Neonatal Sweet Syndrome: A Potential Marker of Serious Systemic Illness

abstract

Sweet syndrome is an inflammatory disease characterized by fever and painful erythematous plaques with a dermal neutrophilic infiltrate. It is most common in adults, where it is often parainflammatory or paraneoplastic, but is rare in children. We describe 3 cases of neonatal Sweet syndrome, including 1 patient who had myelodysplastic syndrome and immunodeficiency, the first report of a premalignancy underlyng infantile Sweet syndrome. We reviewed the literature on patients presenting with neutrophilic dermatosis in the first 6 months of life. Of 20 cases, 6 had a probable viral etiology, 4 primary immunodeficiencies, 3 neonatal lupus syndrome, 1 gastrointestinal involvement, 1 HIV, and 5 probable genetic cases. Three of these had chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome, caused by mutations in the PSMB8 gene. Most children who presented within the first 6 weeks of life had either a serious underlying condition, such as primary immunodeficiency, or a genetic Sweet syndrome, with 2 fatalities among this latter group. The outcome of postinfective cases was good. Extracutaneous involvement was unusual, whereas postinflammatory scarring and cutis laxa occurred in a minority of patients. In conclusion, Sweet syndrome in the neonatal period often heralds a serious underlying disorder and requires thorough investigation. Pediatrics 2012;129:e1353–e1359

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KEY WORDS
Sweet syndrome, neutrophilic dermatosis, myelodysplastic syndrome, neonatal, primary immunodeficiency, chronic granulomatous disease

ABBREVIATIONS
CANDLE—chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
Ig—immunoglobulin
JMML—juvenile myelomonocytic leukemia
MMF—mycophenolate mofetil
NLE—neonatal lupus erythematosus

All of the authors named on this article have made substantive intellectual contributions to the study, and meet the criteria for inclusion as authors.

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Sweet syndrome is a neutrophilic dermatosis characterized by fever, tender erythematous plaques, and peripheral blood neutrophilia. Skin biopsy shows a dense neutrophilic infiltrate with absence of vasculitis. It is commonly a secondary process and has been associated with inflammatory bowel disease, hematologic and solid tumor malignancies, immunodeficiency and certain drugs, and as a postinfectious phenomenon. The cutaneous outcome may vary, with some patients having no residual defect, whereas others demonstrate scarring or postinflammatory acquired cutis laxa. Pediatric Sweet syndrome is rare, accounting for 5% to 8% of cases, and neonatal presentations are even rarer. We present 3 cases of neonatal-onset Sweet syndrome associated with other systemic manifestations, including the first reported case of Sweet syndrome in association with combined myelodysplastic syndrome and B-cell immunodeficiency. We review the literature on Sweet syndrome presenting in the first 6 months of life.

METHODS
A search was performed by using Medline and PubMed, including the following search terms: “Sweet’s syndrome,” “neutrophilic dermatosis,” “neonate,” “neonatal,” “infant,” and “child.” We omitted well-defined neutrophilic entities, including neutrophilic figurate erythema of infancy.

CASE 1
A boy presented soon after birth with numerous sterile skin pustules, which remitted and relapsed until 8 weeks, when a number of lesions on his face and neck increased in size to become firm, edematous red “bulls-eye” plaques (Fig 1A). Biopsy revealed numerous neutrophils in the dermis with associated edema but no vasculitis (Fig 1B), and with an associated peripheral blood neutrophilia he was diagnosed with Sweet syndrome. His skin improved over a week; however, he was left with significant cutis laxa (Fig 1C).

At 3 months of age he developed hematemesis, with biopsies of the upper gastrointestinal tract demonstrating a neutrophilic infiltrate suggestive of Sweet syndrome. At 4 months of age he developed hypertension and renal ultrasound revealed a 1.7 × 1.8 × 0.9-cm mass in the bladder. Fine-needle biopsy showed clumps of neutrophils with occasional eosinophils. Skin and gastrointestinal symptoms responded to prednisolone at 1 mg/kg per day, but he continued to have slow growth and at the age of 6 years of age was finally diagnosed with chronic granulomatous disease after an episode of invasive aspergillosis.

CASE 2
An otherwise well 5-week-old girl presented to the emergency department with fever and multiple sterile crusted erythematous plaques and pustules on the face, neck, and limbs (Fig 2). She had a neutrophilia and skin biopsy revealed a dermal neutrophilic infiltrate with no evidence of vasculitis, consistent with Sweet syndrome. She responded to oral prednisolone at a dose of 1 mg/kg daily. During her admission, she developed diarrhea and a red plaque on the left labia majora, which enlarged, ulcerated, and was found to connect with a rectal fistula. This persisted for 2 years, along with anal fissures and perianal tags; however, they have now settled, and at 5 years she is symptom-free. There is a family history of Crohn disease; however, upper and lower bowel biopsies showed only non-specific changes, although monitoring will continue, as perineal lesions may precede other symptoms of inflammatory bowel disease by many years.

CASE 3
A 14-month-old boy presented shortly after birth with erythematous plaques and nodules over the head, limbs, scrotum, and thorax, which developed into deep ulcerative and scarring lesions (Fig 3A). Skin biopsy demonstrated a dense neutrophilic infiltrate in keeping with Sweet syndrome (Fig 3B). He also had fever, hepatosplenomegaly, anemia, thrombocytopenia, neutrophilia and monocytosis, with bone marrow aspirate showing trilineage dysplasia (Fig 3C). He had severe hypogammaglobulinemia with low immunoglobulin (Ig)G, absent IgA and IgM, and <1% peripheral blood B-cells with reduced bone marrow B-cells (CD19+, CD10+, CD34−). T-cell/natural killer cell function was
normal, as was Bruton tyrosine kinase gene mutation analysis. He has been treated with immunoglobulin replacement, which did not benefit his skin, and unfortunately suffered involvement of other organs, including recurrent non-infective epiglottitis; perforated bowel

associated with a neutrophilic infiltrate in the deep muscle layer; neurodevelopmental delay associated with microcephaly, occasional seizures, and computed tomography scan showing bilateral basal ganglia changes, thought to reflect neutrophilic infiltrates.

A diagnosis of juvenile myelomonocytic leukemia (JMML) was considered; however, no clonal cytogenetic abnormality (eg, monosomy 7) or somatic mutation was identified, which is present in ~90% of cases of JMML, whereas myeloid progenitors failed to demonstrate granulocyte-macrophage colony-stimulating factor sensitivity, and there was no growth on JMML colony assays. He was treated with low-dose chemotherapy, but developed profound pancytopenia. After observation and repeat bone marrow biopsy, it was felt that the most likely explanation for his presentation was a primary myelodysplastic syndrome with associated refractory anemia.

Prednisolone (2 mg/kg per day) brought the rash under control, but with relapse when the dose was reduced. He trialed a number of steroid-sparing agents, finally responding to mycophenolate mofetil (MMF), which also happily controlled disease in his other organs. In fact, after more than a year of transfusion dependency he also experienced partial remission of his myelodysplastic syndrome, and there are signs of his immunodeficiency improving with a reduced requirement for immunoglobulin replacement.

RESULTS OF THE LITERATURE REVIEW

Literature review identified 17 other children presenting while younger than 6 months, who might fit the diagnosis of Sweet syndrome (Table 1). Of the 20 cases, including those presented here, 6 had a presumed viral etiology with a range of antecedent symptoms including rhinorrhea, diarrhea, aseptic meningitis, and parotitis. These children presented on average later, usually between 3 and 6 months of age, and overall had more positive outcomes. Two had had antibiotics before developing the rash, which may have played a role in etiology. There were 3 cases of neonatal lupus erythematosus (NLE) presenting with neutrophilic dermatosis, which were again self-limited with a positive outcome. Four children had a primary immunodeficiency, including 2 presented here, 1 other case of humoral immunodeficiency, and 1 autosomal recessive chronic granulomatous disease. In the 2 cases of humoral immunodeficiency, the rash was protracted and refractory to treatment. There was 1 case of immunodeficiency secondary to HIV infection. Finally, 5 children had presumed genetic causes, 2 of whom were brothers with limited reported extracutaneous symptoms, although 1 of these children died at age 4 years from pulmonary hypertension. Three other possible genetic cases came from an initial report of 4 children with what was presented as a new, probably monogenic condition of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, which is caused by mutations in the PSMB8 gene. The sibling of one of these children, who had a similar disease, was not included, as she was not reported as presenting in the first 6 months; however, importantly, she died at age 14 and therefore this association must be considered as carrying a potentially poorer prognosis. Of note, the CANDLE syndrome biopsy includes a significant CD68-positive macrophage infiltrate, which may assist diagnostically.

Notably, other than the patients with NLE, most children presenting by 6 weeks of age had a serious systemic illness or genetic diagnosis. Other than the cases of CANDLE syndrome, extracutaneous Sweet syndrome was rare.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Presentation</th>
<th>Sex</th>
<th>Other Symptoms/Findings</th>
<th>Underlying Diagnosis</th>
<th>Investigative Findings</th>
<th>Extracutaneous Sweet Syndrome</th>
<th>Postinflammatory Skin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 d</td>
<td>Male</td>
<td>None given</td>
<td>NLE&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Anti-Ro (SSA); less intense neutrophilic infiltrate</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>2</td>
<td>1 d</td>
<td>Male</td>
<td>Hematemesis/melena, Hypertension</td>
<td>Chronic granulomatous disease, Case 1</td>
<td>Initial neutrophilic GI infiltrate with subsequent eosinophilic infiltrate</td>
<td>(1) Esophagitis, (2) Bladder mass</td>
<td>Cuts laxa</td>
<td>Ongoing enteropathy and FTT</td>
</tr>
<tr>
<td>3</td>
<td>1 d</td>
<td>Male</td>
<td>Hepatosplenomegaly, Developmental Delay, Microcephaly, Respiratory distress, Acute abdomen</td>
<td>(1) Myelodysplastic syndrome, (2) B-cell immunodeficiency, Case 3</td>
<td>Severe humoral immunodeficiency, Pancreptopenia</td>
<td>(1)Epiglottitis, (2) Enteropathy, (3) Neurologic</td>
<td>Scarring</td>
<td>Stable on immunosuppression</td>
</tr>
<tr>
<td>4</td>
<td>1 d</td>
<td>Male</td>
<td>Recurrent chest infections and bronchiectasis</td>
<td>Common variable Immunodeficiency (Almost certainly monogenic undiagnosed PID)&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>low IgG/ absent IgM/ absent vaccine antibody responses</td>
<td>No</td>
<td>Normal</td>
<td>Skin lesions into adult life with CVID and bronchiectasis</td>
</tr>
<tr>
<td>5</td>
<td>5 d</td>
<td>Female</td>
<td>Fever/tachycardia</td>
<td>? NLE, ? Strep infection&lt;sup&gt;14&lt;/sup&gt;</td>
<td>(1) Anti-Ro, (2) Group A streptococcus B/culture</td>
<td>No</td>
<td>Normal</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>6</td>
<td>10 d</td>
<td>Male</td>
<td>Siblings of 6</td>
<td>Genetic Sweets syndrome&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Not recorded</td>
<td>None</td>
<td>Normal</td>
<td>Death @ 4 y from Pulm hypertension</td>
</tr>
<tr>
<td>7</td>
<td>15 d</td>
<td>Male</td>
<td>Siblings of 5</td>
<td>Genetic Sweets syndrome&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Essentially normal bloods</td>
<td>None</td>
<td>Normal</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>1 mo</td>
<td>Male</td>
<td>Annular skin lesions, fever, lip/eyelid swell, saddle nose, ear inflammation, aseptic meningitis, FTT, basal ganglia calcification, hepatosplenomegaly, lipodystrophy</td>
<td>CANDLE syndrome&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Multisystem disease</td>
<td>Normal</td>
<td>Ongoing inflammation age 13</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5 wk</td>
<td>Female</td>
<td>Perianal lesions</td>
<td>Suggestive of Crohn disease, Case 2</td>
<td>Endoscopies not indicative of IBD</td>
<td>Normal</td>
<td>Persistent perianal involvement</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5 wk</td>
<td>Female</td>
<td>Annular skin lesions, fever, lip and eyelid swelling, FTT, bloody stools, vomiting/abdominal pain, hepatomegaly, lipodystrophy</td>
<td>CANDLE syndrome&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Multisystem disease</td>
<td>Normal</td>
<td>Ongoing inflammation (older sister died of same disease aged 14)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>6 wk</td>
<td>Female</td>
<td>None given</td>
<td>NLE&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Anti-Ro (SSA) positive, less intense neutrophilic infiltrate</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>12</td>
<td>7 wk</td>
<td>Male</td>
<td>Antecedent URTI, otitis media, and aseptic meningitis</td>
<td>Probable viral infection&lt;sup&gt;19&lt;/sup&gt;</td>
<td>CSF lymphocytosis, Viral studies negative</td>
<td>No</td>
<td>Not reported</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>13</td>
<td>10 wk</td>
<td>Male</td>
<td>Diarrhea, mouth ulcers present at diagnosis</td>
<td>Probable viral infection&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Normal</td>
<td>Complete recovery</td>
<td></td>
</tr>
</tbody>
</table>
with only 1 case of neutrophilic arthritis reported before the current cases. Of 14 children where information is available, 10 had normal postinflammatory skin, 2 had cutis laxa, and 2 had scarring, including 1 each of the patients presented here.

DISCUSSION
Pediatric Sweet syndrome is a rare condition with a previous literature review identifying 66 cases,13,14 58% associated with chronic diseases. 14 Approximately one-third of these are "parainflammatory" with underlying conditions, such as arthritis, osteomyelitis, and polyarteritis, whereas one-fourth are "paraneoplastic." Secondarily associated with acute myeloid or lymphoblastic leukemia, chronic myelogenous leukemia, Fanconi anemia, and aplastic anemia. A number of patients also have immunodeficiencies, such as chronic granulomatous disease, primary immunodeficiency diseases, Sjögren syndrome antigen A, and primary immunodeficiencies. Extracutaneous Sweet syndrome is rare in children14; however, postinflammatory skin changes, including acquired cutis laxa and postinflammatory scarring, are seen in 30% of cases.14

This is the first review to focus specifically on Sweet syndrome in early infancy, identifying 20 cases presenting in the first 6 months. We noted an increased frequency of potentially monogenic conditions (eg, familial Sweet syndrome, CANDLE syndrome, or primary immunodeficiency), especially among those patients presenting in the first 6 weeks of life. As children get older at presentation, they have more antecedent viral symptoms and parainflammatory skin changes, and the prognosis appears better. The disease also more likely to go into remission and the disease course is more benign. The review identified 66 cases, 13,14 58% associated with chronic diseases. 14 Approximately one-third of these are "parainflammatory" with underlying conditions, such as arthritis, osteomyelitis, and polyarteritis, whereas one-fourth are "paraneoplastic." Secondarily associated with acute myeloid or lymphoblastic leukemia, chronic myelogenous leukemia, Fanconi anemia, and aplastic anemia. A number of patients also have immunodeficiencies, such as chronic granulomatous disease, primary immunodeficiency diseases, Sjögren syndrome antigen A, and primary immunodeficiencies. Extracutaneous Sweet syndrome is rare in children14; however, postinflammatory skin changes, including acquired cutis laxa and postinflammatory scarring, are seen in 30% of cases.14

### TABLE 1

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<th>Patient</th>
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<th>Postinflammatory Skin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>10 wk</td>
<td>Male</td>
<td>Fever</td>
<td>AR chronic granulomatous disease26</td>
<td>Abnormal NBT</td>
<td>No</td>
<td>Cutis laxa</td>
<td>Complete recovery of Sweet syndrome</td>
</tr>
<tr>
<td>15</td>
<td>4 mo</td>
<td>Male</td>
<td>Fever and conjunctivitis c. 9 d before treated with ceftriaxone Streptococcus aureus septicemia</td>
<td>? viral infection, ? staph infection,17 ? antibiotic related</td>
<td>Normal immune screen including NBT</td>
<td>Aseptic neutrophilic arthritis age 8 mo</td>
<td>Normal</td>
<td>Well at 18 mo</td>
</tr>
<tr>
<td>16</td>
<td>3 mo</td>
<td>Female</td>
<td>Antecedent URTI before first episode</td>
<td>Probable viral infection21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4 mo</td>
<td>Male</td>
<td>Fever, respiratory distress</td>
<td>HIV5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4 mo</td>
<td>Female</td>
<td>Fever, otitis media, respiratory distress, amoxyl 10 d prior</td>
<td>? viral infection, ? antibiotic related18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>6 mo</td>
<td>Female</td>
<td>Annular skin lesions, fever, lip and eyelid swelling, FTT, arthralgia, conjunctivitis lipodystrophy</td>
<td>CANDLE syndrome28</td>
<td></td>
<td>Multisystem disease</td>
<td>Normal</td>
<td>Ongoing inflammation</td>
</tr>
<tr>
<td>20</td>
<td>6 mo</td>
<td>Male</td>
<td>URTI and recent epidemic parotitis</td>
<td>Probable viral infection22</td>
<td></td>
<td>No</td>
<td>Scarring</td>
<td>Gradual regression of lesions</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; CVID, common variable immune deficiency; FTT, failure to thrive; IBD, inflammatory bowel disease; NBT, nitroblue tetrazolium test; PID, primary immunodeficiency diseases; SSA, Sjögren syndrome antigen A; URTI, upper respiratory tract infection.
Sweet syndrome in association with either malignancy or premalignancy. That case is also important for the use of MMF, which, although it has been successfully used in the treatment of myelodysplastic syndrome, this is the first report of MMF being successfully used in the treatment of Sweet syndrome at any age.

In working up the diagnosis of Sweet syndrome in early infancy, we advise a broad immunodeficiency screen, including neutrophil function and antibody testing. NLE should not be discounted outside of the immediate neonatal period, as NLE presents at an average of 6 weeks of age. When there is multisystem involvement, it is important to consider CANDLE syndrome, and an extensive viral screen, including potential HIV testing, is important. Hematological investigations, such as bone marrow aspirate, would take precedence when there are specific indicators (eg, cytopenias).

CONCLUSIONS

Neonatal Sweet syndrome is rare. Presentation in the first 6 weeks of life may be associated with systemic disease and genetic associations, whereas viral precipitants are more common after the first 3 months. NLE is an important differential, and associated malignancy is rare.

REFERENCES


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