Chronic Recurrent Lymphocytic Sweet Syndrome as a Predictive Marker of Myelodysplasia

A Report of 9 Cases

Marie-Dominique Vignon-Pennamen, MD; Caroline Juillard, MD; Michel Rybojad, MD; Daniel Wallach, MD; Marie-Thérèse Daniel, MD; Patrice Morel, MD; Olivier Verola, MD; Anne Janin, MD, PhD

Background: Sweet syndrome is an acute neutrophilic dermatosis that occurs with malignant diseases, mainly myeloid hemopathies, in about 20% of cases. When associated with myelodysplasia, Sweet syndrome may be clinically atypical. It can be histologically unusual. Concomitant infiltration of mature neutrophils and immature myeloid cells has been reported, and its significance is still debated. In few patients, lymphocytic infiltrates are the presenting feature of Sweet syndrome with myelodysplasia.

Observations: We present 9 male adult patients with chronic Sweet syndrome, all with recurrent eruptions of erythematous and annular plaques that were associated with relapsing polychondritis in 4 of the 9 patients. Results from sequential biopsies showed that infiltrates were initially composed of lymphocytes and that neutrophilic dermal infiltration typical of Sweet syndrome occurred 24 to 96 months later, except in 2 cases. Moreover, atypical mononuclear cells were present on all initial biopsy specimens and strongly reacted to CD68 and myeloperoxidase, indicating a myeloid origin. Myelodysplastic syndrome occurred in all 9 patients, concomitantly with the neutrophilic infiltrate in 4 cases.

Conclusions: Lymphocytic infiltrates with a clinical aspect of Sweet syndrome might represent the initial stage of a cutaneous dysgranulopoiesis syndrome and should lead to the research of atypical myeloid cells in skin infiltrate, blood, and bone marrow for the early detection of an associated myelodysplastic syndrome.

Arch Dermatol. 2006;142:1170-1176
For these 9 patients, at the different times of follow-up, the distribution and occurrence of skin lesions, laboratory abnormalities, hematologic diagnosis, and treatment were reviewed (Table 1). Hematologic diagnoses were established on peripheral blood smears and bone marrow aspiration and then were subclassified according to the French-American-British (FAB) classification scheme. For each patient, 3 to 7 skin biopsies had been performed. On these sequential biopsies, the analysis focused on the distribution of the infiltrates and their density. Cytological composition of the infiltrates was assessed, and their respective density in neutrophils, eosinophils, lymphocytes, macrophages, and atypical mononuclear cells was graded.

For immunohistochemical studies, representative sections were examined by the streptavidin-biotin peroxidase method, using appropriate positive and negative controls. Slides were processed on the automated immunostainer Nexes (Ventana, Tucson, Ariz). The antibodies used, their specificity, their source, and dilution are given in Table 2.

### Table 1. Clinical Findings and Course

<table>
<thead>
<tr>
<th>Patient/ Sex/Age, y</th>
<th>Aspect and Extent of Lesions</th>
<th>Associated Symptoms</th>
<th>AD</th>
<th>Abnormal Laboratory Findings at Onset of Skin Disease</th>
<th>Time Between Initial Clinical Skin Lesions and Neutrophilic Infiltrates</th>
<th>MDS Subtype/Time From Initial Skin Disease to MDS</th>
<th>Time From Neutrophilic Infiltrates to MDS</th>
<th>Outcome; Time From Initial Skin Disease/Neutrophilic Infiltrates/MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/61</td>
<td>Plaques and papules; trunk, face, and limbs</td>
<td>Fever</td>
<td>RP</td>
<td>Anemia (Hb, 7.8 g/dL); MCV, 107 fL</td>
<td>72 mo</td>
<td>RAEB/84 mo</td>
<td>+12 mo</td>
<td>Died of sepsis; 84 mo/12 mo/3 mo</td>
</tr>
<tr>
<td>2/M/71</td>
<td>Plaques; trunk and limbs</td>
<td>Fever</td>
<td>None</td>
<td>Leukopenia; MCV, 101 fL</td>
<td>36 mo</td>
<td>RA/36 mo</td>
<td>//</td>
<td>Died of vascular disease; 36 mo/3 mo/3 mo</td>
</tr>
<tr>
<td>3/M/72</td>
<td>Plaques, papules, and pustules; trunk, face, and limbs</td>
<td>Fever, arthralgia, and myalgia</td>
<td>RP</td>
<td>None</td>
<td>48 mo</td>
<td>RA/24 mo</td>
<td>-24 mo</td>
<td>Died of sepsis; 72 mo/24 mo/48 mo</td>
</tr>
<tr>
<td>4/M/59</td>
<td>Plaques and pustules; trunk and limbs</td>
<td>Fever and arthralgia</td>
<td>None</td>
<td>MCV, 105 fL</td>
<td>96 mo</td>
<td>RA/60 mo</td>
<td>-36 mo</td>
<td>Died of cerebral thrombosis; 108 mo/12 mo/48 mo</td>
</tr>
<tr>
<td>5/M/72</td>
<td>Plaques and papules; trunk and neck</td>
<td>Fever</td>
<td>RP</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Died of vascular disease; 60 mo (initial skin disease)/24 mo (MDS)</td>
</tr>
<tr>
<td>6/M/71</td>
<td>Pапules and nodules; trunk and limbs</td>
<td>Fever</td>
<td>None</td>
<td>Leukopenia</td>
<td>24 mo</td>
<td>MDS/24 mo</td>
<td>//</td>
<td>Died of vascular disease; 36 mo/12 mo/12 mo</td>
</tr>
<tr>
<td>7/M/65</td>
<td>Plaques, papules, and pustules; trunk</td>
<td>Fever</td>
<td>None</td>
<td>None</td>
<td>24 mo</td>
<td>MDS/24 mo</td>
<td>//</td>
<td>Lost to follow-up; 8 y after onset/6 y after SS and MDS</td>
</tr>
<tr>
<td>8/M/58</td>
<td>Plaques and papules; trunk and limbs</td>
<td>Fever, arthralgia, and episcleritis</td>
<td>RP</td>
<td>None</td>
<td>NA</td>
<td>MDS/24 mo</td>
<td>NA</td>
<td>Alive</td>
</tr>
<tr>
<td>9/M/55</td>
<td>Plaques; trunk and limbs</td>
<td>Fever and arthralgia</td>
<td>None</td>
<td>None</td>
<td>48 mo</td>
<td>MDS/48 mo</td>
<td>//</td>
<td>Died of vascular disease; 60 mo/48 mo/48 mo</td>
</tr>
</tbody>
</table>

Abbreviations: AD, associated disease; Hb, hemoglobin; MCV, mean cell volume; MDS, myelodysplastic syndrome; NA, not applicable; RA, refractory anemia; RAEB, refractory anemia with blast excess; RP, relapsing polychondritis; SS, Sweet syndrome; //, concurrently diagnosed.

### Table 2. Antibodies Used in This Study

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Source</th>
<th>Dilution</th>
<th>Main Cellular Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>Polyclonal</td>
<td>D</td>
<td>1:50</td>
<td>Pan-T lymphocytes</td>
</tr>
<tr>
<td>CD20</td>
<td>L26</td>
<td>D</td>
<td>1:40</td>
<td>Pan-B lymphocytes</td>
</tr>
<tr>
<td>CD68</td>
<td>KP1</td>
<td>D</td>
<td>1:100</td>
<td>Monocytes, macrophages, neutrophils, and myeloid precursors</td>
</tr>
<tr>
<td>CD15</td>
<td>80H5</td>
<td>IK</td>
<td>1:50</td>
<td>Mature neutrophils and mononuclear cells</td>
</tr>
<tr>
<td>CD34</td>
<td>O</td>
<td>IK</td>
<td>1:100</td>
<td>Immature myeloid cells</td>
</tr>
<tr>
<td>CD56</td>
<td>1B6</td>
<td>NA</td>
<td>1:50</td>
<td>Natural killer cells and T-cell subset</td>
</tr>
<tr>
<td>MPO</td>
<td>Polyclonal</td>
<td>D</td>
<td>1:3000</td>
<td>Myeloid cells and neutrophils</td>
</tr>
</tbody>
</table>

Abbreviations: D, Dako, Glostrup, Denmark; IK, Immunotech, Marseille, France; NA, Novocastra, Newcastle upon Tyne, England.

For immunohistochemical studies, representative sections were examined by the streptavidin-biotin peroxidase method, using appropriate positive and negative controls. Slides were processed on the automated immunostainer Nexes (Ventana, Tucson, Ariz). The antibodies used, their specificity, their source, and dilution are given in Table 2.

### CLINICAL FINDINGS

The 9 patients were men aged 55 to 72 years (median age, 64.5 years). The clinical features were similar in all patients (Table 1). Clinical aspects of the recurrences were also similar over the course of their disease (Figure 1 A and C), with multiple flares of edematous erythematous plaques over the face, trunk, and arms. On the trunk, plaques had an annular configuration with sharply marked borders. Some of them extended and became confluent.
On the limbs, plaques and purple nodules were observed in 8 cases, with pustules on plaques in cases 3, 4, and 7. Three patients had purpuric papules with vasculitis (cases 1-3). All 9 patients had fever, with arthralgia in cases 3, 4, 8, and 9 or episcleritis in case 8. Findings from laboratory tests showed an elevated erythrocyte sedimentation rate (all patients), leukopenia (cases 2 and 6), and anemia (case 1). The diagnosis of Sweet syndrome was initially proposed on clinical grounds. After analysis of the first results of the skin biopsies, subacute lupus erythematosus and Jessner lymphocytic infiltration were also discussed. In all 9 cases, the lesions resolved spontaneously and recurred. The course of the disease was characterized by multiple relapses with progressively reduced normal intervals. Auricular and nasal chondritis appeared in 4 patients (cases 1, 3, 5, and 8) about 3 years after the onset of skin disease. The diagnosis of relapsing polychondritis was made on clinical grounds and confirmed by cartilage biopsy findings showing necrosis of chondrocytes and vasculitis. There were no systemic manifestations of relapsing polychondritis in our patients.

Though bone marrow aspiration was initially normal in 2 patients (cases 1 and 6), all patients developed leukopenia and/or anemia and macrocytosis when dermatosis relapsed. A myelodysplastic syndrome was finally diagnosed in all patients, 2 to 7 years after the onset of their skin symptoms (median, 3.5 years). The subtypes were refractory anemia (cases 2-5), refractory anemia with blasts excess (case 1), and unclassified myelodysplasia (cases 6-9).

Figure 1. Clinical and histological aspects in “initial” lymphocytic Sweet syndrome (case 2: A and C) and in “late” neutrophilic Sweet syndrome (case 1: B and D). A, Disseminated erythematous plaques over the trunk and arms. B, Erythematous plaques with annular configuration. C, Dense lymphocytic infiltrates located in the superficial and middermis (hematoxylin-eosin, original magnification ×10). D, Massive dermal neutrophilic infiltrates without vasculitis (hematoxylin-eosin, original magnification ×20).
Follow-up ranged from 3 to 10 years (median, 5.4 years). High-dose oral prednisone (60-80 mg/d) provided complete remission in all patients. However, the lesions worsened on tapering dosages, and 25 mg/d was necessary to control the disease. No significant benefit was obtained with hydroxychloroquine sulfate (200 mg twice a day), dapsone (100 mg/d), and colchicine (2 mg/d). Six patients were treated with thalidomide (100 mg/d for about 3 months), leading to complete resolution of cutaneous disease in 4 patients. On discontinuation of the medication for mental confusion, deep venous thrombosis, or thrombotic microangiopathy, skin lesions recurred in 3 other patients. In all 9 patients, the myelodysplastic syndrome was controlled by transfusions (3 patients) and erythropoietin therapy (1 patient). There was no progression to acute myeloid leukemia (median follow-up of 30 months). One patient was lost to follow-up, and 1 patient is alive and receiving oral prednisone (20 mg/d). The 7 other patients died from sepsis or vascular complications 3 to 48 months (median, 26.5 months) after myelodysplasia was diagnosed. The duration of cutaneous disease before patients died ranged from 3 to 9 years (median, 5.5 years).

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL FINDINGS

Forty sequential skin biopsy specimens were reviewed. For each patient, 3 to 7 biopsies were performed from 3 to 54 months. Two histological patterns, lymphocytic and neutrophilic, were observed. A review of the patients’ files showed that in 7 cases, the lymphocytic pattern preceded the neutrophilic pattern. These 2 patterns are accordingly named “initial” and “late” Sweet syndrome in our patients (Figure 1B and D). In the initial stage, 20 biopsy specimens from 7 patients (cases 1, 2, 4-6, 8, and 9) showed mononuclear infiltrates consistent with Jessner lymphocytic infiltrate, lupus erythematosus, or drug-related eruption. The infiltrates were moderate to dense, located in the superficial and deep dermis (Figure 2A and B). Superficial edema was observed in most of the cases and epidermis was spared. The infiltrates were composed predominantly of lymphocytes, histiocytes, and atypical mononuclear cells with large, eccentric, elongated, twisted, or kidney-shaped basophilic or vesicular nuclei and eosinophilic cytoplasm. These cells were located around blood vessels or dispersed in edema. Find-
ings from immunohistochemical studies showed that atypical mononuclear cells were CD68 and myeloperoxidase positive (Figure 2C and D) and CD34 negative. CD56 was expressed by a few cells in 1 patient. The lymphocytes were mainly CD3 positive.

In 2 patients (cases 3 and 7), initial biopsy specimens diagnosed as dermal lymphocytic infiltration were not available for review. These patients were referred to one of us for evaluation of lupus erythematosus that did not respond to conventional therapy.

In the late stage, 16 sequential biopsy specimens from 7 patients (cases 1-4, 6, 7, and 9) were examined 2 to 8 years after the onset of disease and showed neutrophilic infiltrates consistent with the diagnosis of Sweet syndrome. The infiltrates were dense to massive, predominantly or exclusively composed of polymorphonuclear neutrophils in 3 cases (cases 3, 7, and 9) and associated with lymphocytes or histiocytes in the other cases. Superficial edema was observed, but there was no vasculitis. In 5 patients (cases 1, 4, 6, 7, and 9), medium-sized mononuclear atypical cells with eccentric, kidney-shaped nuclei, similar to cells observed in initial biopsy specimens, were also found (Figure 3), with the same immunohistochemical characteristics. In 2 patients (cases 5 and 8), no biopsies were performed in subsequent recurrences, and typical neutrophilic infiltrates were not observed.

Vasculitis was observed in 3 patients (cases 1-3), with relapsing polychondritis in 2 of them. In 5 patients (cases 1, 2, 4, 6, and 9), “initial” lymphocytic and “late” neutrophilic patterns were observed. In these patients, the composition of the infiltrates and their respective density in lymphocytes, neutrophils, and atypical mononuclear cells were compared at the onset of skin disease and the onset of myelodysplasia (Figure 4), revealing that neutrophils were the predominating cells at the time of diagnosis of myelodysplasia.

**COMMENT**

Sweet syndrome was described in 1964 by Robert Douglas Sweet as an “acute febrile neutrophilic dermatosis” with the following characteristics: pyrexia; neutrophilia; erythematous painful cutaneous plaques located...
on the upper extremities, head, and neck; a dense dermal infiltrate of neutrophils; and a prompt response to corticosteroid therapy. All 9 patients we studied had criteria proposed for the diagnosis of Sweet syndrome.\textsuperscript{14} They had both major criteria (clinical aspect of lesions and sequentially acquired neutrophilic infiltrate) and 3 minor criteria (fever, associated disease, and response to corticosteroid therapy). Sweet syndrome associated with myelodysplasia tended to be atypical. There is no sex predilection. Cutaneous lesions are more frequently vesicular, bullous, or even necrotic and ulcerative.\textsuperscript{11} It may lack systemic features such as neutrophilia or fever. Our series confirms most of the atypical features reported in Sweet syndrome associated with myelodysplasia. All of our cases were men. They had recurrent flares of a florid eruption with fever. Tender plaques with a dusky red center and well-defined, sharply demarcated borders were localized on the trunk. When cutaneous lesions appeared, some patients had leukopenia or anemia with macrocytosis. However, findings from bone marrow aspiration initially performed in 2 patients were normal. Four patients had relapsing polychondritis 1 to 4 years after the onset of cutaneous lesions at the time of diagnosis of myelodysplasia in 2 patients. Although unexplained, the association of relapsing polychondritis and myelodysplasia in 2 patients. Although unexplained, the association of relapsing polychondritis and myelodysplasia is considered significant.\textsuperscript{15} The only efficient treatment was corticosteroid therapy (prednisone), at 25 mg/d or more. Four patients had improvement with thalidomide therapy. Unfortunately, severe adverse effects were observed, and treatment was discontinued. The most important point was established by studying the results of sequential biopsies. In all 9 patients, the infiltrates were initially lymphocytic, and neutrophils were observed only after a mean of 4 years of evolution (range, 24-96 months). Lymphocytic infiltrates in the initial biopsy specimens were predominantly composed of T lymphocytes along with a CD68-positive monocytic population. In initial biopsy specimens, monocytic cells with kidney shape or vesicular nuclei and eosinophilic cytoplasm were observed, and the most striking finding was their strong reactivity for myeloperoxidase, a finding suggesting that these cells were immature myeloid cells, possibly precursors of neutrophils. In findings from sequential biopsies, 7 patients had neutrophilic infiltrates mixed with the same atypical mononuclear cells.

Sweet syndrome is associated with myelodysplastic syndromes or hematological malignancies in about 20% of cases.\textsuperscript{6} Sweet syndrome occurs at onset or follows a myelodysplasia\textsuperscript{9} and may herald a transformation into acute myeloid leukemia.\textsuperscript{10} The recurrence of Sweet syndrome may coincide with or precede a hematological relapse.\textsuperscript{6} No transformation into acute myeloid leukemia occurred in our cases. However, 7 of the 9 patients died in a follow-up period of 3 to 9 years, confirming the poor prognosis of Sweet syndrome associated with myelodysplasia.\textsuperscript{11}

Interestingly, cutaneous lesions clinically characteristic of Sweet syndrome, but with lymphocytic infiltrate and atypical mononuclear myeloperoxidase-positive cells, preceded myelodysplasia in all 9 cases. Four other cases (4 men aged 56 to 79 years) of atypical Sweet syndrome associated with myelodysplasia have been reported.\textsuperscript{13,18,19} Myelodysplastic syndrome occurred at the onset of cutaneous disease in 2 patients or followed it 3 years later in 1. Skin disease was clinically diagnosed as Sweet syndrome but was initially composed of lymphocytic infiltrates. With the recurrence of cutaneous lesions, dermal neutrophilic infiltrates were later found in 3 patients. In 2 cases, immunohistochemical staining of mononuclear infiltrates showed a mixed population of CD68\textsuperscript{11}, CD4\textsuperscript{14}, and CD8\textsuperscript{11} cells. No more characterization of cells was reported.

In a series of 37 patients with Sweet syndrome who had undergone sequential biopsies, the initial lymphocytic stage was followed by neutrophilic and then histiocytic infiltrates.\textsuperscript{20} Our findings confirm this view. However, an initial stage of lymphocytic infiltration preceding, for many years, neutrophilic infiltrates had never been recorded. Furthermore, in our patients, lymphocytes were accompanied with monocytic cells that strongly reacted to CD68 and myeloperoxidase.

Abundant histiocytes have already been reported in 2 series of 18 and 12 cases of Sweet syndrome.\textsuperscript{21,22} Unfortunately, myeloperoxidase expression was not studied.

In a recent series of 41 patients with Sweet syndrome, an immunoreactivity for CD15, CD45, CD68, and lysozyme was consistent with a monocytic-histiocytic profile.\textsuperscript{23} Moreover, intense myeloperoxidase reactivity was detected in the histiocytic cells. The authors ruled out the possibility of acute or chronic myelogenous leukemia. All patients were treated with oral prednisone or nonsteroidal anti-inflammatory drugs. The cutaneous lesions resolved within a few days and did not recur. The authors concluded that some acute lesions of Sweet syndrome included immature myeloid cells and proposed to name these forms “histiocytoid Sweet syndrome.” This variant of Sweet syndrome, concerning patients with an acute, nonrelapsing disease, without predominantly lymphocytic infiltrates and without myeloid hemopathy, appears to be different from our cases.

In our 9 cases, the concomitant presence of immature myeloid cells and mature polymorphonuclear neutrophils within the same lesion has already been reported.\textsuperscript{12,24,25} The significance of this population of immature neutrophil granulocytes in the skin is still discussed.\textsuperscript{26} They can constitute the incipient presence of a specific leukemic infiltrate and can represent the well-differentiated type of leukemia cutis. When cutaneous lesions are the initial presentation, an overt leukemia appeared a few months later in most patients.\textsuperscript{27} The circulating immature myeloid cells may also be innocent bystanders recruited to the skin through an inflammatory reaction stimulated by the Sweet syndrome. The ability of immature myeloid cell precursors to migrate to the skin in myelogenous leukemia is well known.\textsuperscript{28} Because blast cells recruited in the skin have the ability to differentiate to a morphologically and phenotypically heterogeneous population including mature granulocytes, it can be suggested that immature myeloid cells admixed with neutrophils constitute a specific infiltrate.\textsuperscript{29} The atypical cells of leukemia cutis might also develop into mature neutrophils of Sweet syndrome through therapy-induced differentiation either with G-CSF\textsuperscript{23} or with all-trans retinoic acid.\textsuperscript{24} Finally, neutrophils infiltrating the skin could also be clonally derived.\textsuperscript{25}
These hypotheses do not clarify the mechanism of the lesions we observed. Timing between the onset of cutaneous disease and myelodysplasia is not compatible with recruitment into the skin of leukemic cells not detected in blood or bone marrow. Our patients never received granulocyte colony-stimulating factor. Moreover, we found immature granulocytes with lymphocytic infiltrates in the initial biopsy specimens. We cannot rule out recruitment by dermal lymphocytes cytokines in our cases. The role of T lymphocytes in regulating neutrophilic skin inflammation is well known. CXCL8-producing T cells facilitate skin inflammation. These lymphocytes can promote the attraction of immature granulocytes by the secretion of cytokines such as interleukin 8, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α, which can prolong cell survival, differentiation, and maturation to neutrophils.

In conclusion, in this series of 9 adult men, recurrent Sweet syndrome was initially characterized by lymphocytic infiltrates and atypical mononuclear cells identified as immature granulocytes. It later evolved to neutrophilic infiltrates and was associated with myelodysplasia. All those features may represent the cutaneous component of the dysgranulopoiesis syndrome. Why cutaneous disease appeared 2 to 8 years before myelodysplastic syndrome was identified remains unexplained, but this fact is of practical clinical importance and may help in the early diagnosis of myelodysplasia and management of patients.

Accepted for Publication: March 1, 2006.

Correspondence: Marie-Dominique Vignon-Pennamen, MD, Hôpital Saint-Louis, 1 ave Claude Vellefaux, 75475 Paris CEDEX 10, France (dominique.vignon-pennamen@wanadoo.fr).

Author Contributions: Study concept and design: Vignon-Pennamen, Wallach, Verola, and Janin. Acquisition of data: Vignon-Pennamen, Juillard, Rybojad, and Morel. Analysis and interpretation of data: Vignon-Pennamen, Juillard, Rybojad, Wallach, Daniel, Morel, Verola, and Janin. Drafting of the manuscript: Vignon-Pennamen, Wallach, Morel, and Janin. Critical revision of the manuscript for important intellectual content: Juillard, Rybojad, Wallach, Daniel, Morel, Verola, and Janin. Administrative, technical, and material support: Vignon-Pennamen, Juillard, Rybojad, and Verola.

Financial Disclosure: None reported.

REFERENCES