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Case Report

Sweet syndrome with panniculitis, arthralgia, episcleritis, and neurologic involvement precipitated by antibiotics

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Abstract

Background: Sweet syndrome is an uncommon skin condition, often idiopathic in origin although it may be reactive to various systemic conditions, recent infections, underlying malignancies, and medications.

Objective & Method: To present a case highlighting a rare clinical presentation and to review the causes of Sweet syndrome with an emphasis on drug-induced etiologies.

Results: We describe a 45-year-old woman who developed Sweet syndrome while receiving nitrofurantoin and ciprofloxacin for a urinary tract infection. Her course of disease was complicated by arthralgias, episcleritis, headaches, and erythema nodosum-like subcutaneous involvement. There was marked improvement with discontinuation of the inciting antibiotics and initiation of systemic steroids.

Conclusion: This case illustrates Sweet syndrome related to nitrofurantoin and/or ciprofloxacin. This is the second report of Sweet syndrome related to these antibiotics and the first associated with ocular, joint, and neurologic involvement.

Keywords: Sweet syndrome, Sweet's syndrome, drug reaction, panniculitis, arthralgia, episcleritis

Case synopsis

A 45-year-old woman presented to the emergency department with a 4-day history of tender nodules and plaques on her shins and shoulders. Six days prior to the onset of her symptoms, she developed a urinary tract infection, culture-positive for *Eschericia coli* (>100 x 10^6 CFU/L), which was treated by combination antibiotics consisting of ciprofloxacin and nitrofurantoin. Review of systems revealed severe occipital headaches, dry, watery eyes, and arthralgias of both knees. Past medical history was significant for cervical cancer, recently treated with hysterectomy and cisplatin/paclitaxel chemotherapy several months prior. Besides her antibiotics, the patient's only current medication was acetaminophen, which she began taking for her new-onset arthralgias.

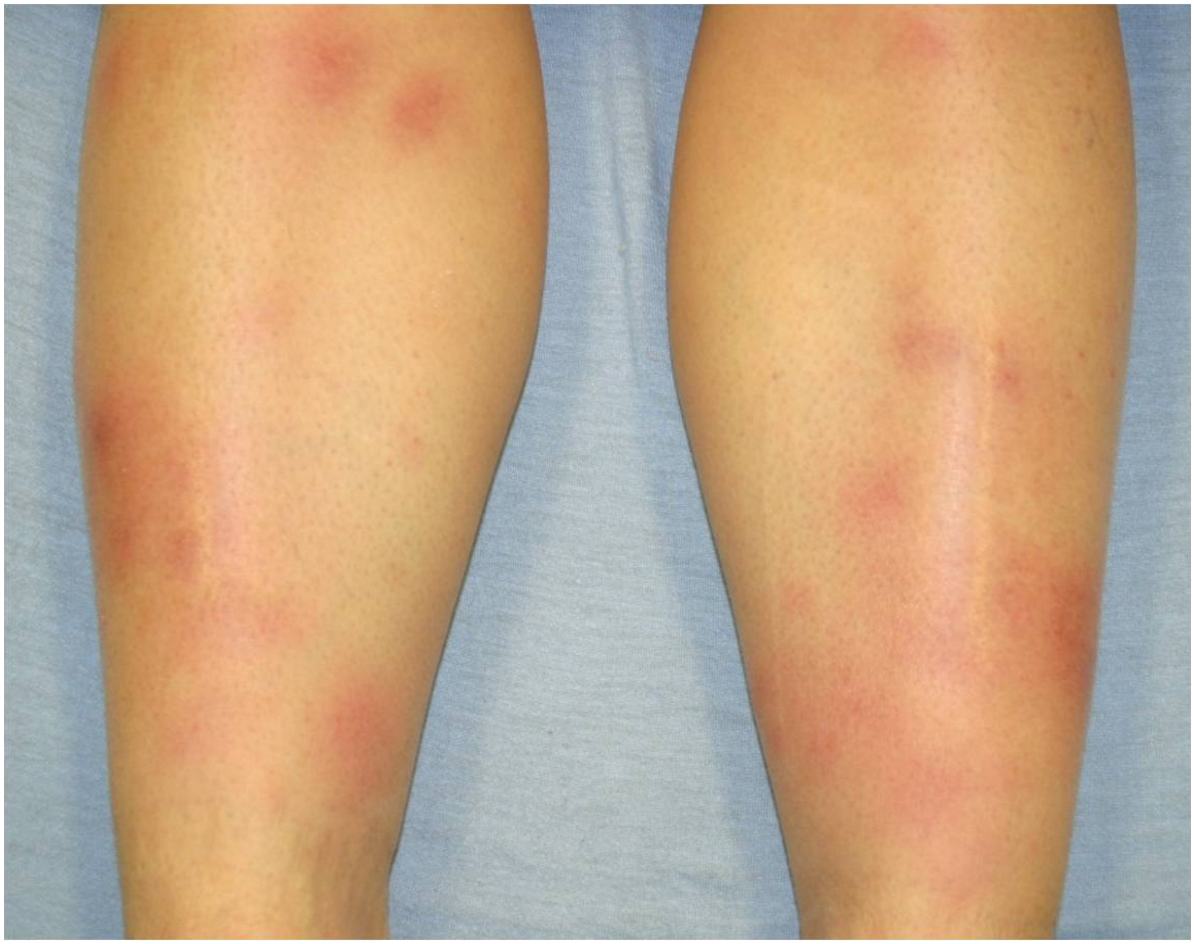

Figure 1. Dozens of tender, erythematous nodules on the bilateral shins

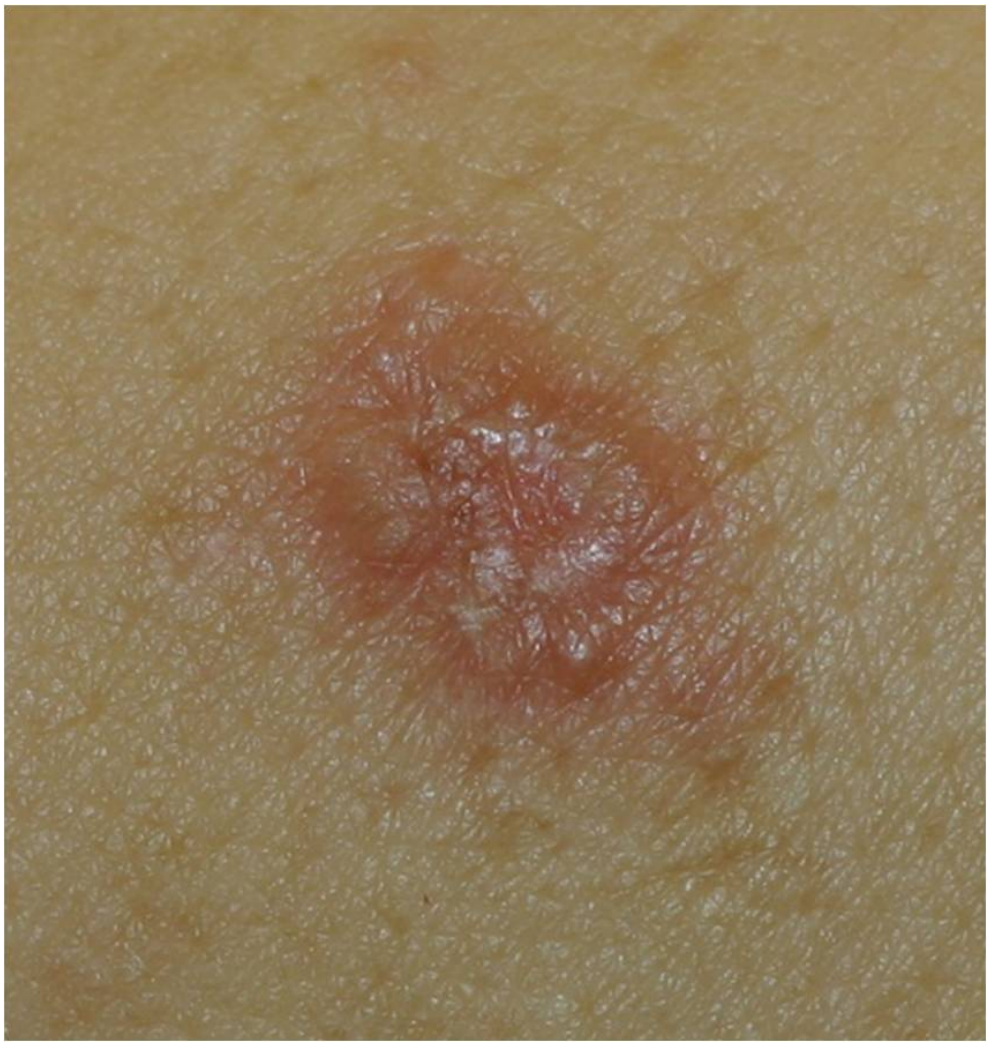

Figure 2. Pseudovesicular plaque on the shoulder

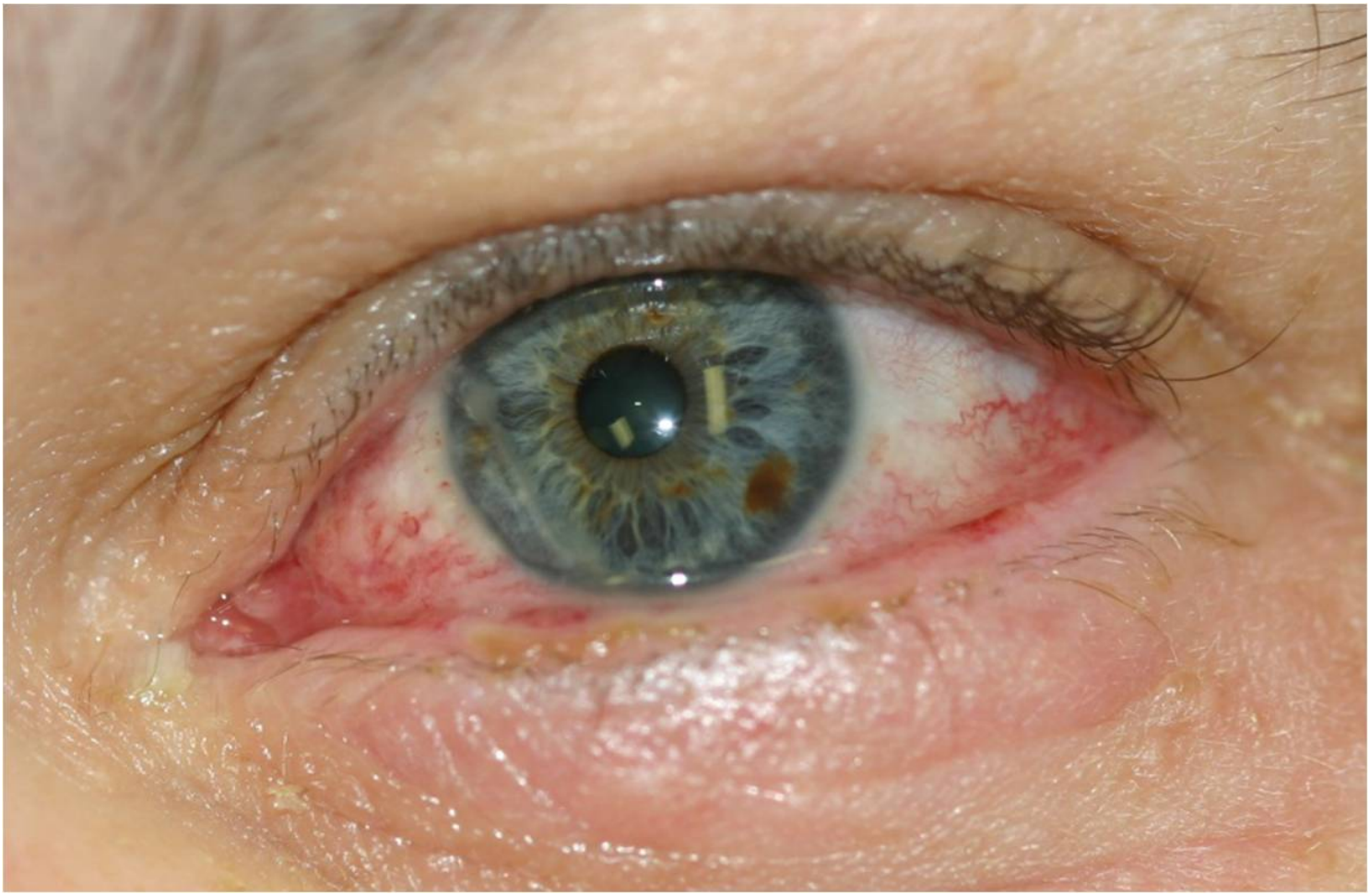

Figure 3. Marked conjunctival injection and episcleritis

Cutaneous examination revealed a bilateral symmetrical eruption consisting of dozens of tender, erythematous subcutaneous nodules on the shins and a few pseudovesicular plaques on the shoulders and upper back. On examination of mucosal surfaces, there were a few pustules on the soft palate, as well as marked conjunctival injection consistent with episcleritis.

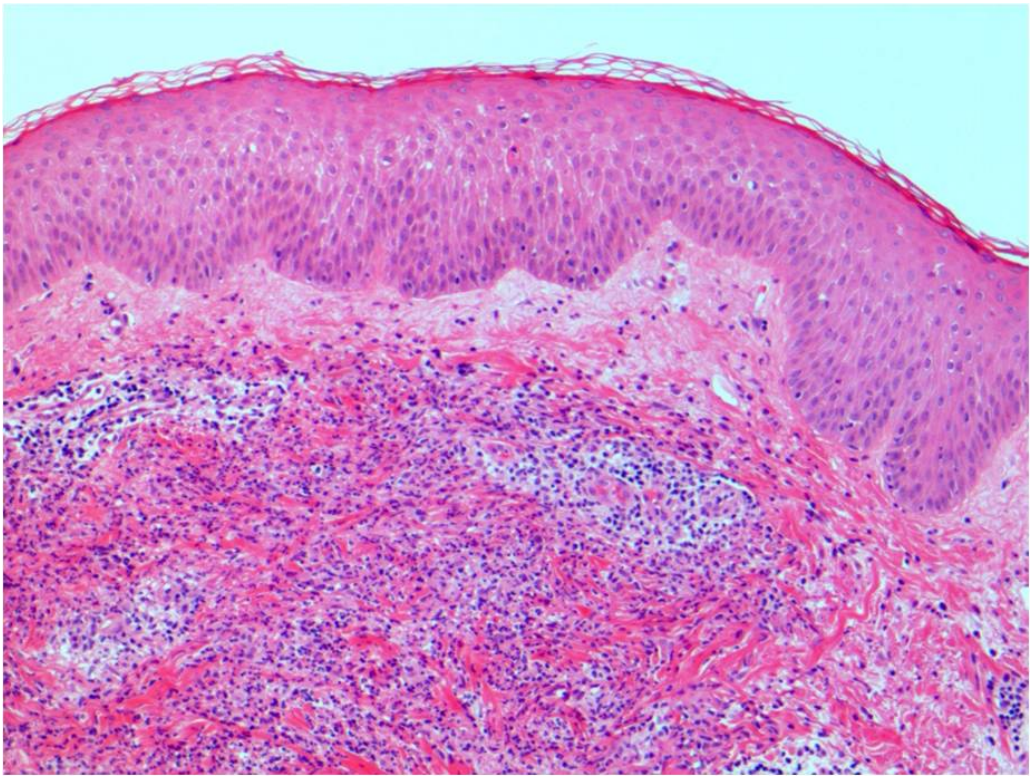

Figure 4. Biopsy from the right shoulder revealed a dense dermal neutrophilic infiltrate with overlying mild papillary dermal edema (x100, Hematoxylin & Eosin)

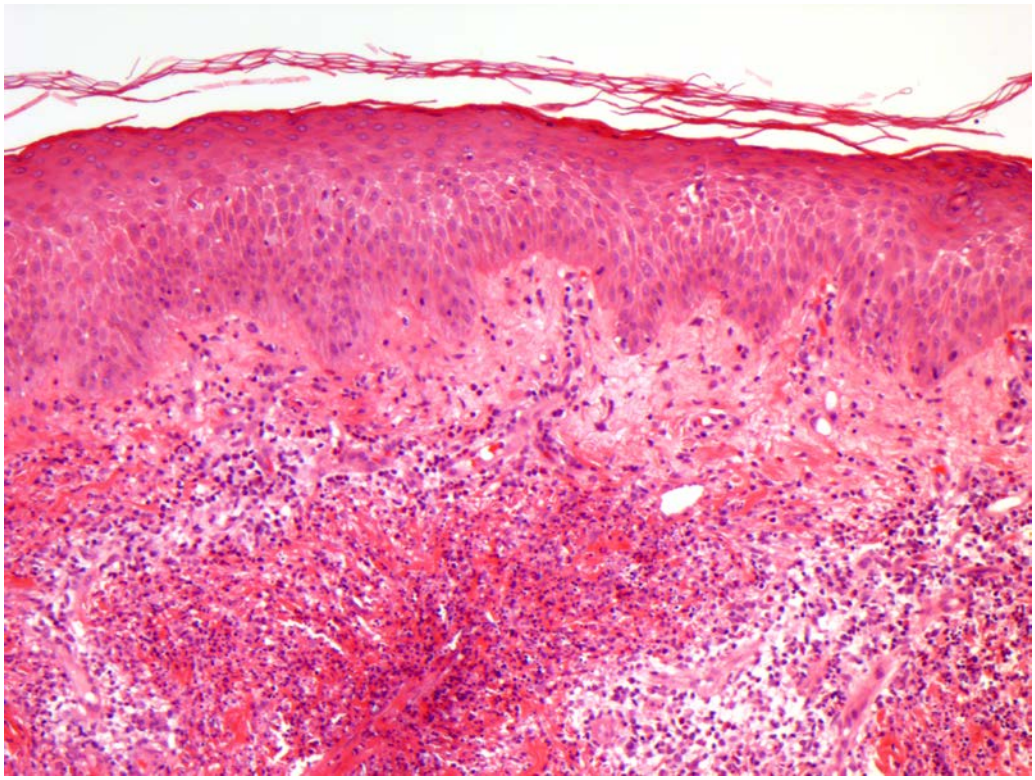

Figure 5. Biopsy from the right shin similarly reveals a dense dermal neutrophilic infiltrate with mild papillary dermal edema (x100, Hematoxylin & Eosin)

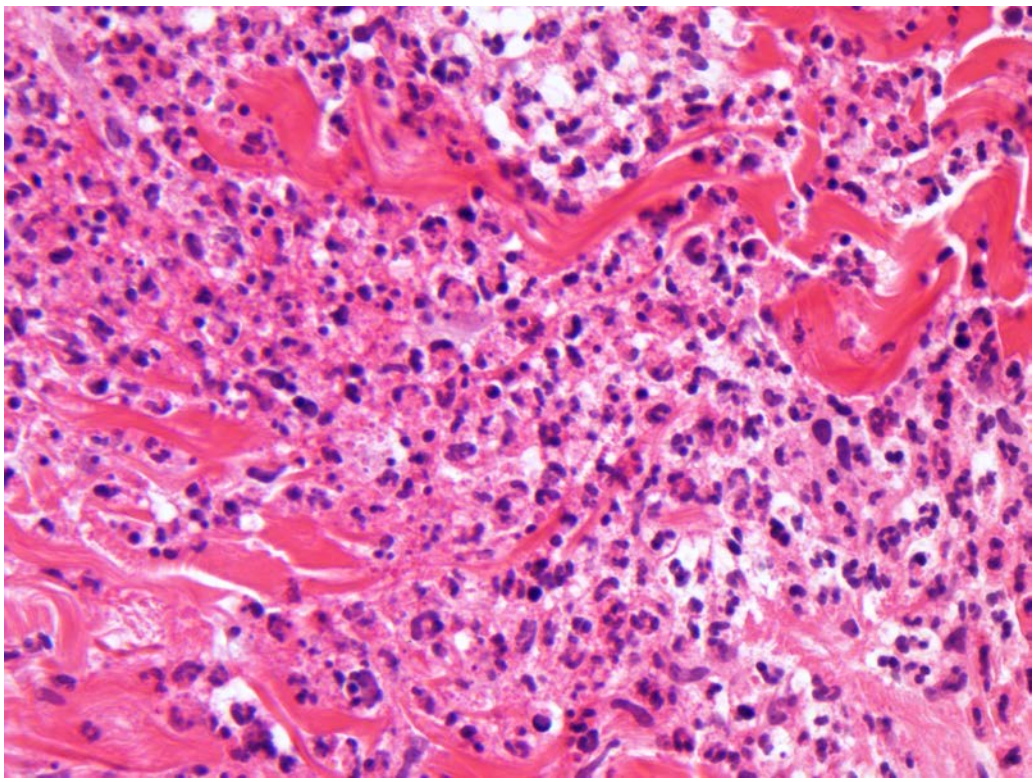

Figure 6. High power microscopic examination of the right shin shows back to back neutrophils in the dermal infiltrate (x400, Hematoxylin & Eosin).

A skin biopsy of a shin nodule revealed a dense and diffuse neutrophilic infiltrate in the dermis and subcutis. A biopsy of a plaque on the shoulder also revealed a dense dermal neutrophilic infiltrate with overlying mild papillary dermal edema. There was no evidence of granuloma formation or vasculitis.

Blood work revealed a minimal leukocytosis of $12.4x10^9$/L and neutrophilia of $9.6x10^9$/L. Erythrocyte sedimentation rate and C-reactive protein were both elevated at 115 mm/hr and 232.2 mg/L, respectively. Creatinine, electrolytes, anti-streptolysin O titer, rheumatoid factor, antinuclear antibody, serum protein electrophoresis, peripheral blood smear, and urinalysis were normal.

Tissue cultures for bacterial, fungal and mycobacterial infection were negative. Repeat urine culture did not show a persistent *E.coli* infection. Blood cultures and CSF cultures were also negative. Spinal tap revealed a normal cell count with slightly increased protein. Imaging of her head, abdomen, and pelvis by CT scan was unremarkable.

Because investigations for infections, rheumatologic disease and hematologic malignancy were negative, the patient was diagnosed with drug-induced Sweet Syndrome attributed to the ciprofloxacin and nitrofurantoin she had received for her urinary tract infection. These antibiotics were discontinued and she was given one dose of intravenous solumedrol 100mg in the emergency department followed by a short course of oral prednisone 50mg per day and prednisolone 1% eye drops twice a day. There was dramatic improvement of her symptoms within 48 hours, with her cutaneous eruption decreasing in erythema and tenderness. Significant improvement of her episcleritis, arthralgias and headaches were also achieved. On discontinuation of her prednisone, her skin and joint symptoms began to worsen and prednisone was restarted with a slow taper over two months. There has not been any recurrence a year and a half later since discontinuing her corticosteroids.

Discussion

Sweet syndrome, or acute febrile neutrophilic dermatosis, is an uncommon skin condition characterized by fever, leukocytosis, and an abrupt onset of characteristic cutaneous lesions that may be accompanied by various systemic symptoms. Cutaneous manifestations include tender erythematous and edematous papules and plaques coalescing to form pseudovesicular and pseudopustular plaques favoring the head, neck, and upper extremities (so-called classic form)[1-5]. Less frequently, subcutaneous nodules consisting of neutrophilic infiltration in the subcutis may appear on the lower legs. This may be difficult to clinically distinguish from erythema nodosum, which may also appear in conjunction with Sweet syndrome. Other cutaneous manifestations include targetoid, erysipeloid, and vesiculobullous variants [2]. The most common extracutaneous manifestations include fever and leukocytosis, reported to occur in 40-80% [2,3,6]. Other common extracutaneous complaints include those affecting musculoskeletal (arthralgias, arthritis, and myalgias), ocular (conjunctivitis, episcleritis, and iridocyclitis), pulmonary (cough, dyspnea, and pleurisy), and renal (hematuria, proteinuria, and renal failure) systems. Rarely, brain involvement such as aseptic meningitis and encephalitis, or gastrointestinal involvement such as hepatitis or pancreatitis may occur [2,6].

Although Sweet syndrome is thought to be a reactive disorder, occurring secondary to an infectious etiology, inflammatory processes, underlying malignancies, pregnancy, or drug-induced causes, many cases are idiopathic in origin. In a recent review, drugs were found to be the cause in 12% of Sweet syndrome cases [3]. The most commonly implicated medication in drug-induced Sweet syndrome is Granulocyte-Colony Stimulating Factor (G-CSF). Other medications commonly implicated are listed in Table 1[2]. Diagnostic criteria for drug-induced Sweet syndrome were proposed in 1996 by Walker and Cohen are listed in Table 2[7]. Each of the 5 criteria are required for diagnosis. On average, the eruption of drug-induced Sweet syndrome occurs 7.5 days after exposure to the offending agent, similar to the onset in our patient 6 days after starting antibiotics [7].

Table 1. Drugs most commonly implicated in Drug-Induced Sweet Syndrome[2]

Drug Class	**Drugs**
Antibiotics	Minocycline, Trimethoprim-Sulfamethoxazole
Antineoplastics	Bortezomib, Imatinib mesylate
Colony Stimulating Factors	Granulocyte-colony stimulating factor, Granulocyte-macrophage-colony stimulating factor
Retinoids	All-trans retinoic acid, 13-cis retinoic acid

Table 2. Diagnostic Criteria for Drug-Induced Sweet Syndrome[7]

1) Abrupt onset of painful erythematous plaques or nodules
2) Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
3) Pyrexia >38°C
4) Temporal relationship between drug ingestion and clinical presentation, OR temporally-related recurrence after oral challenge
5) Temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids

All 5 criteria are required for diagnosis.

Because the screening for hematologic malignancy, streptococcal infection, and rheumatologic disease was negative, we concluded that her condition was incited by her recent antibiotics. There was marked improvement with discontinuation of the presumed offending drugs and initiation of systemic steroids. The patient was presumed to have brain and joint involvement of her Sweet syndrome; onset and response of her headaches and arthralgias closely mirrored that of her cutaneous lesions.

Drug-induced Sweet syndrome associated with nitrofurantoin and ciprofloxacin use has only been reported in the literature on one prior occasion for each antibiotic [8,9]. In the case associated with nitrofurantoin, the patient's classical lesions of Sweet syndrome were not accompanied by any other systemic symptoms other than conjunctival injection [8]. In the case associated with ciprofloxacin, there were no other systemic symptoms besides arthralgias and myalgias [9]. Ocular involvement in drug-induced Sweet syndrome is rare. In a review of Sweet syndrome with associated ocular involvement, etiology was classic in 13/20 cases, and malignancy in 7/20 [10]. The only drug-related case was a patient with acute myelogenous leukemia who received G-CSF and developed Sweet syndrome [10]. Neurologic involvement in Sweet syndrome is uncommon and likely underreported. In a review of Sweet syndrome with neurologic manifestations, the most common presenting symptoms were headaches, seizures, and disturbance of consciousness [11,12]. Normal brain CT or MRI was found in 27% of patients and CSF sampling commonly reveal an increased cell count with lymphocytosis as well as increased CSF protein [11].

Sweet syndrome may also be associated with underlying malignancy, usually hematologic (e.g. acute myelogenous leukemia) in origin, but may also be seen in solid organ tumors such as bowel, genitourinary, or breast. There has only been one case of Sweet syndrome arising in association with cervical cancer. However, the skin changes preceded the diagnosis and treatment of cancer [13]. In our case, her cervical cancer was already fully treated with surgery and chemotherapy, making the relationship with Sweet syndrome less likely.

Sweet syndrome may also be associated with infectious causes, most commonly infections of the upper respiratory tract (*Streptococcus sp.*) and gastrointestinal tract (*Yersinia, Salmonella sp.*). An association with a urinary tract pathogen has been described on one previous occasion, whereby Sweet syndrome developed in tandem with positive *Klebsiella pneumoniae* urinary cultures. Two months prior, the patient was treated for cystitis with antibiotics, but unfortunately culture results and antibiotic choice at that time were not reported [14]. Our patient was found to have an *E.coli* urinary tract infection 6 days prior to onset of Sweet syndrome, but her urine culture was negative by the time she developed this eruption.

Panniculitis associated with nitrofurantoin administration has previously been described. However, it was associated with lymphocytic, histiocytic, and plasma cell infiltrates, rather than a neutrophilic infiltrate as was the case with our patient [15]. Thus, the skin lesions on her shins are suggestive of subcutaneous Sweet syndrome.

Conclusion

This is the second report of Sweet syndrome temporally associated with nitrofurantoin and ciprofloxacin, and first report of these drugs causing subcutaneous Sweet syndrome along with ocular, joint, and neurologic involvement, features that are all rarely reported in association with drug-induced Sweet syndrome.

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