). Although many of his extracutaneous manifestations could be attributable to SS, the patient also met diagnostic criteria for systemic lupus erythematosus. There are no established criteria for the diagnosis of drug-induced lupus erythematosus (DILE), but the presence of antihistone antibodies combined with other lupus symptoms in the setting of long-standing exposure to a medication strongly associated with DILE (hydralazine) is highly suggestive of this entity. Drug-induced lupus erythematosus is the most common pharmacologically induced autoimmune disease and usually presents as mild systemic lupus erythematosus with prominent serositis, as in our patient. Skin manifestations usually are minimal or absent.[4]

We were reluctant to supply this patient with 2 new diagnoses (DILE and SS) and considered that his cutaneous eruption might be a more typical manifestation of lupus. However, no vasculitis, mucin deposition, or interface dermatitis was appreciated on skin histology, and indirect immunofluorescence testing was nonreactive on all substrates, failing to substantiate another potential neutrophilic dermatosis, bullous lupus erythematosus. We concluded that this patient's dermatosis was indeed SS.

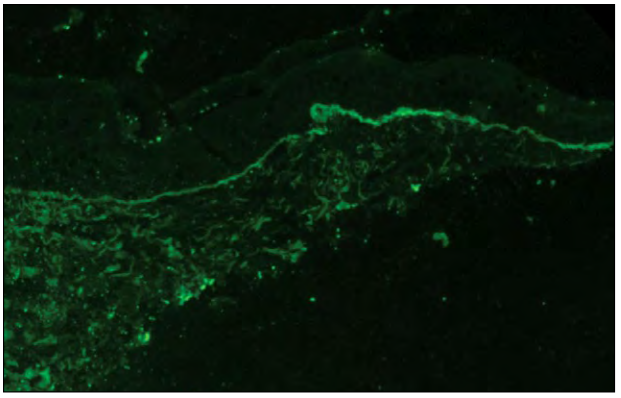

Figure 3. Direct immunofluorescence demonstrated linear IgM deposition at the dermoepidermal junction (anti-human IgM fluorescent antibody staining, original magnification ×10).

A review of the literature revealed a potential unifying interpretation. Three prior cases of SS in the specific setting of hydralazine-induced systemic lupus erythematosus[5-7] and 1 case of SS associated with hydralazine and a positive ANA without overt DILE have been reported.[8] In 2 of these reports, strong evidentiary support for DILE was offered including positive antihistone antibodies.[6,7] Unfortunately, immunofluorescence studies were not conducted in any of the prior patients. However, they did exhibit clinical similarities to our case. One of 3 previously described patients presented with an aphthous stomatitis and microscopic hematuria.[7] A second experienced pleuritic chest pain with presumed serositis, though her chest radiograph was unremarkable and no further imaging to confirm serositis was pursued.[5]

Conclusion

We believe the cogent clinical, histologic, and laboratory evidence presented in this case report justifies concomitant diagnoses of DILE and SS in this patient. Moreover, we propose that DILE represents a unique clinical context in which SS may manifest, with at least 4 patients reported who share this presentation. It is impossible to state with certainty if these cases reflect classical SS triggered by an underlying connective tissue disease or drug-induced SS triggered by hydralazine. However, we favor the former interpretation because all patients had at least a positive ANA titer and 4 of 5 patients had a multisystem

lupuslike syndrome. To our knowledge, no descriptions of hydralazine inducing SS without indications of a comorbid lupuslike syndrome appear in the literature. Overall, our report provides the strongest evidence thus far of an association between these uncommon entities and hopefully will increase awareness that DILE is a potential precipitant of SS.

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