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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Sweet or Not? Azathioprine-Induced Sweet Syndrome Mimicking Erythema Nodosum in a Patient With Inflammatory Bowel Disease

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ABSTRACT

This case report highlights the clinical challenge and need to distinguish Sweet syndrome and erythema nodosum (EN) in a 50-year-old woman with newly initiated azathioprine for inflammatory bowel disease. While she initially presented with clinical features concerning for drug-induced Sweet syndrome, a subsequent histopathological examination confirmed early-stage EN. Both Sweet syndrome and EN share common triggers and therapeutic responses, but have distinctive clinical characteristics. Subtle histologic differences also exist in lesion distribution and depth of infiltration. This case underscores the need for accurate differentiation in patients with inflammatory bowel disease to initiate appropriate management and avoid potential complications.

KEYWORDS: sweet syndrome; acute febrile neutrophilic dermatosis; azathioprine; inflammatory bowel disease; erythema nodosum

INTRODUCTION

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by tender erythematous papules and plaques, which can be pseudovesicular or pustular and may involve the arms, trunk, and neck.[1] The condition is also associated with fever, arthralgias, conjunctivitis, leukocytosis with neutrophilic predominance, and elevated serologic inflammatory markers including erythrocyte sedimentation rate and C-reactive protein (CRP).[2,3] Erythema nodosum (EN) is a form of panniculitis characterized by chronic, tender, erythematous skin nodules, classically of the bilateral shins.[1,3] Sweet syndrome may be differentiated from EN based on histopathologic examination. Sweet syndrome is characterized by marked edema with predominant neutrophilic upper dermis infiltrate without leukocytoclastic vasculitis.[2,3] EN does not present with leukocytoclastic vasculitis, rather it is characterized by septal granulomatous panniculitis with mixed infiltrate of lymphocytes, neutrophils, histiocytes, and giant cells.[2,4]

We present a case of a 50-year-old woman with clinical features consistent with Sweet syndrome shortly following the initiation of azathioprine, but was later diagnosed with EN based on histopathology. It is important to differentiate between Sweet syndrome and EN for appropriate management and to prevent recurrence of symptoms.

CASE REPORT

A 50-year-old woman presented with 3 months of lower abdominal pain and 6–7 loose bowel movements per day containing blood and mucus. Fecal calprotectin (1,959.5 mcg/g Ref <50 mcg/g) was significantly elevated, and endoscopic evaluation showed congestion, erythema, friability, and loss of vascularity in the sigmoid, ascending colon, and cecum on colonoscopy. The initial biopsies demonstrated moderately active chronic colitis in the cecum, ascending, descending, sigmoid colon, and rectum with non-caseating granulomatous inflammation in the descending colon suggestive of Crohn's colitis. After appropriate testing, the initial

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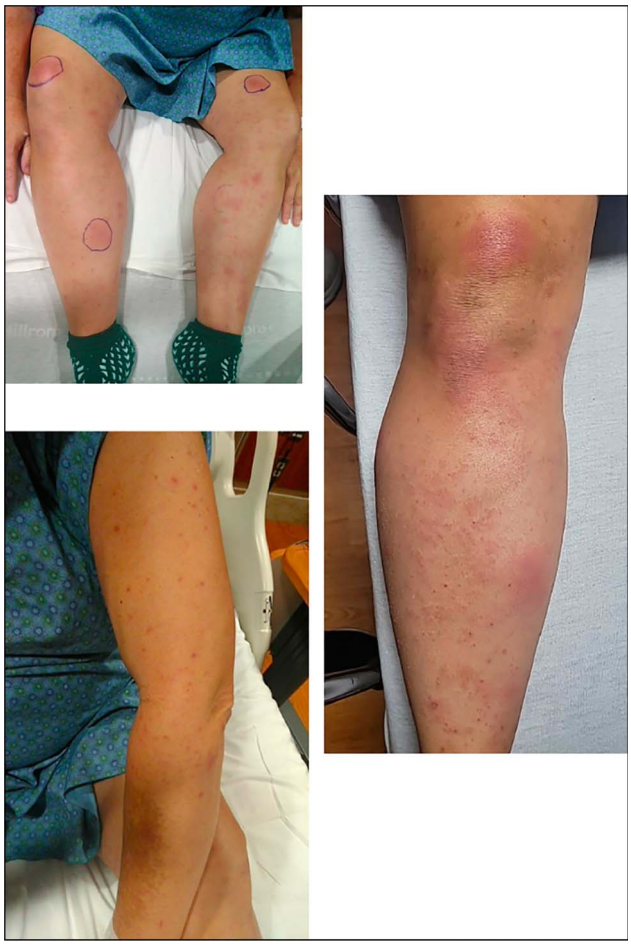

Figure 1. Multiple subcutaneous and deep dermal nodules of 1–4 cm on bilateral lower extremities and arms.

plan was to initiate treatment with infliximab; however, she was started on azathioprine and prednisone as infliximab was not covered by insurance without demonstrated nonresponse to immunomodulator azathioprine and steroids.

After 9 days of treatment with azathioprine and prednisone, she presented with a new painful rash on the knees, eventually spreading to her arms, face, and trunk along with tongue swelling, headache, fever, myalgia, and malaise. Vital signs were significant for fever (Tmax–102.6°F) and a blood pressure of 132/74 mm Hg. She complained of occasional blood-admixed stool but denied any abdominal pain, diarrhea, tenesmus, chills, and urinary symptoms. On examination, the patient had multiple, tender nodules 1–4 cm in size over the shins, abdomen, and dorsum of feet and arms (Figure 1). Laboratory test results were significant for an elevated white blood cell count (27.8 K/mcL: Ref 3.7–11 K/mcL), CRP (16.5 mg/dL: Ref <0.5 mg/dL), erythrocyte sedimentation rate (39 mm/hr: Ref 0–20 mm/hr), and significant improvement in fecal calprotectin (152.3 mcg/g). Based on the initial presentation, a preliminary diagnosis of Sweet syndrome secondary to azathioprine use was made, although EN remained on the list of differential diagnoses. Azathioprine was discontinued, and she was started on intravenous methylprednisolone 125 mg for a total of 3 days. Dermatology was consulted, and subsequent biopsy of the lesion showed unremarkable epidermis, superficial, and mid dermis with septal panniculitis in the deep dermis. No vasculitis or granulomatous inflammation was noted. The histopathology findings were consistent with early-stage EN. Her symptoms improved and the lesions improved after initiation of steroids and discontinuation of azathioprine. The patient's laboratory findings similarly improved to white blood cells (15.3 K/mcL) and CRP (6.8 mg/dL) on day 5. The patient was discharged on prednisone 10 mg for 10 days with a plan to start vedolizumab on an outpatient basis.

DISCUSSION

Sweet syndrome is a rare inflammatory skin condition first described by British dermatologist Dr. Robert D. Sweet in 1964.[5] Classically, Sweet syndrome is commonly associated with inflammatory bowel disease (IBD), malignancy, infections, and certain medications including granulocyte colony-stimulating factor, all-trans retinoic acid, trimethoprim sulfamethoxazole, minocycline hydrochloride, and vaccines.[6,7] Despite the use of azathioprine in various dermatological conditions as well, patients with IBD are more susceptible to develop Sweet syndrome as an adverse reaction to azathioprine irrespective of concomitant steroid use.[7] The diagnostic criteria for drug-induced Sweet syndrome are provided in Table 1.[8,9]

EN is commonly associated with IBD. The condition affects 3%–10% of patients with ulcerative colitis and 4%–15% of patients with Crohn's disease.[10] It is normally seen in patients experiencing increased disease activity in the gut and, therefore, can be managed by treatment and prevention of IBD flares.[10] Sweet syndrome and EN exhibit several analogous clinical and histological characteristics.[11,12] Both conditions share the feature of acute onset and can be linked to similar systemic factors, including upper respiratory infections, certain medications, hematologic malignancies, and autoimmune diseases.[13,14] Both SS and EN are commonly managed with rapid initiation of glucocorticoids.[15] However, in one review, 26.3% of patients with Sweet syndrome were

Table 1. Diagnostic criteria for drug-induced Sweet syndrome

a	The acute initiation of painful erythematous cutaneous plaques or nodules
b	Histological findings associated with dense neutrophilic infiltration within the dermal tissue, with no signs of leukocytoclastic vasculitis
c	Remission of symptoms following discontinuation of the drug or treatment with systemic corticosteroids
d	Pyrexia with a temperature exceeding 100.4°F
e	The temporal correlation between the consumption of a medication and the commencement of symptoms

Table 2. Clinical, diagnostic, and therapeutic differences between erythema nodosum and Sweet syndrome

	Erythema nodosum	Sweet syndrome
Clinical features	• More common in women associated with arthritis and active disease[18,20] • Sudden onset, erythematous, warm, painful, non-ulcerative nodules of 1–5 cm in diameter[19] • Commonly seen in extensor surfaces of lower limbs[19]	• More common in women of 3rd–5th decades of life[22] • Painful erythematous plaques or nodules commonly seen on the face, neck, and upper limbs[22] • Fever and leukocytosis with neutrophilia
Diagnosis	Clinical diagnosis or biopsy: Lymphohistiocytic infiltrate of the lower dermis[21]	Biopsy: Edema of the papillary dermis and dense neutrophilic infiltrate in the dermis[22]
Management	Pain management (NSAIDs, colchicine), systemic corticosteroids, immunosuppressive agents and resistant cases with infliximab[20,21]	Systemic corticosteroids, cyclosporine[22]

already receiving systemic steroid treatment at the time of presentation.[16]

While they share several overlapping clinical features, distinctions do exist between the 2 conditions. Sweet syndrome lesions are predominantly reported in the cephalic, cervical, scapular, and truncal regions, whereas EN lesions are characteristically localized to the pretibial area.[13,17] EN lesions are associated with a deep inflammatory cell infiltration within the subcutaneous adipose tissue, whereas this infiltrate is comparatively shallower within the dermis in Sweet syndrome lesions.[13,17] The differences between EN and Sweet syndrome are summarized in Table 2.[18–22] Aforementioned differentials shall aid in refining the diagnostic approach. In our case, the patient presented with various overlapping features of Sweet syndrome and EN as the onset of symptoms was within the usual time period for the development of Sweet syndrome in patients who are newly started on azathioprine. In addition, the presence of fever and involvement of arms and trunk is not typical for EN and is more often seen in patients with Sweet syndrome.

This case further acts as a reminder for the necessity to promptly identify, diagnose, and effectively address dermatological conditions in patients with IBD. Although the biopsy-proven diagnosis was EN in our case, rechallenge with azathioprine is not recommended in patients diagnosed with azathioprine-induced Sweet syndrome.[23]

DISCLOSURES

Author contributions: All authors contributed to the study's conception and design. Clinical care was provided by R. Mansour and YR Shah. The first draft of the manuscript was written by YR Shah and A. Tiwari. LG Rabinowitz and R. Mansour contributed to the editing and final review of the manuscript. All authors read and approved the final manuscript. YR Shah is the article guarantor.

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