

Dapagliflozin-Induced Sweet Syndrome

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PRACTICE POINTS

- Sweet syndrome consists of 4 cardinal features: fever, leukocytosis, tender red plaques, and a dermal neutrophilic infiltrate.
- In drug-induced Sweet syndrome, there is a temporal relationship between drug ingestion and clinical presentation as well as resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.
- Microscopic findings of Sweet syndrome include a nodular infiltrate of neutrophils, papillary dermal edema, and leukocytoclastic debris.
- Dapagliflozin is a member of a new class of medications (gliflozins) used for treatment of type 2 diabetes mellitus, which may cause drug-induced Sweet syndrome.

To the Editor:

A 75-year-old woman with a history of hypertension, gout, and adult-onset diabetes mellitus was started on dapagliflozin (5 mg) for glycemic control (hemoglobin A_{1c} 7.9 [reference range, 4–7]). Within 1 week of starting the medication, she developed a fine papular eruption in a photodistributed area on the neck and chest with associated malaise. The rash progressed over the next 2 weeks, evolving into edematous papules and plaques, some with vesicles involving the neck, chest, postauricular areas, and nose. Approximately 3 weeks after starting dapagliflozin, the patient also developed bilateral painful, hemorrhagic, bullous plaques (10×3 cm overall) without satellite lesions on the dorsal aspects of the hands. The borders of the bullae had rapidly expanding geographic margins and were extremely painful. The patient's primary care physician advised to discontinue dapagliflozin,

as this medication was thought to be triggering the eruption. She was administered triamcinolone (40 mg intramuscularly) and advised to take ibuprofen as needed. She had malaise and reported that she felt hot but had no known fever. No laboratory tests were ordered.

The lesions on the neck and chest began to fade within 1 week of stopping the medication and administering corticosteroids; however, the hand lesions continued to progress and began to involve the base of the digits (Figure 1). The patient was then seen by a dermatologist who biopsied the hand lesions. Histopathology was characteristic of Sweet syndrome, also known as acute febrile neutrophilic dermatosis and Gomm-Button disease. Notably, there was a dense nodular infiltrate of neutrophils, papillary dermal edema, and leukocytoclastic debris without leukocytoclastic vasculitis (Figure 2).



FIGURE 1. Hemorrhagic bullous plaques on the dorsum of the patient's hands bilaterally.

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The authors report no conflict of interest.

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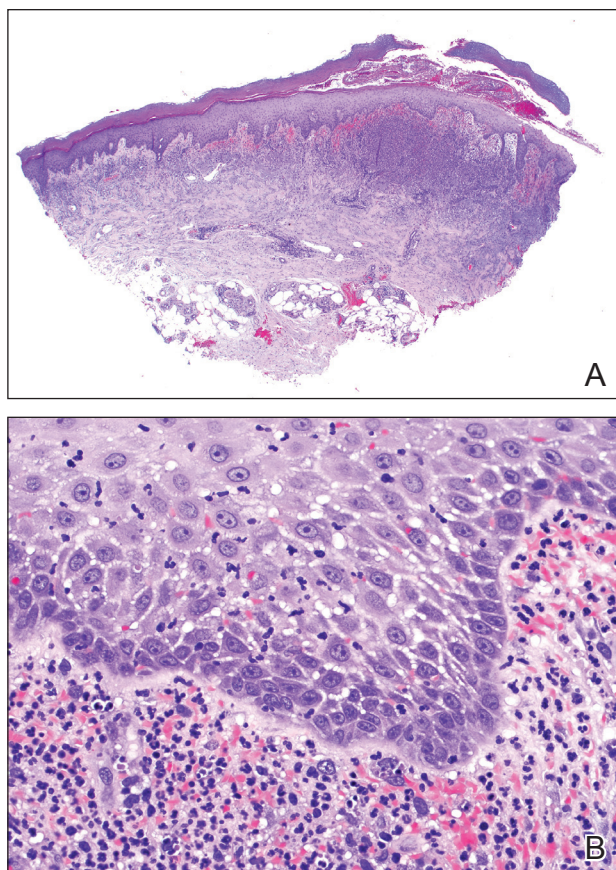


FIGURE 2. A, Histopathology revealed a dense neutrophilic infiltrate (H&E, original magnification $\times 20$). B, High power view of the neutrophilic infiltrate (H&E, original magnification $\times 400$).

The following therapies in addition to gentle wound care were prescribed: betamethasone injectable suspension (9 mg intramuscularly), oral prednisone (60 mg daily for 5 days, tapering off over 2 months), clobetasol ointment 0.05% twice daily, and tacrolimus ointment 0.1% twice daily. The patient responded well to therapy, with complete resolution and healing of the skin lesions except for mild postinflammatory pigment alteration. The systemic steroids were slowly tapered over 2 months, and the patient remained free of symptoms or recurrences more than 3 years after discontinuation of the medication.

Because of the presence of lesions on the dorsal aspects of the hands in our patient, the differential diagnosis included the localized variant of Sweet syndrome known as neutrophilic dermatosis of the dorsal hands, but a diagnosis of classic Sweet syndrome was favored due to the lack of intense papillary dermal edema and vasculitis.^{1,2} Although the hand lesions appeared after the neck and chest lesions, the temporal relationship of their appearance with medication usage and clearing once the medication was stopped favored these lesions as part of the same drug-induced response.

Dapagliflozin is a member of a new class of medications (gliflozins) used for the treatment of type 2

Medications Reported to Cause Drug-Induced Sweet Syndrome^{1,8,11}

Classes of Medications

Antibiotics
Antiepileptics
Antihypertensives
Antineoplastics
Antipsychotics
Antithyroid hormone synthesis drugs
Colony-stimulating factor drugs
Diuretics
HCV medications
HIV medications
NSAIDs
Oral contraceptives
Retinoids

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

diabetes mellitus.^{3,4} The medication lowers blood glucose by inhibiting the sodium-glucose cotransport protein 2, thus lowering the blood glucose levels by increasing urinary excretion of glucose. Because many patients with type 2 diabetes mellitus are overweight, these medications are poised to gain popularity for weight loss and decreased blood pressure side effects. Three other medications in this class also have been approved by US Food and Drug Administration: empagliflozin, canagliflozin, and ertugliflozin.

Sweet syndrome consists of 4 cardinal features that were first described in 1964: fever, leukocytosis, tender red plaques, and a dermal neutrophilic infiltrate.⁵ Since then, Su and Liu⁶ proposed guidelines consisting of major and minor criteria. In 1996, Walker and Cohen⁷ suggested a set of diagnostic criteria specifically for drug-induced Sweet syndrome, including painful erythematous plaques, histopathologic neutrophilic infiltrate, and fever. Additional criteria included a temporal relationship between drug ingestion and clinical presentation as well as resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.⁷ The lesions of drug-induced Sweet syndrome often are described as painful red papules that can form plaques, may appear vesicular, and are more common in women. These lesions classically appear on the upper extremities, as well as the head, neck, trunk, and back.⁸ Clinically, symptoms most commonly

include fever and musculoskeletal involvement, both of which were experienced by the patient who described herself as feeling feverish when the lesions first appeared and reported malaise. Our patient experienced all of these features, and although a fever was not measured in the acute stage of presentation, she reported feeling hot. Other symptoms that may occur include arthralgia, headache, and myalgia.⁹ Microscopically, there is a nodular infiltrate of neutrophils, papillary dermal edema, and leukocytoclastic debris. The pathogenesis of Sweet syndrome remains unclear but can be associated with malignancy, pregnancy, autoimmune disorders, and drug reactions.¹⁰ Many different classes of medications have been reported to cause drug-induced Sweet syndrome and are listed in the Table.^{1,8,11} The recommended treatment of Sweet syndrome is systemic corticosteroids.¹²

The temporal use of dapagliflozin and appearance of the hand lesions, along with the histology, favored drug-induced Sweet syndrome to dapagliflozin as the cause of the plaques. Our patient did not seek medical attention at the onset of the initial chest and neck rash but did so several weeks after the painful hand lesions that were consistent with Sweet syndrome had appeared. Discontinuation of dapagliflozin and treatment with immunosuppressive medications resulted in resolution of the skin lesions on the hands. This scenario raises the question whether or not she would have developed the inflammatory hand lesions if she had stopped the medication earlier. Because dapagliflozin is a relatively new medication and boasts the potentially beneficial side effects of reducing body weight and blood pressure in addition to glucose control,

we expect additional cases may occur, especially if use of this medication notably increases. Furthermore, this reaction may be a drug-class side effect and not one specific to dapagliflozin.

REFERENCES

1. Weedon D. The vasculopathic reaction pattern. *Weedon's Skin Pathology*. 3rd ed. Oxford, UK: Churchill Livingstone; 2010:218-225.
2. Walling HW, Snipes CJ, Gerami P, et al. The relationship between neutrophilic dermatosis of the dorsal hands and Sweet syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch Dermatol*. 2006;142:57-63.
3. Dapagliflozin (Farxiga) for type 2 diabetes. *Med Lett Drugs Ther*. 2014;56:13-15.
4. Aylsworth A, Dean Z, VanNorman C, et al. Dapagliflozin for the treatment of type 2 diabetes mellitus [published online June 20, 2014]. *Ann Pharmacother*. 2014;48:1202-1208.
5. Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol*. 1964;76:349-356.
6. Su WP, Liu HN. Diagnostic criteria for Sweet's syndrome. *Cutis*. 1986;37:167-174.
7. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol*. 1996;34(5 pt 2):918-923.
8. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis*. 2007;2:34.
9. Cohen PR, Kurzrock R. Sweet's syndrome. a neutrophilic dermatosis classically associated with acute onset and fever. *Clin Dermatol*. 2000;18:265-282.
10. Fett DL, Gibson LE, Su WP. Sweet's syndrome: systemic signs and symptoms and associated disorders. *Mayo Clin Proc*. 1995;70:234-240.
11. Thompson DF, Montarella KE. Drug-induced Sweet's syndrome. *Ann Pharmacother*. 2007;41:802-811.
12. Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol*. 2003;42:761-778.