Histiocytoid Sweet Syndrome

A Dermal Infiltration of Immature Neutrophilic Granulocytes

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Objective: To describe a series of 41 patients with fresh lesions of Sweet syndrome in which the histopathologic study demonstrated an inflammatory infiltrate mostly composed of histiocytoid mononuclear cells.

Design: Histopathologic, immunohistochemical, and cytogenetic studies of the inflammatory infiltrate in a case series of histiocytoid Sweet syndrome.

Setting: University departments of dermatology and a private laboratory of dermatopathology.

Methods: Conventional histopathologic study as well as immunohistochemical investigations were performed using the alkaline phosphatase antialkaline phosphatase technique with a large panel of antibodies. In some cases, fluorescent in situ hybridization studies were performed to investigate the presence of the bcr/abl gene fusion.

Results: Immunohistochemical studies demonstrated that most cells of the infiltrate showed immunoreactivity for CD15, CD43, CD45, CD68, MAC-386, HAM56, and lysozyme, which is consistent with a monocytic-histiocytic immunoprofile. However, intense myeloperoxidase reactivity was detected in most of the cells with histiocytic appearance, which raised the possibility of specific cutaneous involvement by myelogenous leukemia. Nevertheless, cytologic peripheral blood examinations, fluorescent in situ hybridization studies to investigate the bcr/abl gene fusion, and follow-up of the patients, taken all together, ruled out this possibility.

Conclusions: This case series demonstrates that some fresh cutaneous lesions of Sweet syndrome are histopathologically characterized by an infiltrate mostly composed of cells that may be misinterpreted as histiocytes, when in fact they are immature myeloid cells. We named this histopathologic variant histiocytoid Sweet syndrome, which should not be mistaken with leukemia cutis or other inflammatory dermatoses that are histopathologically characterized by histiocytes interstitially arranged between collagen bundles of the dermis.

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A CUTE FEBRILE NEUTROPHILIC dermatosis, also called Sweet syndrome (SS), was first described by Robert Douglas Sweet in 1964. It is a reactive disorder of unknown etiology characterized by painful, erythematous, cutaneous plaques and nodules of rapid onset accompanied by fever, leukocytosis, and neutrophilia. Often, the disease follows a viral infection, especially of the upper respiratory tract, but it has been also described in association with hematologic and visceral malignancies, medications (mostly granulocyte colony-stimulating factor), autoimmune diseases, inflammatory bowel diseases, and pregnancy. Sweet syndrome can be classified into the following 3 subtypes: (1) idiopathic or associated with various inflammatory disorders; (2) associated with hematological malignancies; and (3) associated with solid malignant visceral neoplasms. The first category accounts for most (80%-90%) of the reported cases. Histopathologically, SS is categorized as a neutrophilic dermatosis. The usual histopathologic findings consist of intense edema of the papillary dermis, an underlying bandlike, dense, dermal, inflammatory infiltrate mainly composed of mature neutrophils with leukocytoclasia and no features of vasculitis. In rare instances, however, typical lesions of SS may show histopathologic features of leukocytoclastic vasculitis, although this vasculitis appears to be secondary instead of
primary, and its presence does not exclude a diagnosis of SS.\(^4\)

In the present study we describe a series of 41 patients with SS in which the histopathologic study of fresh lesions demonstrated an inflammatory infiltrate mostly composed of histiocytoid mononuclear cells. Immunohistochemical studies, however, demonstrated that the apparent histiocytic mononuclear cells were in fact immature myeloid cells. However, cytologic studies of the peripheral blood, fluorescent in situ hybridization for the presence of the \textit{bcr/abl} gene fusion, and follow-up of the patients ruled out the possibility of cutaneous involvement by chronic myelogenous leukemia. Therefore, the cutaneous lesions were interpreted as unusual histopathologic variants of SS rather than lesions of leukemia cutis. This case series demonstrates that some patients with fresh lesions of SS are histopathologically characterized by an inflammatory infiltrate mostly composed of cells that may be misinterpreted as histiocytes, when in fact these cells are immature neutrophils. We have named this histopathologic variant of SS \textit{histiocytoid Sweet syndrome}. Histopathologic differential diagnosis should be established with leukemia cutis and other inflammatory conditions characterized by histiocytes interstitially arranged between collagen bundles of the dermis.

### METHODS

Records of 41 patients with typical cutaneous lesions of SS in which histopathologic study demonstrated an infiltrate apparently composed mostly of histiocytes were retrieved from the files of the Departments of Dermatology of Hospital Clínico San Carlos (16 cases), Fundación Jiménez Díaz (4 cases), and Hospital Universitario La Princesa (7 cases), Madrid, Spain, and the Dermatohistopathologisches Gemeinschaftslabor (14 cases), Friedrichshafen, Germany. Clinical information was obtained from the hospital records or laboratory request forms. The following data were recorded, if available, in each patient: age, sex, location of the lesions, duration of the lesions before biopsy, associated diseases, laboratory abnormalities, and treatment. When possible, follow-up information was obtained from the clinical records of the patients (Table 1).

For conventional light microscopy, tissue was fixed in 4% formalin, embedded in paraffin wax, and cut and stained with hematoxylin and eosin. For immunohistochemical studies, representative sections of all cases were examined by the alkaline phosphatase antialkaline phosphatase technique using appropriate positive and negative controls. Automated immunostaining was performed on a BioTek Solutions TechMate (TechMate 500; Biotech Solutions, Dako, Glostrup, Denmark). The antibodies used, their specificity, their source, and dilution are given in Table 2.

In 14 cases (cases 28-41), fluorescent in situ hybridization studies were performed on sections from paraffin-embedded tissue to rule out the presence of the \textit{bcr/abl} gene fusion in the cutaneous lesions, which, if present, would define them as lesions of myelogenous leukemia cutis. For the detection of the \textit{bcr/abl} translocation, a spectrum green and spectrum orange labeled probe was used (Abbott Diagnostics, Wiesbaden, Germany). Fluorescent in situ hybridization was performed on 3-µm sections of formalin-fixed, paraffin-embedded tissue after baking at 65°C for 16 hours, deparaffinization with xylene, and dehydration with ethanol. All tissue sections were pretreated with a 30% solution of oncor (QBiogene, Heidelberg, Germany)pretreatment (powder) solution and digested with proteinase K following the instructions of the suppliers (QBiogene). Digestion times were optimized on a case-by-case basis. After a second dehydration step, the probes were applied to the sections and the covered slides were sealed with rubber cement and heat denatured and hybridized at 37°C for 16 hours. The sections were counterstained with DAPI II (Abbott Diagnostics) in mounting medium (125 ng/mL) and visualized under a Zeiss Axiosplan microscope (Carl Zeiss, Oberkothen, Germany) using an HBO100 lamp and the appropriate filters for the 3 fluorescence dyes. \textit{bcr/abl} Fusion can be detected in interphase nuclei using differentially labeled “single-fusion” locus-specific probes located immediately proximal to the \textit{bcr} breakpoint and immediately distal to the \textit{abl} breakpoint. A nucleus that has a \textit{bcr/abl} rearrangement will in most cases show 1 overlapping \textit{bcr/abl} signal representing the derivative chromosome 22 together with 1 native \textit{bcr} signal and 1 native \textit{abl} signal representing the normal chromosome 22 and normal chromosome 9, respectively. In contrast, a nucleus lacking the 9/22 rearrangement will show 2 native \textit{abl} and 2 native \textit{bcr} probe signals.

Biopsy specimens of 3 patients not included in this series, with conventional histopathologic features of SS (namely, a mostly bandlike, neutrophilic infiltrate involving the superficial dermis), were used for comparison. In each one of these 3 patients, we obtained 2 different biopsy specimens during the same episode of SS, one from the early stage of the lesions (during the first 7 days) and another biopsy from late stage or resolving lesions (lesions with >2 weeks of evolution).

Table 1 summarizes the clinical data of the 41 patients. There were 26 women and 15 men. The age range of the patients was from 29 to 79 years (median, 53 years). There were 6 patients with associated malignancies: chronic monocytic leukemia (case 3), “lymphoma” (no more specific diagnosis could be obtained) (case 21), monoclonal gammapathy of undetermined significance (case 24), renal carcinoma (case 29), breast carcinoma (case 28), chronic B lymphocytic leukemia (case 38), and multiple myeloma (case 39). No other malignancies were disclosed during the follow-up of the patients, which ranged from 12 months to 16 years (mean, 8.2 years). In those cases in which complete clinical data are known (25 cases), the latency interval period between the onset of the lesions and the cutaneous biopsy ranged from 24 hours to 20 days (median, 6.8 days). The most common clinical presentation of the cutaneous lesions consisted of edematous erythematous plaques and nodules (Figure 1). The most common laboratory abnormalities consisted of leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, and elevated serum C-reactive protein levels. In 27 cases (cases 1-27), peripheral blood of the patients during the episode with cutaneous lesions was microscopically studied by an expert hematopathologist, who ruled out the possibility of myelogenous leukemia. Circulating antibodies against neutrophilic cytoplasm antigens were investigated in 8 cases, and they were negative in all cases.

Histopathologically, the epidermis was spared in all but 2 biopsy specimens (cases 12 and 17), which showed areas of spongiosis with some exocytosis of inflammatory cells. All biopsy specimens exhibited moderate to intense edema of the papillary dermis and an underlying dense, bandlike, inflammatory infiltrate involving the
superficial and mid-dermis (Figure 2). In 2 cases (cases 12 and 25), the infiltrate extended to the deeper dermis and the connective tissue septa of the subcutaneous tissue, with the presence of the so-called Miescher's radial granulomas in the thickened septa, which consisted of small collections of histiocytes grouped around a central stellate or banana-shaped clef. In none of the biopsy specimens was there histopathologic evidence of vasculitis. The infiltrate varied in its composition from case to case, but in all cases it was predominantly composed of mononuclear cells, namely the cells with the appearance of monocytes or small histiocytes. Small collections of mature lymphocytes were also present in all biopsy specimens, mostly with a perivascular arrangement. In some biopsy specimens, the collagen bundles of the dermis in the center of the histiocytic aggregates showed resemblance with piecemeal fragmentation, which in addition to the presence of interstitial mucin, resulted in a histopathologic pattern closely resembling that of granuloma annulare. No relationship could be established between the duration of the lesions and the composition of the cellular infiltrate, and numerous histiocytoid cells with a sparse number of neutrophils were seen in all cases, including lesions of 24-hour duration (cases 2 and 12) and lesions with 20 days of evolution (cases 18 and 24).

Table 1. Clinical Data of 41 Patients With Histiocytoid Sweet Syndrome

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Duration of the Lesion Biopsy Specimen, d</th>
<th>Location of the Lesions</th>
<th>Associated Diseases</th>
<th>Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/79 10 Abdomen 16</td>
<td>Chronic monocytic leukemia 5 (DUD)</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>2/M/65 1 Back and shoulder 16</td>
<td></td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>3/M/61 2 Palms 14</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4/F/39 8 Arms and forearms 13</td>
<td></td>
<td></td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>5/F/36 7 Neck, back, and arms 12</td>
<td></td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6/F/52 6 Arms and forearms 11</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>7/M/64 3 Forearm 11</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>8/M/75 ? Shoulders 10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>9/F/55 ? ? 10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>10/F/55 4 Back, shoulders, and thighs 10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11/F/62 8 Back and knee 9</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>12/M/60 1 Dorsum of the hands 9</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>13/F/59 4 Back and thighs 8</td>
<td></td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>14/F/54 5 Back, thighs, and ankles 7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>15/M/50 4 Dorsum of the wrists 7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>16/F/49 4 Arms and shoulders 7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>17/F/60 8 Palms 6</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>18/F/60 20 Palms 7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>19/F/71 7 Dorsum of the hands 6</td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>20/F/43 4 Shoulders, chest, and forearms 7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>21/F/60 5 Palms and soles 5 (DOL)</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>22/F/29 12 Forehead, dorsum of the hands, and elbows 8</td>
<td>Conjunctionitis, eyelid edema</td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>23/F/60 10 Elbows, forearms, palms, knees, and legs 5</td>
<td>Conjunctionitis, erythema nodosum</td>
<td>5</td>
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<td></td>
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<tr>
<td>24/F/70 20 Palms and dorsum of the hands 4</td>
<td>Monoclonal gammopathy of undetermined significance</td>
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<tr>
<td>25/F/64 5 Forearms, dorsum of the hands, and abdomen Diabetes mellitus 2</td>
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<td>2</td>
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<td></td>
</tr>
<tr>
<td>26/F/62 7 Face, elbows, dorsum of the hands and knees Renal carcinoma 2</td>
<td></td>
<td>2</td>
<td></td>
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<tr>
<td>27/F/72 ? Palms and dorsum of the hands Breast carcinoma 2</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/F/75 2 Arm Breast carcinoma 2</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29/F/34 ? Upper back 5</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>30/F/36 ? Upper trunk and arms 10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>31/F/65 ? Upper back 1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>32/F/32 ? Upper and lower back and arms 14</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
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<tr>
<td>33/M/62 ? Upper trunk 1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>34/M/50 ? Upper trunk Colitis ulcerosa, immunosuppression 8</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>35/F/66 ? Arms and legs 7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
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<tr>
<td>36/M/58 ? Disseminated plaques on the whole body Breast carcinoma 7</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>37/F/79 ? Upper back LFU</td>
<td></td>
<td></td>
<td>LFU</td>
<td></td>
</tr>
<tr>
<td>38/F/49 ? Upper chest and back and arms B-Chronic lymphocytic leukemia 5</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>39/M/71 ? Trunk Multiple myeloma 1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
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<tr>
<td>40/M/40 ? Trunk 1</td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>41/M/45 ? ? 1</td>
<td></td>
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<td>1</td>
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</table>

Abbreviations: DOL, died of “lymphoma” (no more specific diagnosis could be obtained); DUD, died of unrelated disease; LFU, lost to follow-up; ?, unknown.
Immunohistochemical studies demonstrated that most cells of the infiltrate showed cytoplasmic immunoreactivity for CD15, CD43, CD45 (LCA), CD68, MAC-386, HAM56, and lysozyme (Figure 3), which was interpreted as immunophenotypically indicative of the monocytic-histiocytic lineage of the cells. As for CD68 positivity, the number of cells of the dermal infiltrate that expressed immunoreactivity for KP1 antibody was much higher than those reacting with PGM1. However, the most striking immunohistochemical finding was the intense myeloperoxidase immunoreactivity of most cells with histiocytic appearance (Figure 4). Most of these cells were also positive for CD66abc. Neutrophil elastase immunoreactivity was only detected in mature neutrophils. The lymphocytes were mainly T cells as shown by their positivity for CD3 and CD45RO. Only a few CD20-positive B cells were present.

Fluorescent in situ hybridization studies failed to demonstrate the presence of the bcr/abl gene fusion in all studied cases (Figure 5). The histopathologic study of the biopsy specimens from the 3 cases with late-stage lesions of conventional SS (those not included in this series with a mostly neutrophilic infiltrate in early lesions) showed an inflammatory infiltrate mostly composed of histiocytes, many of them showing prominent phagocytosis of nuclear dust of neutrophils within their cytoplasm. These histiocytes with phagocytosed nuclear material expressed immunoreactivity for CD68 (KP1 and PGM1), HAM-56, MAC-386, and lysozyme, but they did not immunostain for myeloperoxidase (data not shown).

Thirty-nine patients were treated with 30 to 60 mg/d of oral prednisone, and the cutaneous lesions resolved within few days. One patient (case 22) received 1500 mg/d of acetaminophen and another patient (case 25)
was treated with 400 mg/d of aceclofenac, also with resolution of the cutaneous lesions within few days.

**COMMENT**

Histopathologically, a dense, bandlike infiltrate of mature neutrophils in the upper and mid-dermis is the most characteristic finding in lesions of SS. Leukocytoclasis with the formation of nuclear dust is usually present, but there is no true leukocytoclastic vasculitis, although recent reports described secondary vasculitis as an epiphrenomenon in typical lesions of SS. In a histopathologic study carried out on a large series of cases, Jordaan described a diversity of the dermal infiltrate in lesions of SS and recognized lymphocytic, neutrophilic, and histiocytic stages. According to this study, the lymphocytic stage might be first, followed by a neutrophilic and eventually a histiocytic stage. We do not share this view because in our experience the usual histopathologic findings in early lesions of SS consist of a predominantly neutrophilic infiltrate, whereas histiocytes are more abundant in late stages, and we did not see the earliest lymphocytic stage as described by Jordaan. Our findings do not support the observations described by Jordaan because in all our cases, regardless of the duration of the lesions, the infiltrate was mostly composed of monocytic-histiocytic cells with kidney-shaped or vesicular nuclei, inconspicuous nucleoli, and sparse cytoplasm, namely cells that showed a monocytic-histiocytic appearance. Furthermore, these cells expressed the pan-histiocytic markers CD68, HAM-56, MAC-386, and lysozyme. Concerning CD68 immunoreactivity, most of the cells expressed cytoplasmic reactivity with KP1, which stains cells of the monocyte-macrophage lineage as well as mature and immature neutrophilic granulocytes, but only a small proportion of these cells coexpressed immunoreactivity with PGM1, which selectively stains histiocytes but not neutrophils. The appearance of myeloperoxidase precedes that of neutrophil elastase during myeloid cell differentiation. The cases described in this series demonstrate that some lesions of SS may show an infiltrate mostly composed of immature myeloperoxidase-positive myeloid cells. Probably these lesions result from the release of immature myeloid cells from the bone marrow in early acute stages of...
the disease, and these immature myeloid cells are replaced by more mature neutrophilic granulocytes in later stages of evolution.

Histopathologically, the cytologic characteristics of the cells involving the dermis, in addition to their immunohistochemical profile, foremost their strong immunoreactivity for myeloperoxidase, raised also the possibility of specific cutaneous infiltration by myelogenous leukemia. Specific cutaneous lesions of patients with acute or chronic myelogenous leukemia show nodular dermal infiltrates of medium-sized, round to oval, mononuclear cells with slightly eosinophilic cytoplasm and distinct, sometimes indented, kidney-shaped basophilic nuclei. The immunoprofile of the leukemic cells involving the dermis is also similar to that of the mononuclear histiocytoid cells in our cases of SS because neoplastic cells of myelogenous leukemia express immunoreactivity for lysozyme, myeloperoxidase, CD43, CD45, and CD68. However, the cytologic examination of peripheral blood performed in 27 patients failed to demonstrate circulating, immature, dysplastic myeloid cells, and the follow-up of all our patients ruled out the possibility of acute or chronic myelogenous leukemia. Another possibility would be that aleukemic myeloid leukemia cutis, a term that has been used to designate rare cases of myeloid leukemia cutis in which specific cutaneous lesions antedated by months or even years the detection of leukemia cells in the blood or bone marrow. However, chronic myelogenous leukemia is consistently associated with presence of the bcr/abl fusion gene, resulting from the translocation involving the bcr gene on chromosome 22 and the abl gene on chromosome 9, which in most cases can also be identified as Philadelphia chromosome in traditional cytogenetic analysis. Although the absence of bcr/abl fusion gene in the cells of the dermal infiltrate of all studied cases of our series is not an absolutely discriminatory technique to rule out myelogenous leukemia, the negative results of this fusion gene investigation, in addition to the absence of immature myeloid cells in the cytologic studies of the peripheral blood of 27 of our patients and the follow-up of all patients (in many of them for several years), militate against the possibility of aleukemic leukemia cutis.

The histopathologic findings in our 3 cases of late-stage lesions of conventional SS (cases with predominantly neutrophilic infiltrate in early stages) support the notion that the cases that we are describing in the present study as histiocytoid SS do not represent late-stage lesions of SS. Authentic late-stage lesions of SS are histopathologically characterized by a histiocytic infiltrate, with many of the histiocytes showing prominent phagocytosis of nuclear dust of neutrophils within their cytoplasm. These histiocytes expressed immunoreactivity for histiocytic markers but not for myeloperoxidase. In our cases of histiocytoid SS, there was prominent edema of the papillary dermis such as that seen in early lesions;

![Figure 3. Immunohistochemical findings of histiocytoid Sweet syndrome (case 13). A, Most of the cells of the dermal infiltrate expressed immunoreactivity for MAC387. B, Strong immunoeexpression for lysozyme. C, Most of the cells of the infiltrate expressed immunoreactivity for KP1. D, However, only a small proportion of these cells expressed immunoreactivity for PGM1. (Immunoperoxidase stain used for all panels, original magnification ×10; insets, high-power magnification [original magnification ×600] of each immunostaining result.)](image-url)
the infiltrate was mostly composed of immature myeloid cells rather than histiocytes; and cytophagocytosis of nuclear dust was not seen. Furthermore, the duration of the lesions in some cases was only 24 hours, and their clinical appearance consisted of edematous plaques such as those seen in early stages of SS. All these clinicopathologic features militate against the interpretation of these lesions of histiocytoid SS as late-stage lesions.

A possible explanation for the histopathologic findings in the patients of this series of histiocytoid SS might be the influence of the serum levels of granulocyte colony-stimulating factor (G-CSF). Recent studies have demonstrated that the exogenous administration of G-CSF may induce cutaneous lesions of SS12 and that G-CSF levels in peripheral blood are significantly higher in patients with active SS vs patients with inactive stage.13 The G-CSF is a growth factor that promotes the production and maturation of myeloid cells and decreases the neutrophil apoptosis,13 and it might be possible that the patients with histiocytoid SS described in the present series had low levels of G-CSF in peripheral blood, resulting in a dysfunction in the neutrophil maturation or apoptosis. Unfortunately, this possible pathogenesis must remain speculative because we did not determine the serum levels of G-CSF in our patients.

Abundant histiocytes have been described rarely in SS. Only Delabie et al14 reported 18 patients with typical lesions of SS in which the dermal infiltrate contained numerous histiocytes. Because of the small size of these histiocytes, the authors stressed that at first sight these cells appeared to mimic neutrophils. The immunophenotype of these cells, however, was consistent with histiocytes because they expressed pan-histiocytic markers CD68 (KP1), CD14, α1-antichymotrypsin, and factor XIIIa, but they did not express neutrophil elastase. Unfortunately, Delabie et al14 did not study myeloperoxidase expression in their cases. Bourke et al15 investigated CD3, CD20, HLA-DR, CD68, CD11b, and neutrophil elastase expression of the dermal infiltrate in 12 cases of SS. The authors described that CD68 (PGM1)-positive histiocytes were present in increased numbers in all biopsy specimens, although neutrophils outnumbered histiocytes in all cases. The authors, however, concluded that histiocytes might play some pathophysiologic role in SS. They omitted myeloperoxidase stains in their investigations. Finally, Pileri et al16 have reported myeloperoxidase expression by so-called histiocytes in Kikuchi and Kikuchi-like lymphadenopathy. These investigators reported that the polyclonal antibody antimyeloperoxidase stained between 25% and 75% of the CD68 (PGM1)-positive cells in the lymph nodes of patients with Kikuchi and Kikuchi-like lymphadenopathy, and they concluded that these CD68-myeloperoxidase–positive cells corresponded to most nonphagocytosing mononuclear cells and a small proportion of crescentic macrophages and phagocytosing histiocytes. In contrast, the morphologically recog-

Figure 4. Immunohistochemical findings of histiocytoid Sweet syndrome (case 13). A, Strong immunoreactivity for myeloperoxidase in most of the cells of the dermal infiltrate. B, Only a few cells expressed immunoreactivity for neutrophil elastase. C, Many of the cells of the infiltrate expressed CD66abce. D, Sparse number of cells showed immunoreexpression for T-cell intracellular antigen 1. (Immunoperoxidase stain used for all panels, original magnification ×10; inset, high-power magnification [original magnification ×600] of each immunostaining result.)
nizable plasmacytoid monocytes, the characteristic cells of Kikuchi disease, turned out to be myeloperoxidase negative. Pileri et al concluded that the CD68-myeloperoxidase–positive cells corresponded to peripheral blood monocytes accumulating in the lymph node. In our view, the CD68-myeloperoxidase–positive cells described by Pileri et al might also primarily correspond to immature granulocytes, such as those described in our series of patients with histiocytoid Sweet syndrome, rather than to peripheral blood monocytes.

We want to point out that because of their small size, these histiocytoid cells in lesions of SS may easily be misinterpreted as neutrophils. Furthermore, there are some pitfalls in differentiating neutrophils from monocytes/histiocytes by standard immunohistochemical analysis, because neutrophils and monocytes/histiocytes share a series of immunohistochemical markers including some of the widely considered “specific” histiocytic markers that may also stain neutrophils. There are only a limited number of markers that are specific for histiocytes (Table 3). Thus, it seems paramount to study by means of specific immunophenotyping those cases of SS with an infiltrate that seemingly is mostly composed of small histiocytes.

Histopathologic differential diagnosis of histiocytoid SS includes those dermatoses characterized by a dermal infiltrate mostly composed of histiocytes. Interstitial or “incomplete” type of granuloma annulare is histopathologically characterized by histiocytes interstitially arranged between the collagen bundles of the dermis with some mucin deposition. Interstitial granulomatous dermatitis with arthritis is a rare condition, which appeared in patients with long-standing severe rheumatoid arthritis, characterized clinically by red or skin-

Table 3. Discriminatory Antibodies and Immunophenotypes Used for Differentiating Granulocytes From Monocytes/Histiocytes

<table>
<thead>
<tr>
<th>Immunohistochemical Marker</th>
<th>Neutrophils and Monocytes/Histiocytes</th>
<th>Only Monocytes/Histiocytes</th>
<th>Only Neutrophils and Myeloid Cells</th>
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</thead>
<tbody>
<tr>
<td>CD15</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD43</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD45 (LCA)</td>
<td>+</td>
<td></td>
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<tr>
<td>CD68/Baex</td>
<td>+</td>
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<tr>
<td>CD68/KP1</td>
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<tr>
<td>CD68/PGM1</td>
<td>+</td>
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<tr>
<td>Lysozyme</td>
<td>+</td>
<td></td>
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<tr>
<td>MAC387</td>
<td>+</td>
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<tr>
<td>MPO</td>
<td>+</td>
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<tr>
<td>NE</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA-1</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>NASD (Leder stain)</td>
<td>+</td>
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</table>

Abbreviations: MPO, myeloperoxidase; NASD, naphthol AS-D chloroacetate esterase; NE, neutrophilic elastase; TIA-1, T-cell intracellular antigen 1.
cytes have large, pleomorphic nuclei and mitotic figures. Neutrophils and eosinophils, and many of the histio-
matory infiltrate of histiocytes intermingled with some.

Basophilic collagen. In contrast to the histiocytoid SS, how-

ever, the lesions of interstitial granulomatous dermati-
tis with arthritis show a denser, “bottom-heavy,” inflam-
matory infiltrate that in some

tis with arthritis show a denser, “bottom-heavy,” inflam-
matory infiltrate that in some.

by the bone marrow in early acute stages of the disease,

strate that they are immature neutrophils. These lesions

when in fact immunohistochemical studies demon-

lar areas of the extremities. Histopathologically, these

papules show a diffuse interstitial inflammatory infil-

mal areas of the extremities. Histopathologically, these

mately composed of histiocytes and a few neutro-

phils that, in contrast with histiocytoid SS, involve the

full thickness of the dermis without a “top-heavy” pat-

tern. Furthermore, our patients had no history of metho-

trexate intake.

In summary, this case series demonstrates that some

fresh lesions in patients with SS are histopathologically

characterized by an inflammatory infiltrate mostly com-

posed of cells that may be misinterpreted as histiocytes,

when in fact immunohistochemical studies demon-

strate that they are immature neutrophils. These lesions

probably result from the release of immature myeloid cells

by the bone marrow in early acute stages of the disease,

and these immature myeloid cells are replaced by ma-

ture neutrophils in later stages of evolution. The lesions

show a benign biological behavior and respond promptly
to low doses of oral corticosteroids or nonsteroidal anti-

inflammatory drugs.

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REFERENCES

2. Chun HL, Lee YS, Kuo TT. Sweet’s syndrome: clinicopathologic study in eleven


Sweet syndrome: a clinicopathologic study of 28 biopsy specimens from 21

4. Cohen PR. Skin lesions of Sweet syndrome and its dorsal hand variant contain

vasculitis: an oxymoron or an epiphenomenon? Arch Dermatol. 2002;138:

400-403.
5. Jordaan HF. Acute febrile neutrophilic dermatosis: a histopathological study of

37 patients and a review of the literature. Am J Dermatopathol. 1989;11:99-

111.
6. Wong KC, Chan JKC. Anthymeloperoxidase: antibody of choice for labeling of my-


2:65-68.

infiltrates in patients with myelogenous leukemia: a clinicopathologic study of


40:966-978.
8. Heskel NS, White CR, Fryberger S, Neerhout RC, Spraker M, Hanifin JM. Aleu-

kemic leukemia cutis: juvenile chronic granulocytic leukemia presenting with figu-

9. Hansen RM, Barnett J, Hanson G, Klehm D, Schneider T, Ash R. Aleukemic leu-


11. Anastasi J, Vardiman JW. Chronic myelogenous leukemia and chronic myelo-

proliferative diseases. In: Knowles DM, ed. Neoplastic Hematopathology. Phila-

delphia, PA: Lippincott Williams & Wilkins; 2002:1745.
12. Prevost-Blank PL, Shwyader TA. Sweet’s syndrome secondary to granulocyte
stimulating factor levels in patients with active phase of Sweet syndrome and

patients with active Behget disease: implication in neutrophil apoptosis dysfunction.
Arch Dermatol. 2004;140:570-574.
14. Delabie J, de Wolf-Peeters C, Morren M, Marien K, Roskams T, Desmet V. His-

study of the dermal infiltrate and epidermal staining for interleukin 1 in 12 cases


Kikuchi’s and Kikuchi-like lymphadenopathy. Am J Pathol. 2001;159:915-

924.

18. Dykman CJ, Galens GJ, Good AE. Linear subcutaneous bands in rheumatoid ar-


134-140.
19. Gottlieb GJ, Duve RS, Ackerman AB. Interstitial granulomatous dermatitis with
cutaneous cords and arthritis: linear subcutaneous bands in rheumatoid arthri-
20. Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neu-

trophilic and granulomatous dermatitis in patients with collagen vascular disease.
Arch Dermatol. 1994;130:1278-1283.
22. Ackerman AB, Chongchitnant N, Sanchez J, et al. Interstitial granulomatous der-
matitis with arthritis. In: Histologic Diagnosis of Inflammatory Skin Disease: An
Algorithmic Method Based on Pattern Analysis. 2nd ed. Baltimore, Md: Williams
& Wilkins; 1997:459-460.
23. Goerttler E, Kutzner H, Peter HH, Requena L. Methotrexate-induced papular erup-
tion in patients with rheumatic diseases: a distinctive adverse cutaneous reaction
produced by methotrexate in patients with collagen vascular diseases. J Am Acad