Sweet’s Syndrome and Erythema Nodosum

The Simultaneous Occurrence of 2 Reactive Dermatoses

Karen M. Waltz, MD; David Long, MD; James G. Marks, Jr, MD; Elizabeth M. Billingsley, MD

Background: The simultaneous occurrence of Sweet’s syndrome (SS) and erythema nodosum (EN) in 1 patient is rare. Our review of the literature revealed only 11 biopsy-proved cases in which the 2 reactive dermatoses occurred together. None were associated with an underlying malignant neoplasm.

Observations: We report a biopsy-proved case of SS and EN occurring simultaneously in a patient with an underlying malignant neoplasm (specifically, acute myelogenous leukemia). We also report another biopsy-proved case of SS and EN occurring simultaneously in a patient with underlying Crohn’s disease.

Conclusions: The simultaneous occurrence of SS and EN in 1 patient is rarely reported. Both disorders are reactive dermatoses that share many overlapping features. Although individually distinctive, SS and EN are also part of a growing continuum of reactive dermatoses. Our expanded understanding of the similarities and simultaneous manifestation of SS and EN may help us in the future to identify a common underlying mechanism of pathogenesis.


Sweet’s Syndrome (acute febrile neutrophilic dermatosis) is an acute, often recurrent, dermatosis first described by Sweet in 1964. Skin lesions are characteristically tender erythematous papules and plaques that also can be pustular. Additional features of this syndrome include fever, arthralgias, conjunctivitis, leukocytosis with neutrophilia, and an elevated erythrocyte sedimentation rate. Not all features are invariably present in each case. The histopathologic examination typically demonstrates marked edema with a predominately neutrophilic dermal infiltrate in the absence of leukocytoclastic vasculitis. Since Sweet’s initial description, numerous cases have been reported. Although the precise cause remains unknown, Sweet’s syndrome (SS) is believed to represent a hypersensitivity phenomenon that may be idiopathic or may be found in association with various other disorders.

Erythema nodosum (EN) is an acute or chronic dermatosis that manifests with tender, erythematous to violaceous nodules usually involving the pretilial areas bilaterally. As in SS, EN may be associated with constitutional symptoms, such as fatigue and arthralgias. The histopathologic examination demonstrates a septal panniculitis with a mixed inflammatory infiltrate of neutrophils, lymphocytes, histiocytes, and giant cells. Like SS, there is an absence of leukocytoclastic vasculitis. Moreover, EN also is thought to represent a hypersensitivity reaction and has been linked to a variety of conditions.

The simultaneous occurrence of SS and EN in 1 patient seems to be rare. In 1992, Cohen et al reviewed the world literature and found only 8 biopsy-proved cases, none of which was associated with an underlying malignant neoplasm. In 1993, Wilkinson et al described 2 additional cases: 1 occurred in association with sarcoidosis, and 1 occurred after an upper respiratory tract (URTI) infection. In 1995, Ben-Noun also reported a case that occurred after a streptococcal pharyngitis.

In 1995, Suzuki et al described a patient with acute myelogenous leukemia (AML) in whom SS also developed. There was rapid improvement in the patient’s skin lesions after treatment with prednisolone, but 1 year later, EN developed. To our knowledge, this is the first biopsy-proved case of the simultaneous occurrence of SS and EN in a patient with an underlying malignant neoplasm, although the occurrence was sequential and not concurrent.
In the present article, we report 2 cases of concurrent SS and EN: 1 associated with AML, and 1 associated with Crohn’s disease. We believe that the former case represents the first biopsy-proved case of SS and EN occurring simultaneously in a patient with an underlying malignant neoplasm.

REPORT OF CASES

CASE 1

A 26-year-old man was admitted to the hospital with acute epiglottitis. A diagnosis of AML subsequently was made, and induction chemotherapy was given. Multiple antibiotics also were prescribed because of fevers of unknown origin.

Two weeks after admission, a tender erythematous eruption suddenly developed on the face, neck, trunk, and extremities. The examination of the skin revealed pseudovesicular dermal erythematous papules and dermal erythematous plaques on the face, neck, chest, shoulders, and arms (Figure 1). Two tender erythematous subcutaneous nodules were also present on the right leg and left arm (Figure 2). Further physical examination revealed an increased temperature (40°C), mild cervical lymphadenopathy, bilateral axillary lymphadenopathy, and a shallow ulceration in the posterior pharynx. The white blood cell count on admission was 31.2 × 10^9/L, with a subsequent decrease to 3.6 × 10^9/L (after induction chemotherapy) at the onset of the rash. Persistent anemia and thrombocytopenia also were present. Respiratory cultures obtained at the time of admission were positive for normal respiratory flora, Candida albicans, and parainfluenza virus type 3. Blood, urine, and stool cultures were negative for microorganisms, as was a culture for herpesvirus obtained from the pharyngeal ulceration.

A skin biopsy specimen obtained from a chest plaque showed the following histopathologic findings, which are classic for a diagnosis of SS: (1) diffuse inflammation in the upper dermis composed of mature neutrophils, a small amount of nuclear dust, and a few admixed lymphocytes and histiocytes; (2) moderate dermal edema accentuated in the subepidermal region; and (3) an absence of vasculitis. A skin biopsy specimen obtained from the nodule on the left arm showed edematous thickened fat septa containing scattered neutrophils and a few lymphocytes. Vasculitis was absent. A tissue culture from the same site was negative for bacteria, acid-fast bacilli, and fungi. These findings were consistent with a diagnosis of early EN.11

The patient was treated with a 7-day course of prednisone. Defervescence occurred within 3 days, and all skin lesions resolved within 5 days.

CASE 2

A 49-year-old white woman with a history of Crohn’s disease, EN, and aphthous ulcers was examined because of a 1-month history of tender erythematous nodules on the legs and a 2-week history of an erythematous eruption on the arms, hands, and feet. She also had new-onset arthralgias, a recent URTI, and a 5-week history of hematochezia. Treatment with prednisone was started 1 week before she was examined because of the skin lesions; she was taking no other medications.

The examination of the skin revealed the following: (1) pseudovesicular erythematous papules and plaques on the upper extremities, (2) indurated dermal erythematous plaques on the palms and soles, (3) erythematous subcutaneous nodules on the legs, and (4) a 0.5-cm ulcer with a yellow necrotic base on the tongue (Figure 3 and Figure 4). The vital signs were normal,
as were the results of the remainder of the general physical examination. Abnormalities in laboratory test results included mild leukocytosis, mild anemia, and thrombocytosis.

A skin biopsy specimen from an arm plaque showed dense perivascular inflammation in the upper and mid dermis composed primarily of neutrophils with admixed lymphocytes and eosinophils. Leukocytoclastic vasculitis was absent. These findings were consistent with a diagnosis of SS. A skin biopsy specimen obtained from a leg nodule revealed an inflammatory infiltrate composed of lymphocytes, histiocytes, macrophages, and a few neutrophils and multinucleated giant cells in the fibrous septa of the subcutaneous adipose tissue. Vasculitis was absent (Figure 5). These histopathologic findings were diagnostic of EN.

Treatment consisted of a short course of prednisone. All skin lesions resolved rapidly.

COMMENT

During the past few years, there has been a growing knowledge of a wide spectrum of reactive dermatoses, including such distinct entities as SS, EN, pyoderma gangrenosum, and bowel-associated dermatosis-arthitis syndrome. These dermatoses are sometimes associated with the same underlying conditions, and there have been rare reports of the simultaneous occurrence of 2 of the skin eruptions (such as SS and EN, SS and pyoderma gangrenosum, EN and pyoderma gangrenosum, and EN and bowel-associated dermatosis-arthitis syndrome) in 1 person. Sweet’s syndrome and EN are particularly noteworthy, because there have been 11 biopsy-proved cases in which these 2 reactive dermatoses have occurred simultaneously. A careful comparison of these entities reveals that they share many similar clinical and histopathologic features. They both also occur in association with many of the same systemic conditions, and they both respond to several of the same treatments (Table). Their simultaneous occurrence may be even more common than previously recognized, since several large series have shown a substantial percentage (12%-17%) of patients with SS to have EN-like lesions on the legs. Since the histologic features of the EN-like lesions in these series were not reported, however, no absolute conclusions can be drawn.

The 2 cases we report of the simultaneous occurrence of SS and EN are of particular interest in the light of their additional associations with Crohn’s disease and AML. To our knowledge, the association with Crohn’s disease has been reported only twice previously, and the association with AML (or any other malignant neoplasm) has never been reported. Since Crohn’s disease and leukemia have been individually associated with SS and EN, we believe that they also had a key role in triggering the subsequent skin eruptions in both patients we describe. One additional factor is that both patients also had an associated history of a recent URTI. Although the clinical impor-
tance of this history is uncertain, these URTIs could have had triggering roles in both cases that we report.

A review of all 13 biopsy-proved cases of simultaneous SS and EN7-9 (including the 2 cases we report) shows that all clinical features were similar to those found in patients with only 1 of the 2 disorders. Women were predominantly affected (female-male ratio, 10:3), and occurrence usually was during the third to seventh decades of life. The lesions of SS were located most commonly on the head, neck, and upper extremities, while the lesions of EN were located most commonly on the legs. Associated findings were fever (8 of 13), neutrophilia (8 of 13), arthralgias or myalgias (6 of 13), and conjunctivitis (4 of 13). Associated conditions included streptococcal pharyngitis (3 of 13), Crohn’s disease (3 of 13), preceding nonspecific URTI (2 of 13), AML (1 of 13), and sarcoidosis (1 of 13); 1 of 13 patients had used oral contraceptives. Treatment with oral corticosteroids led to rapid resolution of all skin lesions in most patients; 1 patient was treated successfully with a combination of potassium iodide and oral corticosteroids led to rapid resolution of the lesions of EN if they were located in the subcutaneous tissue. Some of these mediators also could be responsible for the various associated systemic abnormalities that commonly are observed.7

Although the pathogenesis of SS and EN is unknown, their many similarities and rare simultaneous occurrence suggest the possible involvement of a common underlying mechanism. One possibility is that immune complex formation is the initiating factor in both disorders. Bondi and Lazarus24 reported that in early EN, direct immunofluorescence often shows immunoglobulin and complement components deposited in the walls of affected vessels. Various other case reports, however, have shown only “occasional” or “minimal” deposits.8,11 Contradictory reports also have been made about SS. A few individual cases have shown immunoglobulin or complement deposits in active lesions15; 2 larger series, however, failed to confirm these findings.37,38 One possible explanation for these contradictory reports about SS and EN is that inflammatory cells rapidly clear any immune complexes that are initially present.37 Another explanation is that other pathogenic processes also are responsible.

In 1992, Cohen et al7 hypothesized that the causative agent of EN or SS may stimulate the production of various cytokines, such as interleukin (IL) 1, IL-8, or granulocyte colony-stimulating factor (G-CSF). These cytokines would then lead to the lesions of SS if they were located in the dermis or the lesions of EN if they were located in the subcutaneous tissue. Some of these mediators also could be responsible for the various associated systemic abnormalities that commonly are observed.7

Interestingly, several reports in the literature provide support for the hypothesis of Cohen et al.7 von den Driesch39 recently described 4 of 10 patients with SS with IL-8–reactive dendritic cells in the dermis. Moreover, Griffin et al40 reported that IL-1 has been produced in vitro by the cells of AML, which is the most common malign-
nant neoplasm associated with SS.30 Griffin et al30 also reported that AML-conditioned media containing IL-1 bioactivity induced human endothelial cells to express the G-CSF gene. Additional reports document the occurrence of SS after treatment with G-CSF.40,41 and Reuss-Borst et al42 described a patient during the acute phase of SS with markedly elevated serum levels of G-CSF and IL-6 (an endogenous pyrogen that also enhances the production of acute phase proteins).43 Other authors, however, have failed to confirm these data.44,45 Additional experiments designed to evaluate the role of cytokines in SS and EN would be useful for further assessment of their potential pathogenic relevance.

We report 2 cases of the simultaneous occurrence of SS and EN. One case was associated with Crohn’s disease, while the other case was associated with AML. Interestingly, SS and EN are similar clinically and histologically. The simultaneous occurrence of SS and EN seems to be rare, although it may be more common than previously suspected. An expanded understanding of the similarities and simultaneous occurrence of SS and EN may help us in the future to identify a common underlying mechanism of pathogenesis.

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Corresponding author: Elizabeth M. Billingsley, MD, Section of Dermatology, UPC II, Room 4300, PO Box 850, Hershey Medical Center, Hershey, PA 17033 (e-mail: ebilling@med.hmc.psu.edu).

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