Vascular Inflammation (Vasculitis) in Sweet Syndrome

A Clinicopathologic Study of 28 Biopsy Specimens From 21 Patients

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Background: Sweet syndrome is characterized by painful, erythematous plaques of rapid onset accompanied by fever. Absence of vasculitis is a histologic criterion for diagnosis. However, recent reports suggest that vasculitis should not exclude the diagnosis. We hypothesized that vasculitis can occur in Sweet syndrome and that it represents an epiphenomenon rather than a primary immune-mediated process.

Design: Skin biopsy specimens from patients with Sweet syndrome were reviewed to determine the prevalence of vasculitis. The clinicopathologic features of cases with vasculitis were evaluated for statistically significant associations. Specimens with vasculitis underwent immunofluorescence staining.

Setting: University department of dermatology, university hospital, and private practice.

Patients: Medical records and biopsy specimens of 21 patients meeting diagnostic criteria for Sweet syndrome were reviewed.

Interventions: None.

Results: The prevalence of vasculitis was 29% (6 of 21 patients). There was a significant association of vasculitis with lesions of longer duration (P = .02). Vascular immunoglobulin and complement could not be demonstrated in cases of Sweet syndrome with vasculitis.

Conclusions: Vasculitis is not a primary, immune-mediated process in Sweet syndrome but occurs secondary to noxious products released from neutrophils. Blood vessels in lesions of longer duration are more likely to develop vasculitis than those of shorter duration because of prolonged exposure to noxious metabolites. Vasculitis does not exclude a diagnosis of Sweet syndrome.

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CUTEL FEBRILE neutrophilic dermatosis (Sweet syndrome), first described by Sweet in 1964, is a disease characterized by painful, erythematous nodules and plaques of rapid onset accompanied by fever and neutrophilia. In many cases the disease follows a viral infection, especially of the upper respiratory tract, and it has also been reported in association with hematologic and visceral malignancies, medication (most commonly granulocyte colony-stimulating factor), autoimmune disease, inflammatory bowel disease, and pregnancy.

Sweet syndrome is histologically categorized as a neutrophilic dermatosis. A dense dermal infiltrate composed of neutrophils with leukocytoclasis and prominent papillary dermal edema occasionally producing subepidermal vesiculation or bullae are the usual findings. The clinicopathologic features of Sweet syndrome are so characteristic as to have elicited diagnostic criteria for the disease, proposed by Su and Liu and subsequently modified by von den Driesch et al to include abnormal laboratory values (elevated erythrocyte sedimentation rate, positive C-reactive protein, and peripheral-blood leukocytosis with >70% neutrophils).

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The histologic absence of vasculitis has been considered a defining characteristic of the disease and a useful feature to differentiate Sweet syndrome from other neutrophilic dermatoses in which vasculitis is commonly seen, such as leukocytoclastic vasculitis and erythema elevatum diutinum. However, a number of reports have described evidence of vessel wall damage in patients with clinical signs and symptoms of the disease. We postulated that vasculitis may be present in Sweet syndrome and that it represents an epiphenomenon rather than primary immune complex-mediated disease. Using the diag-
PATIENTS AND METHODS

The medical records of patients coded with the diagnosis of Sweet syndrome were reviewed in a dermatology practice that examines both private and university-based patients. Of 36 cases retrieved from the search (from January 1, 1989, through December 21, 1999) and with materials available for review, 21 cases (28 biopsy specimens) satisfied the diagnostic criteria for Sweet syndrome* (Table 1) and were included in the study. Of the 7 patients who underwent more than 1 biopsy, 6 had different lesions sampled concurrently; 1 patient required biopsy on a later occasion to establish the diagnosis.

Standard hematoxylin-eosin-stained sections from archival paraffin-embedded tissues were evaluated. Immunofluorescence staining was performed on paraffin-embedded biopsy specimens showing evidence of vasculitis (fibrinoid necrosis and intramural inflammation). Each case was examined for the presence of IgG, IgM, IgA, and C3 by means of appropriate positive and negative paraffin-embedded control tissues. Positive controls included skin biopsy specimens from 3 patients with bullous pemphigoid that showed positive staining with antibody against IgG, IgM, and C3. Biopsy specimens from 2 patients with pemphigus vulgaris and IgA pemphigus demonstrated immunofluorescence reactivity with antibody against IgG and IgA, respectively. Negative control tissues comprised sections of patient tissues lacking antibody application. Sections 4 μm thick were placed on sialinized slides (to improve tissue adhesion) after flotation on a protein-free water bath and allowed to air-dry. After overnight drying at 37°C, slides were deparaffinized in xylene and rehydrated successively in 100%, 95%, and 50% alcohol baths. After distilled water and phosphate-buffered saline rinses, sections were incubated in Streptomyces griseus (Promega, Madison, Wis) and 75 µg/100 mL of Tris buffer at 37°C for 75 minutes. Sections were then rinsed 3 times for 10 minutes each in phosphate-buffered saline. Sections were incubated in fluorescein isothiocyanate–labeled antibody at room temperature for 2 hours. All antisera were applied in 1:4 dilution. After incubation, slides were washed in phosphate-buffered saline 6 times for 5 minutes each. Sections were coverslipped with an aqueous mounting medium with fluorescence-preserving properties (Aquamount; Lerner Laboratories, Pittsburgh, Pa) and examined within 6 hours using a fluorescence microscope (Olympus BX60; Olympus Corporation, Lake Success, NY).

Ordered measures (age and lesion duration) were compared by means of the nonparametric Mann-Whitney test. Categorical tables (disease association, sex, lesion location, and inflammatory intensity and pattern) were analyzed with the Fisher-Freeman-Halton exact test, which computes correct P values even in cases of sparse tables. The statistical software used was SPSS, version 8.0 (SPSS Inc, Chicago, Ill), and StatXact, version 4.0 (CYTEL Software Corp, Cambridge, Mass).

RESULTS

CLINICAL FINDINGS

Clinical characteristics of patients are listed in Table 2. Two patients have been described previously.7,8 In our 21 cases (18 women and 3 men), the age ranged from 25 to 73 years (average age, 49 years). Two of the men had hematologic malignancies. An associated disease process was seen in 15 patients (71%): 6 (29%) had inflammatory disease, 5 (24%) had infectious disease, and 4 (19%) had hematologic malignancy. Three of 6 patients with an inflammatory condition had rheumatoid arthritis, and 4 of 5 patients with a suspected infectious association described a recent or ongoing viral upper respiratory tract infection. In the majority of patients (68%), lesions involved the head and neck area and/or the upper extremity. Most patients who had more than 1 lesion described a uniform eruption of multiple lesions, although 6 (29%) described outbreaks at varying time intervals.

Table 1. Diagnostic Criteria for Sweet Syndrome*

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>1. Abrupt onset of tender erythematous plaques or nodules</td>
<td>1. Fever, temperature &gt;38°C</td>
</tr>
<tr>
<td>2. Dense neutrophilic infiltrate on biopsy</td>
<td>2. Association with an underlying hematologic malignancy, inflammatory disease, or pregnancy or preceded by an upper respiratory or gastrointestinal tract infection</td>
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<tr>
<td></td>
<td>3. Excellent response to treatment with systemic corticosteroids</td>
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<tr>
<td></td>
<td>4. Abnormal laboratory values at presentation (3 of 4): erythrocyte sedimentation rate &gt;20 mm/h; positive C-reactive protein; leukocyte count &gt;10 x 10^9/L; &gt;70% neutrophils</td>
</tr>
</tbody>
</table>

*Adapted from Honigsmann et al.6 The presence of both major criteria and 2 of the 4 minor criteria is required for the diagnosis of Sweet syndrome.

MICROSCOPIC FINDINGS

All biopsy specimens demonstrated a dermal infiltrate composed predominately of neutrophils (Figure 1). The infiltrate occurred in a diffuse pattern (16 [47%] of the 34 patterns seen), bandlike pattern (8/34 [24%]), and a vaguely perivascular pattern (10/34 [29%]), although overlap was occasionally seen within the same biopsy specimen (Table 3). The infiltrate was described as moderate in the majority (54%) of cases.

Vasculitis was seen in 6 biopsy specimens (21%), although evidence of vessel wall damage, including intramural inflammatory cells and/or extravasated erythrocytes, was identified in most cases (21 specimens [79%]). Within individual biopsy specimens, evidence of vessel wall damage was usually diffuse; however, of the 6 biopsy specimens that met the criteria for vasculitis, often only a single vessel demonstrated both fibrinoid change and intramural inflamma-
tion (Figure 2). Of the 6 patients who had multiple concurrent biopsies performed, only 1 (patient 7) demonstrated vasculitis in 1 specimen. In the patient who underwent biopsy on separate occasions (patient 19), neither of the 2 specimens showed evidence of vessel wall damage (Figure 3). The presence or absence of vasculitis did not show an association with the pattern or intensity of the inflammatory infiltrate, although the majority of specimens demonstrating vasculitis showed a moderate or extensive inflammatory infiltrate. The presence of vasculitis was significantly associated with lesions that had been present for a longer duration before their biopsy ($P = .02$). The median duration of lesions with and without vasculitis was 17.5 and 6 days, respectively. Two of the 6 patients whose biopsy specimens demonstrated vasculitis had had lesions present between 1 and 3 months before their biopsy, and only 1 of the 15 patients whose specimens did not demonstrate vasculitis described the lesion as having been present 3 months before biopsy. Only 1 biopsy specimen that demonstrated vasculitis came from a lesion that had been present a week or less (3 days), whereas 14 specimens (50%) without evidence of vasculitis had been present a week or less. Patient age did not show an association with the presence or absence of vasculitis ($P = .18$), although specimens that showed vasculitis tended to occur in older patients compared with specimens that lacked vasculitis (median age, 61 and 47 years, respectively). No significant association was found between associated disease state and sex and the presence or absence of vasculitis.

Immunofluorescence staining of the 6 biopsy specimens demonstrating vasculitis was negative for both immunoglobulin and complement within vessel walls. Control skin biopsy specimens stained appropriately.

Since Sweet’s original description of 8 female patients with acute onset of fever, leukocytosis, and erythematous plaques
demonstrating a neutrophilic infiltrate, more than 500 cases of Sweet syndrome have been reported in the literature. The clinical and pathologic findings of the disease were so distinctive as to have been developed into diagnostic criteria. Of note, histologic evidence of vasculitis strongly militated against a diagnosis of Sweet syndrome. The absence of vasculitis has been considered a useful method to distinguish this disease from other diseases presenting with predominantly neutrophilic infiltrates with vasculitis. Several studies challenge this dictum. In his study of 54 biopsy specimens from 37 patients with Sweet syndrome, Jordaan found evidence of vessel wall damage with fibrinoid necrosis and extravasated erythrocytes in 18% and 76% of biopsy specimens, respectively. In addition, von den Driesch reported vasculitis-like changes in 30% of cases of Sweet syndrome. Another study described 6 female patients with lesions of the hands resembling Sweet syndrome and typical systemic manifestations but with histologic evidence of vasculitis. Several studies challenge this dictum. In his study of 54 biopsy specimens from 37 patients with Sweet syndrome, Jordaan found evidence of vessel wall damage with fibrinoid necrosis and extravasated erythrocytes in 18% and 76% of biopsy specimens, respectively. In addition, von den Driesch reported vasculitis-like changes in 30% of cases of Sweet syndrome. Another study described 6 female patients with lesions of the hands resembling Sweet syndrome and typical systemic manifestations but with histologic evidence of vasculitis. Strictly adhering to the classic diagnostic criteria for Sweet syndrome, the authors chose to classify this disease as a distinct entity termed pustular vasculitis of the hands.

We found unequivocal evidence of vasculitis in lesions from patients who met the clinical criteria for Sweet syndrome. Microscopic evidence of vasculitis is defined as the presence of inflammatory cells within blood vessel walls in association with necrosis. Commonly associated with vasculitis, but not essential for its diagnosis, are extravasated erythrocytes and intraluminal thrombi. The cause of necrotizing vasculitis in the dermatologic diseases leukocytoclastic vasculitis and Arthus reaction has been well defined. Both are type III immune complex–mediated diseases. Leukocytoclastic vasculitis results from the passive deposition of circulating immune complexes in vessel walls, whereas the experimentally produced Arthus reaction follows localized formation and precipitation of immune complexes at the site of antigen entry in a host carrying circulating antibodies to that antigen. Activation of the complement cascade and induction of macrophages and neutrophils through their Fc receptors results in the production of chemotactic factors, anaphylatoxins, and a variety of additional proinflammatory mediators that produce vessel wall damage.

Unlike the Arthus reaction and leukocytoclastic vasculitis, the stimulus for neutrophil diapedesis and activation in Sweet syndrome is unknown. A possible role for bacterial, viral, or tumor antigens; circulating autoantibodies; immune complexes; or cytokines has been postulated. The drug most frequently implicated in the disease is granulocyte colony-stimulating factor, further suggesting a role for cytokines in the pathogenesis. Antibodies to neutrophil cytoplasmic antigens have been reported in Sweet syndrome. Three of our patients underwent testing for antibodies to neutrophil cytoplasmic antigens, with a negative result. Immunofluorescence evaluation of skin lesions in Sweet syndrome failed to yield consistent results. Perivascular C3 and fibrin have been reported, probably representing nonspecific leakage from damaged vessels.

Table 3. Degree and Pattern of Infiltrate in Biopsy Specimens of Sweet Syndrome

<table>
<thead>
<tr>
<th>Degree of Infiltrate</th>
<th>Diffuse</th>
<th>Bandlike</th>
<th>Perivascular</th>
<th>Diffuse and Bandlike</th>
<th>Diffuse and Perivascular</th>
<th>Bandlike and Perivascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sparse</td>
<td>2A, 5, 7, 14,</td>
<td>11, 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1, 2B, 3, 4, 6A, 8B, 21B</td>
<td>9A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>9, 12, 13, 15, 17B, 21A</td>
<td>17A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Specimens are listed by patient number and specimen letter from Table 2. Boldface numbers represent biopsy specimens that demonstrated vasculitis.†None of the patients’ specimens had a diffuse, bandlike, and perivascular pattern of infiltrate.
Although the stimulus for transmigration of neutrophils across dermal venules has not been elucidated, the final common pathway for vessel wall damage is the release of toxic metabolites and proteases from activated neutrophils. The longer that dermal blood vessels are exposed to toxic substances, the more damage will be incurred. The varying pattern of dermal inflammatory infiltrate seen in association with damaged blood vessels suggests a variety of mechanisms responsible for the occurrence of secondary vasculitis. A perivascular infiltrate was seen in approximately one third of biopsy specimens that demonstrated vasculitis, suggesting a “de novo” epiphenomenon, ie, vasculitis resulting from vascular wall transmigration of inflammatory cells. The remaining two thirds of cases demonstrating vasculitis showed evidence of vessel wall damage in areas involved by a diffuse or bandlike inflammatory infiltrate, suggesting an “innocent bystander” epiphenomenon of vessel wall damage.

Our findings of unequivocal vasculitis in lesions of long duration and absence of immunoglobulin and complement in vessel walls support the theory of secondary vessel wall damage. Obviously, pathogenic factors other than lesion duration are at play, since not all lesions of long duration contained damaged vessel walls and one of the lesions of short duration (<7 days) showed evidence of vasculitis. This apparent miscorrelation is magnified in light of the fact that a single patient who underwent concurrent biopsy of 2 separate lesions, both of long duration, had evidence of vessel wall damage in 1 biopsy specimen but not in the second biopsy specimen. Although supportive of an absence of systemic vasculitis in this patient, varying evidence of vasculitis may have resulted from the clinician’s or pathologist’s sampling error.

We confirmed a female preponderance in the disease overall (6:1), as well as the lack of sex bias in malignancy-associated Sweet syndrome. All cases associated with neoplasia occurred in patients with hematologic malignancies. None of our patients had unequivocal evidence of a drug-related cause. Patient 1 presented with disease approximately 6 weeks after starting isotretinoin therapy for acne vulgaris, but an association could not be proved, as treatment was provided at the same time the drug was withdrawn. She responded well to oral prednisone therapy, with resolution of multiple facial lesions in 3 days. A rechallenge with the drug was not attempted.

Patients with lesions demonstrating vasculitis tended to be older than patients whose biopsy specimens did not demonstrate vasculitis, although this difference was not statistically significant (P = .18). This may have been the result of a delay in seeking medical attention, which is known to occur more frequently in the elderly population, who frequently suffer various social and financial restrictions. Patients’ inability to remember the duration of long-standing lesions may have imposed a source of error in this study. For uniform statistical calculations, durations of lesions were input as days, although the patients’ reports of long-standing durations tended to be on the order of months. In addition, patients who had multiple lesions may have miscalculated the duration of the lesion or lesions that underwent biopsy.

In summary, we found evidence of vasculitis (fibrinoid degeneration of vessel walls and intramural inflammation) in 21% of biopsy specimens taken from patients exhibiting clinical signs and symptoms diagnostic of Sweet syndrome. Had we applied less stringent criteria for the diagnosis of vasculitis, this percentage would have been greater, as many biopsy specimens demonstrated intramural inflammation and perivascular hemorrhage without fibrinoid necrosis of the vessel walls. Immunofluorescence microscopy failed to detect immune complex deposition in vessel walls. We propose that the absence of vasculitis is not an absolute criterion for lesions of Sweet syndrome; alternatively, the presence of vasculitis does not rule out a diagnosis of Sweet syndrome. We concur with the theory proposed by Jordaan and championed by others5,13 that vasculitis in Sweet syndrome is not a result of immune complex–mediated injury but represents secondary vessel wall damage due to toxic metabolites released by activated neutrophils.

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REFERENCES