***no patient handout*

# Sweet syndrome

## Synopsis

Sweet syndrome, or acute febrile neutrophilic dermatosis, is an inflammatory disorder manifesting as multiple sterile, painful, edematous, erythematous plaques that are usually associated with fever and leukocytosis. The disease is typically skin-limited, although any organ system may also be affected. It may be seen in patients of all ages, but it is most common in healthy women aged 20-60 and individuals with inflammatory bowel disease (IBD) or hematologic malignancies (especially **myeloid leukemias** and **myelodysplastic syndrome**). Other common associations include pregnancy, **streptococcal pneumonia**, **rheumatoid arthritis**, and medications (sulfamethoxazole-trimethoprim, minocycline, G-CSF). Most cases are idiopathic or associated with benign conditions; about 15%-20% are associated with malignancy.

Although the exact etiology is still unclear, Sweet syndrome has been considered a dysregulated cytokine response associated with inflammatory, infectious, and malignant disease. Pathergy is frequently associated, and lesions will arise in sites of cutaneous injury, such as needle sticks.

Sweet syndrome frequently includes extracutaneous manifestations such as fever, headaches, myalgias, malaise, arthralgias, and ocular inflammation. Other sites that may be affected include the oral mucosa, gastrointestinal tract, musculoskeletal system, lungs, kidneys, heart, and central nervous system (CNS). Hypotension and tachycardia are rare but can occur as a result of systemic inflammation.

Sweet syndrome typically responds dramatically to systemic corticosteroids, but recurrences are common.

## Codes

ICD10CM:
L98.2 – Febrile neutrophilic dermatosis [Sweet]

SNOMEDCT:
84625002 – Sweet's syndrome

## Look For

Deep red, sharply demarcated plaques or nodules that appear edematous or vesiculated but have no expressible fluid. Ulcers and bullae may occur; these findings are associated more often with underlying malignancy. Subcutaneous forms may mimic erythema nodosum. Rare reports exist of a deeper involvement of the muscles or fascia and may be misdiagnosed as necrotizing fasciitis.

The plaques are typically distributed asymmetrically on the extremities, face, neck, and upper

trunk. On occasion, lesions may be predominantly distributed over the dorsum of the hands and fingers; some experts consider this to be an anatomically limited subset of Sweet syndrome, so-called neutrophilic dermatosis of the dorsal hands. Another variant presentation is erysipelas-like facial involvement.

Conjunctivitis, episcleritis, or other evidence of ocular inflammation may be present.

Mucosal lesions are infrequent. When present, they usually consist of ulcerations.

The lesions resolve without scarring, but recurrences are frequent, often in the previous sites.

There is evidence of pathergy at IV sites or other sites of trauma.

Diagnostic criteria for Sweet syndrome include 2 major and 2 of 4 minor diagnostic criteria outlined below.

**Major criteria:**

1. Typical skin lesions – abrupt onset of painful erythematous plaques and nodules
2. Typical histopathology – sterile, dense collections of neutrophils without leukocytoclastic vasculitis

**Minor criteria:**

1. Fevers higher than 38°C (100.4°F)
2. Excellent response to corticosteroids or potassium iodide
3. Association with an underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy, OR preceded by an upper respiratory or gastrointestinal infection or vaccination
4. Abnormal laboratory values at presentation (3 of 4): erythrocyte sedimentation rate >20 mm/hour; positive C-reactive protein; >8000 leukocytes; >70% neutrophils

## Diagnostic Pearls

Fever often precedes skin lesions.

Lesions are classically dermal and edematous, taking on a "pseudovesiculated" appearance. The edema may progress to frank bullae.

Lesions are typically tender, less commonly asymptomatic. Pruritus would point toward another diagnosis.

Overlap features of other neutrophilic disorders including pyoderma gangrenosum, leukocytoclastic vasculitis, neutrophilic eccrine hidradenitis, subcorneal pustular dermatosis, and erythema elevatum diutinum may occur.

Appearance on imaging of the lungs and viscera is entirely nonspecific and cannot be distinguished from infection. Aseptic meningitis may be seen with CNS involvement.

Lesions may form at sites of IV insertion or other areas of skin trauma (pathergy).

Oral lesions may occur as well as conjunctivitis and episcleritis.

## Differential Diagnosis & Pitfalls

- **Pyoderma gangrenosum** – Begins as a pustule and evolves into a purulent ulcer with rolled borders. Has similar associations, including IBD and malignancy.
- **Neutrophilic eccrine hidradenitis** – Drug-induced toxicity of the eccrine coils 1-2 weeks following chemotherapy. Palmar involvement is more suggestive of this diagnosis. Patients typically lack fevers but pathology may be required to differentiate these entities.
- **Bowel-associated dermatosis-arthritis syndrome** – Pustular skin lesions and aseptic arthritis in bowel-bypass patients.
- **Wells syndrome** – Involved skin is typically neither tender nor warm. Eosinophilia present in 50%, neutrophilia would be unusual. Eosinophils and flame figures seen on pathology.
- **Erythema multiforme** – Should display classic target lesions with 3 zones of color, favors acral surfaces. Oral involvement common.
- Azathioprine hypersensitivity syndrome – Acute neutrophilic and systemic reaction after initiating azathioprine.
- **Urticarial vasculitis**
- **Erythema elevatum diutinum** – Primarily over extensor surfaces.
- Cutaneous small vessel **vasculitis** – Presents symmetrically on lower extremities, typically smaller than the plaques of Sweet syndrome.
- **Behçet disease** – Rare, recurrent, and associated with oral or genital ulcers.
- **Bromoderma** or **iododerma**
- Bacterial infections (**furunculosis**, **cellulitis**)
- **Sporotrichosis**

- *Mycobacteria* sp. infections (typical and **atypical**), including ***Mycobacterium marinum***
- **Erythema nodosum** – Primarily over the shins.
- Leishmaniasis (**New World** and **Old World**) – Recent travel to endemic areas.
- **Lymphoma** / **leukemia cutis**
- **Metastatic carcinoma**
- **Majocchi granuloma**
- **Sarcoidosis**
- **Orf**
- **Cat-scratch disease**
- **Cutaneous anthrax**
- **Coccidioidomycosis**

## Best Tests

Skin biopsy is used to confirm the diagnosis.

**Histopathology Findings:**
Common features

- Diffuse infiltrate of neutrophils in the upper dermis or full extent of the dermis
- Papillary dermal edema
- Neutrophilic spongiosis and subcorneal neutrophilic pustules
- Leukocytoclasia, but no leukocytoclastic vasculitis

Occasional features

- Vasculitis as a "secondary" phenomenon
- Subepidermal cleft from advanced papillary dermal edema
- Neutrophils in the fat in subcutaneous Sweet syndrome variant

Consider a medical work-up to narrow the differential or elucidate the underlying cause of the condition, such as an infection or hematologic malignancy. Such investigations may include:

- CBC with differential
- Urinalysis
- Erythrocyte sedimentation rate and/or C-reactive protein level
- Pregnancy test
- Tissue culture of lesions
- Comprehensive age- and sex-appropriate screening for malignancy
- Serum protein electrophoresis (SPEP)
- Chest x-ray
- PET scan, ultrasound, CT, or MRI for malignancy
- Bone marrow biopsy
- Colonoscopy

## Management Pearls

Identify and optimize treatment of any underlying associated condition. Withdraw any suspected triggering medication.

Corticosteroids are first-line therapies. Other treatments, including dapsone and colchicine, do not have as rapid onset of action.

Rapid, significant response to adequate dosages of prednisone, with cessation of fever, within 24-48 hours is typical and one of the diagnostic criteria.

Systemic symptoms, internal organ involvement, or widespread cutaneous involvement mandates systemic therapy. Limited disease may be treated topically or intralesionally, but cessation of fever is an important marker of adequate treatment response.

In cases with hypotension, respiratory distress, other profound organ involvement, or disease refractory to standard dosing, pulsed dosing of methylprednisolone 500-1000 mg IV daily for 3-5 days followed by a typical corticosteroid has been employed.

Recurrences are common, and the required duration of corticosteroids may be 4-6 weeks. An additional 2-3 months of low-dose therapy may be useful to suppress recurrences. Topical, intralesional, and steroid-sparing agents such as dapsone and colchicine facilitate tapering and

prolonged therapy.

Cessation of systemic inflammation and cytokine disruption is the goal of treatment. A patient with topical or intralesional treatment who has regression of cutaneous lesions but persistence of fevers should be considered inadequately treated.

## Therapy

**First-line therapy:**
Systemic corticosteroids

- Prednisone 0.5-1 mg/kg p.o. every 24 hours. Taper over 4 to 6 weeks, or
- Methylprednisolone 0.4–0.8 mg/kg p.o. or IV. Typically divided twice daily but may be given daily, or
- Methylprednisolone 500–1000 mg IV daily for 3-5 days followed by typical steroid dosing

For limited skin disease without systemic symptoms, consider:

Topical corticosteroids

- Clobetasol, halobetasol, or other Class I agent every 12 hours, or

Intralesional steroids

- Triamcinolone 3-10 mg/mL

**Alternative first-line therapies** (also may be used adjunctively with corticosteroids to facilitate tapering):

- Dapsone: Check for glucose-6-phosphate-dehydrogenase (G6PD) deficiency and initiate at 25 mg. Increase as tolerated to goal dose of 100-200 mg daily. Monitor for hemolysis, agranulocytosis, methemoglobinemia, and peripheral neuropathy.
- Colchicine (0.5-0.6 mg p.o. every 8-12 hours)
- Saturated solution of potassium iodide (SSKI or Lugol's solution): 3 drops in orange juice every 8 hours and advance every 24 hours by 1 drop, as tolerated, to 7-10 drops every 8 hours.
- Potassium-iodide enteric coated tablets 900 mg every 24 hours. **Note:** In long-term use, monitor thyroid function.

**Other reported therapies:**

- Indomethacin (100-150 mg p.o. every 24 hours)
- Clofazimine (100-200 mg p.o. every 24 hours)
- Cyclosporine
- Thalidomide
- Anakinra
- Adalimumab
- Etanercept
- Rituximab
- Interferon alpha
- Intravenous immunoglobin (IVIG)

## Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

| Medication | Citations |
|---|---|
| 5-aminosalicylic acid derivative | 1 |
| abacavir | 1 |
| aceclofenac | 1 |
| adalimumab | 1 |

| Medication | Citations |
| --- | --- |
| Alkylating agent | 1 |
| all-trans-retinoic acid (ATRA) | 5 |
| amoxapine | 1 |
| Antifungal | 1 |
| Antimalarials | 1 |
| Antimetabolite | 5 |
| Antineoplastic antibiotic | 2 |
| Atypical antipsychotic | 2 |
| azacitidine | 3 |
| azathioprine | 11 |
| BCR-ABL tyrosine kinase inhibitor | 5 |
| benzodiazepine | 1 |
| bortezomib | 10 |

| Medication | Citations |
| --- | --- |
| BRAF kinase inhibitor | 2 |
| celecoxib | 3 |
| chloroquine | 1 |
| clindamycin | 2 |
| clozapine | 2 |
| cyclophosphamide | 1 |
| decitabine | 2 |
| diazepam | 1 |
| diclofenac | 1 |
| Diuretic | 2 |
| doxorubicin | 1 |
| doxycycline | 1 |
| Estrogen | 3 |

| Medication | Citations |
| --- | --- |
| filgrastim | 1 |
| fluoroquinolone | 1 |
| furosemide | 2 |
| gemcitabine | 1 |
| Granulocyte colony-stimulating factor | 19 |
| hydralazine | 4 |
| imatinib | 3 |
| infliximab | 1 |
| interferon | 2 |
| ipilimumab | 3 |
| Isotretinoin | 3 |
| ketoconazole | 1 |
| lenalidomide | 2 |

| Medication | Citations |
| --- | --- |
| Lincosamides | 2 |
| minocycline | 4 |
| mitoxantrone | 1 |
| Nilotinib | 3 |
| nitrofurantoin | 1 |
| norfloxacin | 1 |
| NRTI antiretroviral | 1 |
| NSAID | 3 |
| omeprazole | 1 |
| Oral contraceptives | 3 |
| penicillin antibiotic class | 1 |
| piperacillin + tazobactam | 1 |
| propylthiouracil | 2 |

| Medication | Citations |
| --- | --- |
| Proton pump inhibitor | 1 |
| quinupristin + dalfopristin | 1 |
| Retinoid | 8 |
| rofecoxib | 1 |
| sulfamethoxazole + trimethoprim | 7 |
| sulfasalazine | 1 |
| sulfonamide | 7 |
| tetracycline antibiotic class | 5 |
| Tricyclic antidepressant | 1 |
| trimethoprim | 1 |
| vemurafenib | 2 |
| vorinostat | 1 |