Sweet Syndrome and Neutrophilic Dermatosis of the Dorsal Hands

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KEYWORDS

• Acute febrile neutrophilic dermatosis • Dorsal hands • Sweet syndrome

KEY POINTS

- Sweet syndrome is generally categorized into 1 of 3 forms: classic, malignancy-associated, and drug-induced.
- Onset of malignancy-associated Sweet syndrome can be a sign of cancer recurrence and/or development of a new cancer.
- Extracutaneous involvements are uncommon and can be life-threatening.
- Systemic corticosteroids can provide rapid improvements; several nonsteroidal agents seem to be effective with growing evidence.
- There are a multitude of possible triggers, and Sweet syndrome's pathogenesis is incompletely characterized.

INTRODUCTION

History

Sweet syndrome (acute febrile neutrophilic dermatosis) is a rare cutaneous condition originally described by Dr Robert Douglas Sweet in 1964.[1] While Dr Sweet's case series included several patients with preceding mucosal tract infections, Sweet syndrome is also associated with several autoimmune diseases, pregnancy, malignancies (hematologic and solid tumors), and medication exposures.[2] Although the pathogenesis of Sweet syndrome is not well characterized, it can be classified into 3 main categories based on the clinical context in which it presents: classic (idiopathic), malignancy-associated, and drug-induced. In this article, the authors summarize and discuss the up-to-date medical literature on Sweet syndrome and neutrophilic dermatosis of the dorsal hands—a condition that is frequently recognized as a clinical variant of Sweet syndrome.

DEFINITIONS

Background

Epidemiology

Sweet syndrome is a rare entity, and its incidence is difficult to precisely estimate. Classic Sweet syndrome comprises roughly 28% to 61% of cases, malignancy-associated Sweet syndrome has been reported in frequencies between 3% and 67%, and drug-induced Sweet syndrome has been reported at rates between 1% and 27%.[3] Typically, disease onset occurs in middle-aged individuals, and malignancy-associated cases seem to tend to occur in slightly older patients (average age 68 years) than classic cases (average age 51 years).[4] Although Sweet syndrome can also affect children (average age 5 years), pediatric patients comprise less than 10% of cases.[5] Women generally seem to be affected more commonly than men in the classic variant (roughly 4:1 ratio); however, malignancy-associated (1:1), solid-tumor associated (1.4:1),

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and drug-induced (2.4:1) cases tend to be slightly less female predominant, and there is growing evidence that suggests there may not be a significant sex predilection.[6–8]

Evaluation

Observation/assessment

Clinical hallmarks of Sweet syndrome include an acute onset of tender, nonpruritic, erythematous or violaceous papules/plaques with or without central yellow discoloration and/or mammillated surfaces; lesions can also present as vesicles, pustules, and bullae (**Fig. 1**).[9]

Cutaneous findings characteristically asymmetrically involve the head, neck, and upper extremities (such as the dorsal hands) and can onset either concurrently with constitutional signs and symptoms (fever, malaise, arthralgia, myalgia, headache, and so forth) or manifest days to weeks after. An estimated 28% to 85% of patients experience fevers.[3]

Extracutaneous manifestations

Although uncommon, multiorgan involvement in Sweet syndrome can be serious and potentially life-threatening.[8] A wide variety of systemic manifestations have been reported involving the cardiovascular (myocarditis, aortitis, coronary artery occlusion, neutrophilic infiltration of myocardium), nervous (meningitis, encephalitis), gastrointestinal (hepatomegaly, splenomegaly, intestinal neutrophilic inflammation), musculoskeletal (osteomyelitis), pulmonary (pleurisy, alveolitis, radiologic findings of infiltrations, pleural effusions), and renal (glomerulonephritis, hematuria, proteinuria) systems.[10,11]

Hisanaga and colleagues coined the term "neuro-Sweet disease" in 1999 after managing a patient with recurrent encephalitis found to have associated biopsy-proven Sweet syndrome.[12]

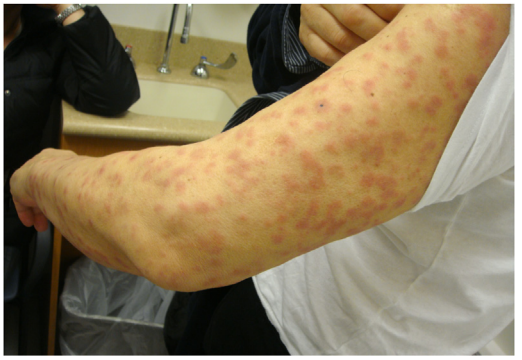

Fig. 1. Clinical findings of Sweet syndrome: erythematous edematous papules and plaques involving the upper extremity. (Image courtesy of PathPresenter.)

The most common neurologic manifestations are aseptic meningitis and encephalitis; other complications include epilepsy, paresis, dyskinesia, and psychiatric disorders.[13]

Mucous membrane involvement is relatively rare and tends to occur more often in malignancy-associated cases compared with classic.[10,14–16] Ocular Sweet syndrome typically presents as a mild-moderate conjunctivitis with characteristic rapid responsiveness to corticosteroids; however, several ophthalmologic pathologies have been reported (retinal vasculitis, choroiditis, scleritis, episcleritis, iritis, central retinal artery occlusion), some of which can lead to blindness.[8,15,17,18] The oral cavity may also be affected and present with ulcers.

Pulmonary manifestations can be resistant to treatment and fatal.[19] Symptoms can range from mild dyspnea to acute respiratory distress syndrome. Diagnostic bronchoalveolar lavages and/or pleural fluid analyses are often obtained to assess for malignancy/infection and typically exhibit characteristic neutrophilic predominance and negative microbial cultures. Bronchoscopy may reveal erythematous pustules with ulcerations.[20]

Systemic inflammatory response syndrome may also occur in the setting of Sweet syndrome.[21–25]

Approach

Diagnosis

Establishing a diagnosis of classic or malignancy-induced Sweet syndrome relies on meeting both 2 major ([1] abrupt onset of painful erythematous plaques or nodules occasionally with vesicles, pustules, or bullae; [2] histopathology consistent with Sweet syndrome) and 2 of 4 minor clinical criteria ([1] preceded by one of the following: an associated infection, vaccination, malignancy, inflammatory disorder, drug exposure, or pregnancy; [2] presence of fever > 38°C [100.4°F], general malaise, constitutional signs and symptoms; [3] three of the following 4 laboratory values: erythrocyte sedimentation rate (ESR) > 20 mm, c-reactive protein (CRP) positive, segmented nuclear neutrophils, and stabs > 70% in peripheral blood smear, leukocytosis > 8000; [4] excellent response to systemic corticosteroids or potassium iodide) developed by Su and colleagues in 1986 and revised by von den Driesch in 1994.[26,27] Drug-induced cases are diagnosed using similar and distinct criteria: (1) abrupt onset of painful erythematous plaques or nodules, (2) histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, (3) pyrexia greater than 38°C (100.4°F), (4) temporal relationship between drug ingestion and clinical presentation or temporally related recurrence after

oral challenge, (5) temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.[10]

Classic (idiopathic) Sweet syndrome

Classic Sweet syndrome is the most common form and typically presents 1 to 3 weeks following an upper respiratory tract and/or gastrointestinal infection. The most highly associated infectious causes include various viruses (cytomegalovirus, hepatitis B and C, human immunodeficiency virus, coronavirus-19), bacteria (yersinia, streptococcus, chlamydia, treponema palladium, helicobacter pylori, typical and atypical mycobacteria [*Mycobacterium tuberculosis* and *Mycobacterium leprae*]), and fungi (sporotrichosis, coccidiomycosis).[9,28–31] Other associated conditions include inflammatory bowel disease (ulcerative colitis and Crohn disease), Behcet disease, relapsing polychondritis, erythema nodosum, rheumatoid arthritis, dermatomyositis, relapsing polychondritis, Sjogren syndrome, sarcoidosis, and autoimmune thyroid disease (Hashimoto and Graves).[11,32–37] There are many other disorders with growing evidence for potential associations, including autoimmune diseases, vasculitides, immunodeficiencies, hereditary syndromes, and a wide variety of infections.[10,11] A more detailed list of disorders potentially associated with Sweet syndrome can be found in **Table 1**.

Similar to pyoderma gangrenosum, pathergy is a feature that may occur in Sweet syndrome as a hypersensitivity reaction to skin trauma such as biopsies, injections, and line placements.[5] Sweet syndrome has developed after relatively minor traumas such as hair plucking and tattoos.[38,39]

Pregnancy-associated Sweet syndrome (classic)

Pregnancy-associated disease rarely occurs (1%–4% of cases) and typically presents in either the first or the second trimester.[3] Prognosis is favorable with spontaneous resolution after delivery and is not associated with a significantly increased risk for infant or maternal morbidity or mortality. However, extra-cutaneous manifestations may cause complications, and spontaneous abortions have been reported.[40–42] Recurrence can occur before, during, and after pregnancy and may present in sequential pregnancies.[40]

Atypical clinical and histologic variants

Less common presentations of Sweet syndrome include bullous Sweet syndrome, pustular Sweet syndrome, subcutaneous panniculitis Sweet syndrome, cryptococcoid Sweet syndrome, histiocytoid Sweet syndrome, giant cellulitis-like Sweet syndrome, and necrotizing Sweet syndrome. Although bullous Sweet syndrome is rare, it is most commonly malignancy-associated and can clinically resemble pyoderma gangrenosum.[9,20,43] Subcutaneous Sweet syndrome presents with nodules that may clinically mimic erythema nodosum and have biopsies demonstrating neutrophilic infiltration of the subcutaneous fat instead of the dermis (correlating clinically with nodules with minimal superficial changes).[44] Cryptococcoid Sweet syndrome was initially described by Ko and colleagues in 2013 and assigned its "cryptococcoid" nomenclature by Wilson and colleagues in 2017 due to its characteristic microscopic findings of vacuolated mononuclear cells with basophilic yeast bodies.[45,46] It can be distinguished from cryptococcosis through negative periodic acid Schiff staining, lack of fungal elements on biopsy, and nonresponsiveness to antifungal therapy.[8] Histiocytoid Sweet syndrome was initially reported by Requena and colleagues in 2005.[47] It can be particularly difficult to distinguish both clinically and histologically from leukemia cutis, and leukemia cutis lesions may occur within the same lesion as Sweet syndrome; the main distinguishing factor is the presence of polymorphonuclear neutrophils of myeloid lineage in Sweet syndrome versus malignant immature leukocytes in leukemia cutis.[48,49] Both the histiocytoid and subcutaneous histologic variants of Sweet syndrome may be associated with increased risk for malignancy, although reporting bias of malignancy-induced cases may exist.[50,51] Giant cellulitis-like Sweet syndrome is another rare presentation characterized by large infiltrated inflammatory plaques and bullae that can clinically resemble bacterial cellulitis and be differentiated through negative bacterial cultures and nonresponsiveness to antibiotics.[8,52] Necrotizing Sweet syndrome resembles necrotizing fasciitis and presents as rapidly progressive lesions with underlying soft tissue necrosis; it is crucial to swiftly and accurately distinguish it from necrotizing fasciitis, as surgical debridement can cause lesion expansion and disease exacerbation.[8] It may have underlying risk factors such as granulocyte colony-stimulating factor and malignancy.[53,54] In 2021, a new variant of Sweet syndrome associated with myelodysplastic syndrome was described: normolipemic xanthomatized Sweet syndrome, characterized histologically by infiltration of CD163 (+) xanthomatous cells and neutrophils with leukocytoclasia.[55] Because the aforementioned patterns include both clinical and histologic findings that can represent atypical presentations of Sweet syndrome, there may be overlap, and variants can evolve over time.[56,57]

Malignancy-associated Sweet syndrome

Roughly 21% of Sweet syndrome cases are associated with malignancies, and cutaneous findings

Table 1
Conditions possibly associated with Sweet syndrome

Disease Process	Conditions
Autoimmune rheumatologic disorders	Ankylosing spondylitis [18204874, 25201185, 10544847], lupus erythematous (systemic and subacute) [23682962, 15934441, 1568805, 22937442, 19276309, 21550284], pemphigus vulgaris [22513066, 15482319], mixed connective tissue disease [33040354], polymyalgia rheumatica [31921506], Still disease [15097938]
Cardiovascular	Dressler syndrome [2411241]
Dermatologic	Acquired cutis lava (Marshall syndrome) [31437319], chronic urticaria, eosinophilic granuloma, granuloma annulare [11722452], Grover disease (transient acantholytic dermatosis) [10877140], hidradenitis suppurativa [32274056, 27002570, 32567672], middermal elastolysis [14675289], psoriasis vulgaris, urticaria pigmentosa
Environmental exposure	Chemical fertilizer [15482306], thermal injury [14641120]
Gastrointestinal	Autoimmune hepatitis [10599643], celiac [19658449], cirrhosis (cryptogenic) [22735879, 29054908, 1794170], common bile duct and intrahepatic duct stones, malabsorption
Hematologic derangements	Aplastic anemia [11902745, 8689342, 7519039], congenital dyserythropoietic anemia [17671383, 2809904], congenital neutropenia (Kostmann syndrome) [15858487, 24387761, 8859296], Fanconi anemia [34403507, 18300309, 21501135, 11196274], hemophagocytic syndrome [18289342, 23955621]
Hereditary syndromes and inherited disorders	Alpha-1-antitrypsin deficiency [7574835], antifactor 8 inhibitor [10759106], antiphospholipid syndrome, glycogen storage disease (type Ib) [8604280], POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) [8479179], VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) [17655751, 22508923]
Infectious	Anaplasma phagocytophilum (human granulocytic anaplasmosis) [16027306], aseptic meningitis [1488383], bacterial endocarditis [15097971, 17292496, 22605716], campylobacter [22723255], *Capnocytophaga canimorsus* [11411932], *Chlamydia pneumoniae* [11312438], cholangitis [18360136], cholecystitis [27060356], coccidioidomycosis [16027305, 10923132], cytomegalovirus [14693024], dermatophyte [17076728], *Entamoeba histolytica* [16179788], Epstein-Barr virus, *Francisella tularensis* [11903682, 21699525], *Helicobacter pylori* [9216537], hepatitis B [22735879, 11069494], hepatitis C [25348767, 25348767, 12823297, 19052408], herpes simplex [12854387, 29054908, 12100632], herpes zoster [22220147, 10354095], histoplasmosis [32035234], human immunodeficiency virus [10397569, 26396453, 21679803, 18206098, 10545563, 33052291], leprosy, leptospirosis [21771425], lymphadenitis [1504437, 7653187], *Mycobacterium avium* [29171446, 18485019], *Mycobacterium chelonae* [12854387], nontuberculous mycobacteria [9764159, 15222531], otitis media, pancreatitis, parvovirus B19 [23113722, 20534986], *Pasteurella multocida* [10871983], penicillium spp., *Pneumocystis carinii* [10914942, 6816688], sialadenitis

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Table 1
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Disease Process	Conditions
	[18420076], sporotrichosis [33025874, 21711340], *Staphylococcus aureus* [15569025], *Staphylococcus epidermidis* [17352724], tonsillitis [34054456], toxoplasmosis [4043468, 30918190], tuberculosis [29332658, 30238576, 23669432, 26891891, 21717890, 11229305]
Immunodeficiencies	Adult-onset immunodeficiency precipitated by antiinterferon gamma antibodies [34676591], chronic granulomatous disease [22246153], common variable immunodeficiency [31089823, 18782323], complement deficiency [2803964], human immunodeficiency virus [10397569, 26396453, 21679803, 18206098, 10545563, 33052291], primary T-cell immunodeficiency disease [10321630], T-cell lymphopenia [10321630]
Musculoskeletal	Chronic recurrent multifocal osteomyelitis [3591758, 19840301, 10383779, 2809904]
Pulmonary	Bronchiolitis obliterans [11460854, 1951419, 17071150], lung transplant [34366039], organizing pneumonia [11460854, 25196175, 1951419, 25163580, 17071150], postoperative pneumonectomy [15223465], rhinosinusitis [16527036]
Renal/genitourinary	Amyloid nephropathy [32681397], end-stage renal disease [22605810], IgA nephropathy (Berger disease), ureter obstruction [2618175], urinary stone disease [1628515]
Vasculitides	ANCA vasculitis [35495970], eosinophilic granulomatosis with polyangiitis [32611774, 33060325], granulomatosis with polyangiitis [22605810], microscopic polyangiitis [22513149], Takayasu arteritis [15608327, 19569285, 35925217, 22011145]
Miscellaneous, autoinflammatory, and complex multisystem disorders	Chronic fatigue syndrome, differentiation syndrome [34026142, 34970368, 25685768], familial Mediterranean fever [19586502], 34159892, 18824843], Kikuchi disease [23955621]

Pubmed Identifiers for associated references are enclosed in brackets.
Abbreviations: ANCA, antineutrophilic cytoplasmic antibody; IgA, immunoglobulin A.
Adapted from Cohen, P.R. and Kurzrock, R. (2003), Sweet's syndrome revisited: a review of disease concepts. International Journal of Dermatology, 42: 761-778. https://doi.org/10.1046/j.1365-4362.2003.01891.x.

can precede, follow, or onset concurrently with a hematologic or solid tumor malignancy.[58] The first reported malignancy-induced case was in 1955 by Costello and colleagues (acute myelogenous leukemia); the first solid-tumor associated case (testicular carcinoma) was reported by Shapiro and colleagues in 1971.[59,60]

Most of the malignancy-associated cases are linked to hematologic disorders (82%), most commonly acute myelogenous leukemia.[50] Other relatively common hematogenous disorders that might be correlated with Sweet syndrome include myelodysplasia, chronic myelogenous leukemia, multiple myeloma, and monoclonal gammopathy. Differences in clinical course between acute myelogenous leukemia (commonly a single episode) and myelodysplasia-associated (usually chronic relapsing) Sweet syndrome seem to exist.[61]

Solid tumors comprise a smaller proportion (18%) of malignancy-associated cases and typically include carcinomas of the breast, genitourinary, and gastrointestinal systems.[50,58,62] The rash can precede the associated hematologic malignancy by up to 11 years and/or can occur as a paraneoplastic syndrome.[58]

Development of Sweet syndrome can be an initial sign of cancer recurrence in patients with histories of malignancy and/or a sign that a new cancer has emerged.[10] Although it can sometimes

be difficult to gauge whether suspicion for an underlying neoplasm is warranted, leukopenia, anemia, thrombocytopenia, and absence of arthralgia may be associated with malignancy-associated disease.[50]

There are other neutrophilic dermatoses associated with hematologic malignancies (eg, atypical bullous pyoderma gangrenosum, neutrophilic eccrine hidradenitis) that may present similarly to Sweet syndrome; however, Sweet syndrome can be differentiated from these conditions through its histopathology and systemic manifestations (neutrophilia vs neutropenia in neutrophilic eccrine hidradenitis; lack of systemic features in atypical bullous pyoderma gangrenosum).[9]

Drug-induced Sweet syndrome

Drug-induced cases are a relatively uncommonly observed disease form and typically develop a couple of weeks after an inciting drug exposure. The first report of drug-induced Sweet syndrome involved trimethoprim-sulfamethoxazole and was published by Su and Liu in 1986.[26] Since then, there have been reports involving a broad spectrum of medications from a wide variety of drug classes, including antibiotics, antihypertensive medications, nonsteroidal antiinflammatory drugs, immunosuppressive and immunomodulating therapies, immunostimulants, antiepileptic drugs, antineoplastic agents, antipsychotics, immune checkpoint inhibitors, antithyroid medications, and antidepressants, among others. The most common iatrogenic trigger is granulocyte colony-stimulating factor.[11] A more detailed list of reported contributors can be found in **Table 2**. Disease oftentimes resolves on discontinuation of the provoking medication.

Other potential triggers

In addition to the iatrogenic triggers listed in **Table 2**, there are reports of Sweet syndrome developing following exposures to ultraviolet light, areas of long-standing lymphedema, radioiodine contrast, and vaccines.[63–74] Several coronavirus-19 vaccine–induced Sweet syndrome cases have been reported as well as a few cases involving measles-mumps-rubella-varicella, pneumococcal, influenza, and Bacillus Calmette–Guérin vaccines.[75–92] It is unclear what role, if any, pathergy and/or immune dysregulation played in the development of Sweet syndrome following vaccination. Sweet syndrome has also developed in other altered states of immunity such as renal transplants and autologous stem cell transplants.[93,94]

Neutrophilic dermatosis of the dorsal hands

Neutrophilic dermatosis of the dorsal hands is a condition that clinically and histologically resembles Sweet syndrome and is sometimes considered a subset of Sweet syndrome; however, larger ulcerated plaques and nodules may resemble and be on a spectrum with bullous pyoderma gangrenosum.[95] It was initially described by Strutton and colleagues in 1995 as a pustular vasculitis, although assigned its current name by Galaria and colleagues in 2000.[96,97] Although it is sometimes classified as a cutaneous vasculitis due to a few reported cases demonstrating leukocytoclastic vasculitis, a relatively small proportion of cases display this secondary effect, and the primary pathogenic mechanism is dermal infiltration.[96,98–100] Clinically, it is a localized cutaneous condition characterized by tender erythematous nodules and plaques that can form pustules, bullae, and ulcers. Lesions tend to affect the dorsal aspect of the hand between thumb and index finger bilaterally, although it may involve other areas of the body (eg, mucous membranes, arms, legs, trunk, and face).[95,101] Its morphology, treatment regimens, and response to treatment closely follow Sweet syndrome, predominantly corticosteroids, with alternative options including dapsone, colchicine, and potassium iodide.[102] There may also be an overlap in human leukocyte antigen markers.[103] Nonspecific systemic inflammatory markers, such as ESR and CRP, may be less frequently elevated compared with Sweet syndrome because it is a localized variant; however, they are still elevated most of the time (as are leukocytosis and neutrophilia).[104] Triggers generally closely mirror inciting factors for Sweet syndrome; patients may have coexistent comorbidities that can occur before, during, or after diagnosis, such as hematologic disorders, solid tumors, inflammatory bowel disease, and mucosal tract infections—most commonly respiratory tract infections.[104] It may also be triggered by trauma (eg, gardening injuries, thermal injuries, intravenous line insertion), exposures to chemicals such as fertilizer, and cocaine use.[98,105–108] Thus timely and accurate diagnosis is crucial, as procedural interventions, such as surgical debridement, can exacerbate the condition.[98] Medications may also be related to disease onset such as thalidomide, lenalidomide, and indomethacin.[109–111] Other possible factors, similar to Sweet syndrome, include vaccines.[112]

Although its rarity has generally precluded extensive study, a 123-patient case series reported a slight female predominance 58%, mean age 62 years (range 3–89 years).[104] Other case series have reported incidences in older individuals with a lower female predominance.[98,113] Concomitant pulmonary disease (eg, chronic obstructive pulmonary disease, asthma, secondhand smoke

Table 2
Drugs associated with development of Sweet syndrome

Drug Class	Medication Name
Analgesics	Aceclofenac [21506881], acetaminophen codeine [29121137], aspirin [28300447], celecoxib [11464196, 27060586], diclofenac [26288456], ibuprofen [28300447], metamizole [19702979], phenylbutazone [18420076]
Antibiotics	Amoxicillin-clavulanate [35170473], azithromycin [28300447], cephalexin [28300447], ciprofloxacin [21893237], clindamycin [20398826, 17723089], doxycycline [18779110], levofloxacin [35170473], minocycline [23158645, 1469130, 1826487], nitrofurantoin [10190073], norfloxacin [14702513], ofloxacin [16213026], piperacillin-tazobactam [18360136], quinupristin-dalfopristin [14619389], tetracyclines [12207601], trimethoprim-sulfamethoxazole [8621829, 35866718, 29538086, 20199454, 19221284, 19002360, 18576306]
Anticoagulants	Dabigatran [36041703], low-molecular-weight heparin [30907689]
Antidepressants	Amoxapine [14690466], citalopram [14690466]
Antiepileptic drugs	Carbamazepine [21152216], diazepam [11095204], gabapentin [28958741], lamotrigine [32995432]
Antifungals	Fluconazole [28891066], ketoconazole [25590289]
Antigout	Allopurinol [26684631]
Anti-HIV drugs	Abacavir [15337997]
Antihypertensives	Captopril [28300447], enalapril [28300447], hydralazine [8547013, 1895286, 2193156, 31720352, 22530328, 2944382]
Antimalarial	Chloroquine [19171233], hydroxychloroquine [31540835]
Antineoplastics	Azacitidine [33406304, 31820051, 29044459, 26327709, 24341928, 22555082, 21496689], bortezomib [25784226, 24338786, 23905772, 19442799, 19231647, 16464758, 16197442], capecitabine [28011887], carboplatin [35725278], cytosine arabinoside [10914942], dabrafenib [30724336, 29683894], dasatinib [30932238, 26825166], decitabine [23178879], docetaxel [35725278], enasidenib [34026142], erlotinib [35841359], gemcitabine [22082849], gilteritinib [26886840], ibrutinib [33112465], imatinib [15781678], ipilimumab [32089071, 29396853, 25437997, 24629370, 24113862], ixazomib [34114780, 31828594, 31455150], lenalidomide [19577327], letrozole [32206641], midostaurin [35495179, 34417240], mitoxantrone [21148263], nilotinib [18347292], palbociclib [32598526], pemetrexed [33028131], quizartinib [26886840], ruxolitinib [33112465, 34529266, 28824063, 25707420], sorafenib [23687091], topotecan [24371676], trametinib [30724336, 29683894], vedolizumab [29900741], vemurafenib [24617955, 24372055], vorinostat [21870904]
Antiplatelets	Clopidogrel [32888004], ticagrelor [27146134]
Antipsychotics	Clozapine [12411238], perphenazine [14690466]

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Table 2
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Drug Class	Medication Name
Antiviral	Acyclovir [28300447], interferon beta [23786157, 25756490], pegylated interferon alpha [18937663], ribavirin [18937663]
Biological immunomodulators	Abatacept [25117161], adalimumab [22670004, 32567672], infliximab [21798483], risankizumab [35135798], toclizumab [31921506]
Diabetes/heart failure medications	Dapagliflozin [31603973]
Diuretics	Furosemide [15954518]
Erythropoiesis-stimulating agents	Erythropoietin [18457725]
Hormonal agents	Benzylthiouracil [19442798], levonorgestrel-releasing intrauterine device [15086998], oral contraceptives [25772734, 11834860, 1834046], propylthiouracil [10583195], triphasil [1834046]
Immunostimulants	Granulocyte colony-stimulating factor (pegfilgrastim [35389579, 15858487, 1375012]), granulocyte-monocyte colony-stimulating factor (sargramostim [15224368]), IL-2 [20486462]
Other small molecule antiinflammatory agents	Mesalamine [29574433], sulfasalazine [27235662, 23879316]
Proton pump inhibitors	Esomeprazole, omeprazole [26114067]
Retinoids	13-cis retinoid acid [12461805], acitretin, all-trans retinoid acid [9922053], isotretinoin [25324016, 12461805]
Small molecule immunosuppressives	Azathioprine [35983669, 30074533, 28203157, 27090551, 26299606, 26219289, 25791317, 26120462, 23955987, 23294021, 22448458, 18775203, 18623176, 23677084]

Pubmed Identifiers for associated references are enclosed in brackets.
Abbreviation: IL-2, interleukin-2.
Adapted from Cohen, P.R. Sweet's syndrome - a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis 2, 34 (2007). https://doi.org/10.1186/1750-1172-2-34.

exposures, oxygen dependence) was reported in 66% of patients in a 2019 retrospective case series; it is possible that disease onset may be related to vascular disruption and/or acral cyanosis.[113]

Histopathology

The clinical differential for Sweet syndrome is broad, and thus, histologic correlation can facilitate an accurate diagnosis. Lesional punch biopsies extending into the subcutis of active papules/plaques are standard. In some cases, a second biopsy specimen may be useful for bacterial, fungal, and mycobacterial cultures. Swab specimens can be obtained from pustules to be sent for culture, and the authors recommend microbial pathology, as Sweet syndrome can present similarly, both clinically and histologically, to skin infections such as cellulitis and/or abscesses.

Typical histologic features include prominent superficial edema, dense neutrophilic infiltrate in the upper and middermis, leukocytoclasia, endothelial swelling, possible eosinophils, and/or lymphocytes/macrophages in older lesions. However, several atypical histologic variants exist as mentioned earlier (**Fig. 2**).

Imaging

Laboratory testing

Leukocytosis with neutrophilia is common in all forms, and ESR and CRP elevations are also common. Extracutaneous involvement may drive abnormalities on a complete metabolic panel and/or urinalysis. Thus, obtaining a complete blood count with differential, complete metabolic panel, ESR, CRP, urinalysis, and pregnancy test (in childbearing aged women) is recommended. Additional tests may be appropriate depending on the clinical context, such as chest radiographs for patients with suspected pulmonary involvement. Computerized tomography scans to assess for underlying malignancy may be warranted, although further

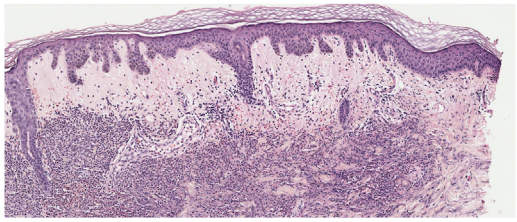

Fig. 2. Typical histopathologic findings of Sweet syndrome: prominent superficial edema with a dense neutrophilic infiltrate primarily in the dermis. (Image courtesy of PathPresenter.)

workup with laboratory tests and/or imaging is generally appropriate only when suspicion is relatively high (ie, weight loss and so on). Age-appropriate cancer screening and a comprehensive review of medications are advised in all patients with Sweet syndrome.

DISCUSSION

Guidelines/Therapeutic Options

Current evidence

Therapeutic ladder Evidence to guide management for Sweet syndrome is primarily limited to small nonexperimental descriptive studies. Although classic Sweet syndrome may resolve spontaneously, its disease course can be unpredictable, and treatment may accelerate resolution.[1] In addition, reports of spontaneous resolution seem to be relatively sparse; in a retrospective study of 80 patients, resolution without treatment occurred in 20% of patients.[114] Another retrospective case series of 48 patients reported resolution without therapy in only 6% of patients.[115] Malignancy-associated cases tend to be recalcitrant and warrant treatment.

Systemic corticosteroids (oral prednisone, 0.5–1 mg/kg/d) are first-line therapy for Sweet syndrome and typically result in rapid improvement (within 48 hours), which can aid in establishing a diagnosis.[4,116] After achieving disease control, corticosteroids can be tapered over 4 to 6 weeks.[116] However, they are associated with potential side effects, and several common comorbidities can make systemic corticosteroids unfavorable such as hypertension, hypercholesterolemia, diabetes, and osteoporosis. Patients with extensive disease severity typically require oral systemic treatment, and severe refractory disease may warrant pulse-dosed intravenous corticosteroids (methylprednisolone 500–1000 mg daily for 3–5 days).[11] Because Sweet syndrome can exhibit pathergy, it may be appropriate to attempt oral pharmacologic management before intravenous medications, injectables, and/or procedural intervention.[5] High-potency topical (clobetasol 0.05% ointment) and/or intralesional corticosteroids (triamcinolone 3–10 mg/mL) may be appropriate for localized involvement and/or as adjunctive therapies to systemic treatment.[116]

The most commonly used nonsteroidal systemic therapies are dapsone, colchicine, and potassium iodide.

Dapsone (25–200 mg daily) can be a favorable treatment option for Sweet syndrome.[116,117] Improvements are generally observed within 1 to 3 weeks.[117] Because dapsone is associated with agranulocytosis and drug-induced hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, it is important to test G6PD enzyme levels before initiation of therapy and routinely monitor blood counts.

Colchicine (0.6 mg 2 to 3 times daily) is used for several neutrophilic dermatoses, including Sweet syndrome. Similar to dapsone, small uncontrolled studies have reported high response rates and improvements within 1 to 3 weeks.[118–120] Colchicine is associated with several side effects such as myelosuppression, neuropathy, and myopathy; however, the most common treatment-limiting side effect is gastrointestinal upset.[121]

Potassium iodide (20–30 drops [1000–1500 mg] saturated solution daily or 300 mg pills 3 times daily) has shown comparable response times as corticosteroids (within 48 hours) and may be a particularly effective option for cases associated with underlying vasculitis and thyroid disease.[20] Potential side effects include gastrointestinal upset, reversible hypothyroidism, acneiform skin eruptions, and headache.[122]

Other small molecule immunosuppressants and nonsteroidal antiinflammatory drugs can be effective. Cyclosporine (2–4 mg/kg/d) is a fast-acting steroid-sparing option (initial responses within 1 week) although its side effects (hypertension and nephrotoxicity) can preclude prolonged use.[20] Methotrexate (5–20 mg weekly) can address inflammatory conditions associated with Sweet syndrome and, in our experience, may be favored by oncologists for malignancy-associated cases. Initial responses (median 1.5 months) may occur slightly slower than both systemic corticosteroids (0.25–0.5 months) and dapsone (1 month).[27,117,123] Indomethacin (150 mg daily for 1 week then 100 mg daily for 2 weeks) has been studied prospectively (n = 18) with a high (94%) response rate.[124]

Other systemic therapies with growing evidence can be found in **Table 3**.

Pediatric Sweet syndrome lacks extensive study, and approach to treatment follows the management ladder for adults.

Treatment of neutrophilic dermatosis of the dorsal hands also closely follows Sweet syndrome; oral

glucocorticoids and dapsone have been effective in small case series.[97,98,125] It is unclear whether minocycline can yield sustained responses.[125]

CLINICAL OUTCOMES

Prognosis and risk of recurrence vary based on the underlying cause. Classic Sweet syndrome can spontaneously resolve within 5 to 12 weeks or within a few weeks in patients who receive systemic treatment.[9] In contrast, malignancy-associated disease is typically more resistant to treatment and may take longer to resolve. Relapses may occur on tapering or discontinuation of therapy and seem to be more likely in patients with malignancy-associated disease; recurrence rates are roughly 69% in patients with underlying hematologic malignancy compared with 30% in patients with classic Sweet syndrome.[10,126,127] Leukocytoclasia may be associated with higher recurrence rates.[128]

On healing, milia and scarring may occur, and postinflammatory hyperpigmentation typically takes several months to resolve.[6,40] However, cutaneous lesions of Sweet syndrome usually heal without scarring if ulceration does not occur.[10]

CONTROVERSIES AND CONSIDERATIONS

There are several limitations that preclude definitive conclusions.

Regarding interpretation of treatment data, the characteristic relapsing-remitting course of Sweet syndrome can make outcomes difficult to interpret. Furthermore, studies to support these medications are limited by their sample size and, in some cases, by the concomitant use of corticosteroids. Numerous studies had heterogeneous

Table 3
Medications with growing evidence for the treatment of Sweet syndrome

Drug Class	Medication Name
Antibiotics	
Antimycobacterial	Clofazimine [8089280, 11893223]
Nitroimidazoles	Metronidazole [7799365]
Tetracyclines	Doxycycline [8504055, 11893223, 28108184], minocycline [2099706]
Antineoplastics	Azacitidine, chlorambucil [2758862], cyclophosphamide [22115387, 12072085, 1466198]
Biologics	
Anti-CD20	Rituximab [26998300, 35333375]
IL-1 antagonists	Anakinra [18192308, 21464561, 31263644], rilonacept [21464561]
IL-12, IL-23 antagonists	Ustekinumab [36447766, 30003991]
JAK inhibitors	Baricitinib [27051705, 26998300, 27028556, 35157247, 33914946], tocilizumab [32681397, 31089823]
TNF-alpha inhibitors	Adalimumab [27028556, 32833303, 34897822], etanercept [19509095, 17043542], infliximab [30376667, 30074533, 32901971, 29474532]
Immune globulins	Intravenous immunoglobulin [24395855, 20369066, 16354255]
Immunosuppressive small molecules	Azathioprine [11893223, 8089280, 17655751, 9091476], cyclosporine [8033398, 1637692, 24750407, 1467297, 11893223], lenalidomide [24850455], tacrolimus [11253280], thalidomide [16021163]
Other immunomodulator	Interferon alpha [11893223, 7727840]
Other small molecule antiinflammatory agents	Sulfasalazine [21062595]
Retinoids	Acitretin [32207168, 34676629], etretinate [8900854, 11893223]

Pubmed Identifiers for associated references are enclosed in brackets.
Abbreviations: IL, interleukin; JAK, Janus kinase; TNF, tumor necrosis factor.

samples with a combination of classic, malignancy-associated, and drug-induced cases that may have variable responses to therapy. Recurrence rates and time to relapse are also not well characterized.

Determining precise triggers and underlying causes can be difficult. Several medications effective at treating Sweet syndrome have paradoxically been associated with induction of disease such as azathioprine, ipilimumab, adalimumab, nivolumab, abatacept, tocilizumab, and vedolizumab, among others.[129–131] Because several reports of drug-induced disease have involved therapies that can be used to treat Sweet syndrome and/or underlying conditions associated with Sweet syndrome, it is unclear whether the conditions contributed to the onset of disease versus solely the drug. Some drug reactions can also present as neutrophilic dermatoses and closely resemble Sweet syndrome such as azathioprine hypersensitivity syndrome.[132] Nevertheless, there is an increasing incidence of reports of drug-induced disease that has occurred in conjunction with more widespread use of cancer therapies.[20] It has also been hypothesized that malignancy-associated disease and anticancer therapy–induced disease may exhibit distinguishable behavior; however, further study is needed to more clearly define these differences.[20]

SUMMARY

Recommendations

Conclusions and future directions

In summary, the precise cause of Sweet syndrome remains unclear. It seems to be multifactorial and related to immune stimulation/alteration/dysregulation (infection, autoimmune disease/malignancy, transplant, immunodeficient states), chemical and physical insults, and various medication exposures. It may share features with other neutrophil-rich cutaneous disorders such as pyoderma gangrenosum. Although systemic corticosteroids provide rapid improvements and are first-line therapy for Sweet syndrome, there are a multitude of steroid-sparing small molecule and biological therapies that seem effective with variable response times. However, most of the evidence is limited to retrospective nonexperimental descriptive studies such as case series and case reports. Although more robust investigations with larger sample sizes are needed, future studies might consider separating malignancy-induced cases from classic and drug-induced for analyzing disease courses and responses to therapy.

CLINICS CARE POINTS

- Lesional biopsies of active lesions and tissue cultures should be obtained to evaluate for alternative diagnoses.
- Basic laboratory workup is indicated in all patients with Sweet syndrome, and in some cases, additional imaging/specimen sampling is warranted based on suspected underlying cause and/or extracutaneous involvements.
- There are several nonsteroidal small molecule and biological therapies with growing evidence for their effectiveness that can be used for patients who cannot tolerate corticosteroids and/or require prolonged therapy.

DISCLOSURES

The authors have no relevant conflicts to disclose.

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