Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis) Associated With Pulmonary Coccidioidomycosis

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Background: Sweet syndrome (acute febrile neutrophilic dermatosis) may arise in association with a variety of underlying systemic diseases. Only 1 case of coccidioidomycosis-associated Sweet syndrome has previously been reported.

Observations: We describe 2 patients who developed Sweet syndrome during the onset of acute pulmonary coccidioidomycosis. Systemic antifungal therapy was given in both cases. Respiratory symptoms and skin lesions resolved within 5 weeks.

Conclusions: Sweet syndrome may be a presenting feature of coccidioidomycosis. Recognition of the underlying pulmonary infection is important so that inappropriate treatment with systemic corticosteroids can be avoided.

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IN 1964, SWEET1 DESCRIBED 8 PATIENTS who had abruptly developed a distinctive syndrome, which he termed "an acute febrile neutrophilic dermatosis." Four characteristic features were noted: fever, peripheral blood leukocytosis, painful raised cutaneous plaques, and a dense histologic infiltrate of neutrophils in the dermis. Cultures from skin lesions yielded no growth of organisms, and treatment with systemic antibiotics was ineffective. With the administration of systemic corticosteroid therapy, Sweet observed rapid resolution of the skin lesions. Subsequent reports have described variations in the clinical features of the syndrome. Leukocytosis and fever have been present in many but not all patients, and an elevated erythrocyte sedimentation rate and arthralgias have frequently been noted.2-4

Sweet syndrome may be idiopathic, disease associated, drug induced, or pregnancy related.5-7 Underlying systemic diseases include hematologic malignancies, solid tumors, connective tissue diseases, inflammatory bowel disease, and infections. A nonspecific upper respiratory tract infection frequently precedes the onset of skin lesions by several weeks. Specific underlying infections have occasionally been identified. One case of coccidioidomycosis-associated Sweet syndrome has been described in a European patient who had recently traveled to Mexico.8

We describe 2 Arizona residents who presented with Sweet syndrome and acute pulmonary coccidioidomycosis. Although systemic corticosteroids are usually the mainstay of therapy for Sweet syndrome, recognition of underlying coccidioidomycosis is important so that immunosuppressive therapy with corticosteroids can be avoided.

The Mayo Clinic institutional review board approved the present retrospective study of medical records and histopathologic specimens from the 2 patients.

REPORT OF CASES

CASE 1

A 54-year-old woman developed widespread plaques on the face, trunk, and extremities over a 24-hour period. She complained also of fever, mild sore throat, and cough. Her medical history was remarkable for a chronic seizure disorder. Her only medication was oral phenytoin sodium, which she had taken for more than 6 years.

Physical examination findings revealed 50 nontender, well-demarcated, boggy plaques, 1 to 15 cm in diameter, on the eyelids, back, and all 4 extremities. Most of the plaques had a targetlike appearance with a violaceous center, a pale yellow middle zone, and a dusky red peripheral rim (Figure 1).

Significant laboratory findings in the peripheral blood included a mildly elevated
erythrocyte sedimentation rate (30 mm/h; normal, 0-29 mm/h), an elevated absolute neutrophil count (6.94 × 10^9/µL; normal, 1.4-6.6 × 10^9/µL), and a mildly decreased hemoglobin level (11.4 g/dL; normal, 11.5-14.9 g/dL). The results of her complete blood cell count were otherwise unremarkable. By immunofixation technique, serum Coccidioides IgM antibodies were identified (titer, 1:4); IgG antibodies were not detected. A chest radiograph revealed a new 2.5-cm nodule in the right lung base. Blood cultures yielded no growth of bacteria or fungi.

The initial skin biopsy specimen from the back showed marked subepidermal edema with diffuse necro-

sisis of the overlying epidermis. The dermis contained a moderately dense interstitial and perivascular infiltrate of lymphocytes, histiocytes, and eosinophils. Three days later, an additional skin biopsy was performed on the back. In this second specimen (Figure 2 and Figure 3), there was a moderately dense dermal infiltrate of neutrophils and histiocytes. Mild subepidermal edema was evident. Histochemical stains for fungi revealed no organisms. The findings were consistent with Sweet syndrome. A separate skin biopsy specimen from the back was submitted for bacterial and fungal cultures and yielded no growth.

For treatment of Sweet syndrome, we prescribed oral diaminodiphenylsulfone (100 mg/d for 3 days, then 150 mg/d for 5 weeks). Twice daily 0.05% clobetasol propionate cream (0.05%) was applied to the affected areas on the trunk and extremities. Oral fluconazole (400 mg/d for 3 weeks) was prescribed for treatment of the pulmonary coccidioidomycosis. Five weeks after the initiation of treatment, the lung nodule on her chest radiograph had resolved, and her cough had subsided. Physical examination findings revealed only patches of postinflammatory hyperpigmentation.

CASE 2

A 69-year-old woman was hospitalized for cough, myalgias, intermittent fever, and an asymptomatic cutaneous eruption. All symptoms had begun 6 days earlier. Her medical history was remarkable for hyperlipidemia. Her only oral medication was simvastatin, which she had taken for more than 5 years.

Results of physical examination revealed a symmetrical eruption of red edematous plaques involving the medial thighs, arms, abdomen, back, lips, and nose. She was afebrile.

In the peripheral blood, the absolute neutrophil count was elevated (7.38 × 10^9/µL; normal, 1.4-6.6 × 10^9/µL). The results of the complete blood cell count were otherwise unremarkable. By immunofixation technique, IgM and IgG Coccidioides antibodies were identified in the serum (titer, 1:2). A chest radiograph revealed a new 3-cm opaque mass in the right upper lobe and large infiltrates in the left lingula and left lower lobe. Blood cultures yielded no growth of bacteria or fungi.

In skin biopsy specimens from the thigh and back (Figure 4), there was a dense dermal infiltrate of neutrophils, histiocytes, and leukocytoclastic debris. Marked subepidermal edema was present. No organisms were revealed by histochemical stains for fungi, acid-fast organisms, and bacteria. Another skin biopsy specimen from the thigh was submitted for fungal, bacterial, mycobacterial, and viral cultures and yielded no growth of organisms.

For treatment of coccidioidomycosis, 400 mg/d of fluconazole was taken by mouth for 5 weeks. A 0.1% triamcinolone acetonide cream was applied twice daily to affected areas on the trunk and extremities. One week after the initiation of treatment, only faintly pink patches remained in the previously affected areas. The cough improved after 1 month, and chest radiographic findings resolved after 2 months.
Coccidioidomycosis is endemic to Arizona, California, northern Mexico, and other arid regions of North and South America.\textsuperscript{9} Coccidioides immitis, a dimorphic fungus, lives as a saprophyte in the soil and produces pulmonary infection via airborne arthroconidia. In most cases, the infection is asymptomatic or produces a mild, self-limited respiratory illness. A fulminant course can ensue in immunocompromised patients\textsuperscript{10-15} or rarely in previously healthy individuals.\textsuperscript{9}

A variety of cutaneous signs may be seen in association with coccidioidomycosis.\textsuperscript{16-19} Both reactive and organism-specific lesions may occur (Table). Organism-specific lesions contain \textit{Coccidioides}, which may be identified in skin biopsy specimens by routine histochmical stains, special fungal stains, or fungal cultures.\textsuperscript{17} Reactive cutaneous lesions, which contain no viable organisms, result from the immune response of the host. Sweet syndrome has been described as a reactive manifestation of coccidioidomycosis in only 1 previous case.\textsuperscript{9}

In this report we describe 2 additional patients with Sweet syndrome and pulmonary coccidioidomycosis. The patients presented with fever, cough, and cutaneous plaques. Skin biopsy specimens from both patients were consistent with Sweet syndrome, although the initial skin biopsy specimen in case 1 showed nonspecific findings. This first biopsy specimen revealed marked subepidermal edema, as is usually seen in Sweet syndrome; however, neutrophils were not a significant component of the dermal inflammatory infiltrate. Although nonspecific, the histopathologic pattern was compatible with an evolving lesion of Sweet syndrome. Lymphocytic and lymphohistiocytic dermal infiltrates have previously been described in early lesions.\textsuperscript{20,21} Three days later, a subsequent biopsy specimen from the same patient revealed a diffuse neutrophilic and histiocytic dermal infiltrate. In this second specimen from case 1 and in both biopsy specimens from case 2, the findings were consistent with the classic description of Sweet syndrome.

In both patients, the respiratory symptoms and cutaneous lesions resolved within 5 weeks after the initiation of treatment. Because mild pulmonary coccidioidomycosis may often resolve without treatment, it is unclear whether the patient in case 1 benefited from treatment with fluconazole and diaminodiphenylsulfone. In case 2, the patient was more severely ill, and fluconazole therapy was indicated for severe pulmonary involvement.\textsuperscript{22} Treatment of the pulmonary coccidioidomycosis might have contributed to the rapid resolution of Sweet syndrome in case 2.

Treatment of Sweet syndrome should be guided by consideration of the underlying cause. Although incompletely understood, the pathogenesis may involve cytokine-mediated recruitment of neutrophils to the skin.\textsuperscript{23-28} Accordingly, therapeutic approaches to Sweet syndrome include modification of the immune response or treatment of the underlying cause. When no specific cause is evident, systemic corticosteroids are the mainstay of therapy.\textsuperscript{29} Colchicine, potassium iodide, diaminodiphenylsulfone, cyclosporine, and other agents may also be helpful in the treatment of Sweet syndrome.\textsuperscript{5,7,29}

In our 2 patients, recognition of the underlying infection was important so that the appropriate treatment could be chosen. In case 1, the respiratory symptoms were mild and mimicked a viral respiratory infection. Since a nonspecific respiratory illness frequently precedes Sweet syndrome, treatment with systemic corticosteroids might have been considered, if coccidioidomycosis had not been detected by serologic analysis. Immunosuppressive therapy with systemic corticosteroids may exacerbate the infection\textsuperscript{12-15,30} and generally should not be given for coccidioidomycosis-associated Sweet syndrome.

Sweet syndrome may occur as a presenting feature of coccidioidomycosis. This association should be considered in patients with Sweet syndrome who live in or who have traveled to an endemic area. Recognition of coccidioidomycosis is important so that inappropriate treatment with systemic corticosteroids may be avoided.

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