Sweet’s Syndrome
Jennifer Hsiao, MD
UCLA Dermatology

Disclosures
• I have no conflicts of interest
• Will discuss off-label uses of medications

Outline
• Background information
• Classification of Sweet’s Syndrome
• Histopathology variants
• Extracutaneous manifestations
• Clinical variants
• Work-up
• Treatment

Background
• 1964: Dr. Robert Douglas Sweet described 8 female patients with acute onset of fever and erythematous plaques, and a dense neutrophilic dermal infiltrate on histology. He described this skin condition as “acute febrile neutrophilic dermatosis.”
• 1968: Whittle and colleagues described a similar case and used the term “Sweet’s syndrome.”

Background
• Average age of onset 30-60 years old
• Female predominance
• 15-30% have an internal malignancy (hematologic > solid organ)
• Pathogenesis is unknown

Clinical Presentation
• Tender, non-pruritic, erythematous, edematous papules and plaques
• Vesicles, bullae, or pustules may develop within the plaques
• Favors the face, neck, and upper extremities
• Usually resolves spontaneously within weeks to months but recurs in up to 30% of patients
• Pathergy seen (dermatosis-associated skin lesions appearing at sites of cutaneous trauma)
Classification of Sweet’s Syndrome

- Classical Sweet’s syndrome
- Malignancy-associated Sweet’s syndrome
- Drug-induced Sweet’s syndrome

Classical Sweet’s Syndrome

- Not associated with malignancy or drug exposure
- Most frequent associations:
  - Infections (most commonly of the upper respiratory tract and the gastrointestinal tract)
  - Inflammatory bowel disease
  - Pregnancy
- Other possible associations: Behcet’s disease, relapsing polychondritis, rheumatoid arthritis, sarcoidosis, autoimmune thyroid disease

Diagnostic Criteria for Sweet’s

- Major Criteria (both needed)
  1. Abrupt onset of tender or painful erythematous plaques or nodules
  2. Predominantly neutrophilic dermal infiltrate without leukocytoclastic vasculitis

- Minor Criteria (2/4)
  1. Fever >38°C (100.4°F)
  2. Association with underlying malignancy, inflammatory disease or pregnancy, OR preceded by nonspecific respiratory infection, gastrointestinal infection or vaccination
  3. Excellent response to systemic corticosteroids or potassium iodide
  4. Abnormal lab values at presentation (1.4%): ESR >20, elevated CRP, leukocytosis, neutrophilia

Diagnostic Criteria for Drug-Induced Sweet’s

All 5 criteria required for diagnosis:

1. Abrupt onset of painful erythematous plaques or nodules
2. Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
3. Fever >38°C
4. Temporal relationship between drug ingestion and clinical presentation, OR temporally-related recurrence after oral rechallenge
5. Temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids

Table 3: Medications associated with drug-induced Sweet’s syndrome (x=2)

<table>
<thead>
<tr>
<th>Antileukemics</th>
<th>Granulocyte colony-stimulating factor (GCSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin (30)</td>
</tr>
<tr>
<td>Topoisomerase</td>
<td>Busulfan (2)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone (11)</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Peginterferon-α 2b, Sunitinib (2)</td>
</tr>
<tr>
<td>Retinoids</td>
<td>All-trans retinoic acid (4)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Sulfamethoxazole + Trimethoprim (3)</td>
</tr>
</tbody>
</table>

Top 5 Drugs Related to Sweet’s Syndrome

- Recent review of Sweet’s syndrome looked at top 5 reports of drug-induced Sweet’s syndrome available in PubMed
  - Granulocyte colony-stimulating factor (GCSF) – most widely reported
  - All-trans retinoic acid
  - Sulfamethoxazole + Trimethoprim
  - Bortezomib
  - Azathioprine

Cohen. Orphanet J Rare Dis. 2007
Malignancy-associated Sweet’s Syndrome

- Hematologic malignancy more common than solid organ malignancy
- Most common malignancies: acute myelogenous leukemia, followed by myelodysplastic syndrome

Malignancy-associated Sweet’s Syndrome

- Review of 83 patients: Leukopenia, anemia, thrombocytopenia, absence of arthralgia, and histiocytoid or subcutaneous histopathology
- Review of 138 patients: Older age, anemia, thrombocytopenia, absence of arthralgia
- Review of 90 patients: Vesiculobullous lesions, anemia
- Review of 62 patients: Histiocytoid histopathology
- Review of 37 patients: Subcutaneous neutrophilic inflammation, anemia

Take home point: Patients with anemia, thrombocytopenia, absence of arthralgia, histiocytoid or subcutaneous histopathology may be more likely to have an underlying malignancy

Chronic Idiopathic Sweet’s Syndrome

- Report of 2 cases
  - 50 yo woman with Sweet’s syndrome with outbreaks for over 5 years of follow-up and no evidence of malignancy despite work-up.
  - 73 yo woman with Sweet’s syndrome, had lung cancer diagnosed 5 months after her initial visit and melanoma diagnosed 19 months later, however, despite tumor excision and cancer remission, active skin lesions persisted. She has been followed for more than 4 years for her Sweet’s syndrome.

Both patients had Sweet’s syndrome for a period longer than expected with no identifiable triggers, thought to be a chronic variant of classical Sweet’s syndrome.

Histiocytoid variant

- Previous studies have suggested a relationship between histiocytoid Sweet’s syndrome and underlying myeloproliferative disease
- A recent retrospective study of 33 patients with histiocytoid Sweet’s syndrome found that the dermal infiltrate was composed mostly of myeloperoxidase-positive immature cells of myeloid lineage and that the infiltrate should not be interpreted as leukemia cutis; mature histiocytes appeared to be a minor component of the infiltrate. In this study, 30% (11/33) had an associated malignancy, 80% of which (8/11) were hematologic malignancies.

Lymphocytic variant

- Few studies in the literature suggesting that lymphocyte-rich histological variant of Sweet’s syndrome may be associated with myelodysplasia
- Recent study looked at histology from 8 patients with diagnosis of Sweet’s syndrome, all cases had a mixed inflammatory infiltrate including lymphocytes, neutrophils and frequently eosinophils, and in most cases the perivascular component consisted predominantly of lymphocytes (none of the 8 patients had MDS)
Eosinophilic variant

- Eosinophils are frequently seen in Sweet's syndrome, not limited to drug-induced Sweet’s (a review of 73 cases of Sweet’s showed presence of eosinophils in 41% of biopsies, most unrelated to drug use)
- Some cases of Sweet’s syndrome have an eosinophil rich infiltrate
  - 90 yo man with history of celiac disease presented with GI bleeding, developed a rash while in the hospital (path shown)
  - Patient passed away, postmortem exam showed enteropathy-associated T-cell lymphoma, type I

Subcutaneous variant

- Skin lesions are usually erythematous, tender dermal nodules on the extremities
- Can mimic erythema nodosum when located on the legs
- Neutrophilic infiltrate seen in subcutaneous fat
- Possibly more common in patients with an associated underlying malignancy

Extracutaneous Manifestations

- Can have systemic manifestations, including involvement of the joints, muscles, eyes, lungs, bones, kidneys, liver, spleen, pancreas, intestines, brain, heart

Sweet Heart

Cardiac involvement from Sweet’s is rare but can be dangerous:

- 32 yo pregnant woman with cutaneous Sweet’s as well as myopericarditis that required surgical therapy for cardiac tamponade. She also underwent a cesarean section. She was prescribed prednisone and her skin lesions and pericarditis resolved
- 64 yo woman with myelodysplastic syndrome who had chest pain, SOB, fever and was diagnosed with pericarditis and CHF. Also had an erythematous nodule on her right lower leg that was consistent with Sweet’s. Four months later, patient died of cardiac arrest. Autopsy showed a perivascular and myocardial infiltration by neutrophils.

Blindness

- 40 yo man with pain, swelling, and redness of the left eye for 10 days. Had fever and no light perception in the left eye on exam. Started on IV antibiotics and a steroid. Developed an erythematous plaque on his right cheek that was consistent with Sweet’s. Biopsies of the extracocular muscles and conjunctiva were also consistent with Sweet’s. Bone marrow examination was suggestive of myelodysplastic syndrome.
  - Two weeks after starting steroid treatment, eyelid and conjunctival swelling almost completely resolved, but still completely blind in his left eye.
  - Take home point: In a patient with orbital inflammation with an underlying hematologic disorder, include Sweet’s syndrome in differential diagnosis.

Neuro-Sweet Syndrome

- CNS involvement in Sweet’s is rare, reported more among Asian patients
- Neurologic symptoms include: altered state of consciousness, headache, memory disorders
- Clinical features
  - Both sexes can be affected
  - Ages 30-70 years old
  - Encephalitis and meningitis are common neurologic manifestations
  - Any region of the CNS can be involved
  - Association with HLA-B54 and HLA-Cw1 (as opposed to HLA-B51 in Behcet’s)
  - Systemic steroids highly effective for most of the neurologic manifestations
Oral Sweet’s

- Oral lesions may occur more frequently in Sweet’s syndrome patients with hematologic disorders.

Cryptococoid Sweet’s Syndrome

- Cases that are clinically consistent with Sweet’s syndrome with a histologic presentation suggestive of cryptococcal infection (vacuolated capsule-like spaces, cellular debris imitating yeast forms)
- Fungal stains and myeloperoxidase immunohistochemistry should be performed

Necrotizing Sweet’s Syndrome

- Necrotizing fasciitis is a rapidly progressing infection of the soft tissue that can be fatal
- Treatment is prompt surgical debridement and broad antimicrobial therapy
- Histology shows necrosis of superficial fascia, infiltration of acute inflammatory cells, thrombosis of blood vessels, abundant bacteria spreading along fascial planes
- In Sweet’s syndrome will see absence of bacteria on gram stain

Take home points:

- In patients with a background of possible triggers of Sweet’s syndrome like hematologic malignancy or treatment with g-CSF, think about Sweet’s as a mimic of necrotizing fasciitis, otherwise there may be a vicious cycle of debridement → pathergy and expansion of disease → further debridement
- Necrotizing Sweet’s syndrome should be considered in cases of suspected necrotizing fasciitis failing to respond to therapy and lacking a causative organism (pathergy may be a helpful clue)

Giant Cellulitis-like Sweet’s Syndrome

- Variant of Sweet’s syndrome with relapsing widespread giant infiltrated inflammatory plaques
- A 2015 review found 6 patients reported in the literature, 4 with obesity, 2 with hematologic malignancy, 1 with breast cancer

Table 8: Clinical differential diagnosis of Sweet’s syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Acneiform dermatoses</th>
<th>Dermatomyositis</th>
<th>Psoriasis</th>
<th>Rosacea</th>
<th>Sarcoidosis</th>
<th>Systemic sarcoidosis</th>
<th>Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Aerobacter aerogenes</td>
<td>Acinetobacter</td>
<td>Bacteroides</td>
<td>Capnocytophaga</td>
<td>Haemophilus influenzae</td>
<td>Pasteurella</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Rheumatoid arthritis</td>
<td>Rheumatic fever</td>
<td>Sarcoidosis</td>
<td>Syphilis</td>
<td>Syphilitic lymphadenitis</td>
<td>Syphilis</td>
<td>Tularomyces</td>
</tr>
</tbody>
</table>

Patients with a background of possible triggers of Sweet’s syndrome like hematologic malignancy or treatment with g-CSF, think about Sweet’s as a mimic of necrotizing fasciitis, otherwise there may be a vicious cycle of debridement → pathergy and expansion of disease → further debridement.
Xanthomatized Sweet’s Syndrome

• 58 yo man with history of histiocytoid Sweet’s syndrome and MDS presented with new tender plaques on oral commissures
• Exam showed orange-yellow, fleshy plaques on the lower mucosal lip and bilateral oral commissures
• HDL was low (27 mg/dL), all other lipid studies were normal
• Biopsy of the oral commissures showed a neutrophilic infiltrate as well as xanthomatized cells
• Oral lesions improved with high dose steroids, colchicine, and cyclosporine

Neutrophilic Dermatosis of the Dorsal Hands

• Tender erythematous to violaceous plaques that may become bullous or ulcerative
• Vasculitis may be seen on pathology
• Some consider this to be a variant of Sweet’s syndrome
• Has also been called “pustular vasculitis,” “atypical pyoderma gangrenosum,” and “bullous pyoderma gangrenosum”

Work-Up

• Biopsy for H&E and for bacterial, fungal, mycobacterial cultures
• Consider viral cultures
• Labs
  • Complete blood count with platelets and differential
  • Complete metabolic panel (evaluate hepatic function and renal function)
  • Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
  • Urinalysis
  • Pregnancy test in women of childbearing age
• May be reasonable to perform antistreptolysin-O antibody (ASO), rheumatoid factor, and thyroid function tests

Malignancy Work-Up

• Malignancy work-up proposed by Cohen and Kurzrock in 1993
  • Complete medical history and physical exam (including thyroid and lymph node examinations, as well as breast, cervical, uterine, and ovarian cancer screening in women, and prostate and testicular examinations in men)
  • Caninembryonic antigen level
  • Colon cancer screening
  • Chest X-ray
• If there is reasonable clinical suspicion for a malignancy of unknown source, can consider chest, abdomen, and pelvis CT imaging or PET-CT imaging

1st Line Treatment

• Topical or intralesional corticosteroids if lesions are few and localized
• Systemic corticosteroids: oral prednisone 0.5-1.0 mg/kg/day tapered over 4-6 weeks (though some patients may need 2 to 3 months of treatment to suppress recurrences)
• Potassium iodide: 300mg enteric coated tablets, 3 times a day (900mg daily dose), or saturated solution of potassium iodide (SSKI, 1000mg/ml) titrated up to 900-1500mg/day
• Colchicine: 1.5mg/day
2nd Line Treatment

- Dapsone: 100-200mg/day
- Indomethacin: 150mg daily for 7 days, then 100mg daily for 14 days
- Clofazimine: 200mg daily for 4 weeks, then 100mg daily for 4 weeks
- Cyclosporine: varied dosing

Other Treatments

- Azathioprine
- Chlorambucil
- Cyclophosphamide
- Doxycycline
- Etretinate
- Hydroxyurea
- Interferon-alpha
- Methotrexate
- Metronidazole
- Thalidomide
- IVIG

* Also with reports of inducing Sweet’s syndrome

Doxycycline

- 61 yo man with Sweet’s syndrome treated with doxycycline 200mg/day: fever subsided within 1 day and the skin eruptions improved rapidly.1
- 51 yo woman with Sweet’s syndrome treated with 100mg PO BID with improvement after 1 week of treatment and resolution of skin lesions over the next 2 weeks. She was then treated with 100mg daily for 3 weeks. No further lesions during a 25 month follow-up period.6
- 37 yo woman with Sweet’s syndrome, initially treated with prednisolone, lesions flared with reduction of prednisolone dose. Doxycycline 100mg PO BID added and patient was weaned off prednisolone. She became pregnant, doxycycline stopped. Doxycycline 100mg PO BID re-started after pregnancy and she had great improvement within 2 weeks.2

Biologics

- Anakinra
- Etanercept
- Adalimumab
- Infliximab
- Rituximab

Anakinra

- IL-1 receptor antagonist
- 55 yo woman with Sweet’s syndrome refractory to prednisone, colchicine, methotrexate, dapsone, rituximab, was treated with anakinra 100mg SC daily with stabilization of his skin eruption within 4-5 days and progressive resolution. Anakinra was withdrawn at day 35 and the lesions recurred, so patient re-started on anakinra, improved again, and remained disease free for 6 months with anakinra. Medication was stopped and three months later his disease was still quiescent.1
- 56 yo man with Sweet’s syndrome refractory to prednisone, colchicine, methotrexate, dapsone, azathioprine, cyclophosphamide, adalimumab. Was on prednisone 10mg daily and adalimumab 40mg weekly with persistent fever and skin disease. Prednisone 10mg daily with anakinra 100mg SC daily and symptoms resolved quickly.2

Etanercept

- Soluble TNF-alpha receptor
- Two female patients with rheumatoid arthritis and Sweet’s syndrome treated with etanercept 50mg weekly with improvement of skin and joint disease.1
- 55 yo man with history of liver cirrhosis, seronegative inflammatory arthritis and Sweet’s syndrome treated with etanercept 50mg weekly and maintained on prednisolone 20mg daily with dramatic improvement of his synovitis within 2 weeks and gradual but marked improvement in his skin disease over 6 months. Prednisolone could be tapered down to 7.5mg daily.2
Adalimumab

- Fully human monoclonal antibody against TNF-alpha
- Man in his 50s with subcutaneous Sweet’s syndrome, had complete remission with mid-dose oral corticosteroids, but tapering below 20mg daily resulted in recurrent relapses despite the addition of dapsone 200mg daily. Patient started on adalimumab 40mg every other week and had a dramatic clinical response to adalimumab with lasting resolution of all symptoms.
- There are reports in the literature of patients who developed Sweet’s syndrome while on adalimumab for another condition (inflammatory bowel disease, relapsing polychondritis).

Infliximab

- Chimeric (mouse/human) monoclonal antibody against TNF-alpha
- Few case reports in the literature of patients with Sweet’s syndrome (mostly associated with inflammatory bowel disease) who were treated with infliximab with resolution of skin lesions.

Infliximab

- One case report of a 62 yo man with myelodysplastic disease and treatment-refractory Sweet’s syndrome who was admitted to the hospital with the onset of purpuric lesions. Methylprednisolone and infliximab infusions were given. The patient developed disseminated Nocardia infection and ultimately passed away.1
- Another case report of a 51 yo man with relapsing polychondritis with Sweet’s syndrome who started infliximab treatment (3mg/kg) and developed severe septicemia and passed away.2

Rituximab

- Monoclonal anti-CD20 antibody
- 48 yo man with CLL with refractory Sweet’s syndrome whose symptoms improved after two doses of rituximab (375mg/m2 body surface), given 8 days apart.1
- 60 yo man with RA, interstitial lung disease, and refractory Sweet’s syndrome, on prednisone 20mg daily, treated with rituximab 1000mg on days 1 and 15. Four months later patient was able to taper his prednisone to 4mg daily without relapse of his cutaneous disease, also had improvement of his dyspnea. Received 2 more cycles of rituximab at 6 months and 18 months.2

Granulocyte and Monocyte Adsorption Apheresis

- 55 yo Japanese woman with recurrent Sweet’s, no identifiable trigger
- Prednisolone was effective but even while on low dose as maintenance, her Sweet’s syndrome recurred
- NSAIDs ineffective, colchicine not tolerated
- Treated with granulocyte and monocyte adsorption apheresis therapy once a week for 3 weeks
- After the first session, fever and skin lesions resolved and serum G-CSF level was reduced
- Symptoms have not appeared for at least 4 months without steroids

Take Home Points

- Anemia, thrombocytopenia, absence of arthralgia, presence of oral lesions, histiocytoid or subcutaneous histology → heightened concern for malignancy
- Histologic variants of Sweet’s syndrome include subcutaneous, histiocytoid, lymphocytic, and eosinophilic
- Clinical variants include Cryptococcoid, Necrotizing, Giant cellulitis-like, and Xanthomatized Sweet’s syndrome
- Sweet’s syndrome can have severe extracutaneous manifestations
- There is a broad differential: Rule out infectious, neoplastic and other inflammatory disorders
- If 1st and 2nd line treatments (like steroids, potassium iodide, colchicine, dapsone) fail, there are other systemic agents to try, including doxycycline and biologic agents like anakinra, TNF-alpha antagonists, and rituximab