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AUTOIMMUNITY (T. TARRANT, SECTION EDITOR)

Idiopathic, Refractory Sweet's Syndrome Associated with Common Variable Immunodeficiency: a Case Report and Literature Review

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Abstract

Purpose of Review Sweet's syndrome (SS) is classically considered a hypersensitivity reaction often associated with autoimmune disorders and malignancy. SS has also been increasingly reported to occur with immunodeficiencies. We present a case of treatment-refractory, systemic SS as the initial manifestation in a young child with common variable immunodeficiency (CVID). We also review current literature about SS and concurrent immunodeficiencies and autoimmunity in CVID patients.

Recent Findings Few case reports exist regarding the co-occurrence of Sweet's syndrome and primary immunodeficiencies. SS is characterized by a pro-inflammatory state with a neutrophil predominance resulting in a spectrum of clinical manifestations. CVID is a multifactorial antibody deficiency that can be associated with autoimmunity, which some studies have proposed to be secondary to altered CD21 expression. SS occurring in patients with CVID has been infrequently reported, and one case study demonstrated improvement of Sweet's associated skin lesions with immunoglobulin replacement. In our case, the patient had multi-system SS refractory to multiple immunomodulatory therapies. To our knowledge, this is the first report of the effective and safe use of intravenous tocilizumab and oral lenalidomide to treat SS in a child with CVID. Immunoglobulin replacement reduced the frequency of infections and may have contributed to the opportunity to wean the immunosuppressive therapies for Sweet's syndrome.

Summary Sweet's syndrome as an initial manifestation of co-occurring immunodeficiencies is rare, and providers need a high index of suspicion. In addition, treatment of SS associated with an immunodeficiency can be a challenge. Treatment with immunoglobulin replacement reduces the frequency of infections, and in some patients with concurrent SS may improve skin lesions and reduce the need for immunomodulator therapy. Further study is necessary to better understand the pathogenesis of CVID in patients with SS and to identify possible biomarkers that predict who with SS are at risk for developing hypogammaglobulinemia.

Keywords Neutrophilic dermatoses · Sweet's syndrome · Common variable immunodeficiency · Primary immunodeficiency · Hypogammaglobulinemia

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Abbreviations

AGEP	Acute generalized exanthematic pustulosis
BAFF-R	B cell activating factor receptor
CVID	Common variable immunodeficiency
CGD	Chronic granulomatous disease
G-CSF	Granulocyte-colony stimulating factor
GLILD	Granulomatous lymphocytic interstitial lung disease
HIV	Human immunodeficiency virus
ICOS	Inducible co-stimulator
RA	Rheumatoid arthritis
SCID	Severe combined immunodeficiency
SS	Sweet's syndrome

SLE Systemic lupus erythematosus
TACI Transmembrane activator calcium-modulator and cyclophilin ligand interactor

Introduction

Common variable immunodeficiency (CVID) is an immune deficiency disorder characterized by impaired antibody production and a heterogeneous presentation of varied levels of immune dysregulation [1]. Noninfectious manifestations of CVID include autoimmunity, chronic lung disease, enteropathy, granulomatous inflammation, and an increased risk for malignancy. Proper management of CVID includes immunoglobulin replacement and close surveillance for the development of additional comorbidities [2]. Sweet's syndrome, or acute febrile neutrophilic dermatosis, is a hypersensitivity reaction characterized by fever, neutrophilia of the blood and upper dermis, and painful cutaneous eruptions [3]. This inflammatory skin condition is typically associated with autoimmune disease and malignancy. Few reports exist describing Sweet's syndrome in association with primary immunodeficiencies [4–11]. In this case report and literature review, we present a young child with idiopathic, treatment-refractory Sweet's syndrome who was subsequently diagnosed with CVID. To our knowledge, this is one of very few cases reporting the development of CVID in the setting of Sweet's syndrome. In addition, this is the first case reporting the effective and safe use of intravenous tocilizumab in combination with lenalidomide for treatment of severe, refractory Sweet's syndrome. We will also review current literature regarding additional humoral and cellular immunodeficiencies that have been reported with Sweet's syndrome. Most importantly, we hope to educate the reader regarding the importance of screening patients with acute febrile neutrophilic dermatoses, such as Sweet's syndrome, for underlying primary and acquired immunodeficiencies.

Case Report

A 9-year-old Caucasian male presented to medical care for evaluation of persistent fever, neutrophilia, and diffuse mucocutaneous lesions affecting the eyelids, oral mucosa, and skin. His medical history was notable for asthma, neonatal stroke, seizure disorder, Factor V Leiden deficiency, gastroesophageal reflux disease (status post Nissen fundoplication), and gastrostomy tube. He had a diffuse rash consisting of multiple erythematous papules and plaques with central and nodular crusting (Fig. 1). He was originally admitted to an outside pediatric intensive care unit after developing respiratory failure. During fiber optic intubation, he was found to have tracheal lesions. Chest radiography demonstrated increased narrowing of the patient's trachea compared to prior imaging. Complete blood count demonstrated an absolute neutrophil count of 11,000 cells/mm^3.

Due to his diffuse mucocutaneous disease and airway involvement, he was transferred to our institution's burn unit for subspecialty care. A skin biopsy revealed a dense dermal neutrophilic infiltrate characteristic of a neutrophilic dermatosis with no malignant cells or leukocytoclastic vasculitis (Fig. 2). He also underwent an airway evaluation that showed active tracheobronchial lesions with epithelial sloughing, as well as nasal lesions resulting in a near total septal perforation (Fig. 3). Bronchoalveolar lavage fluid was notable for 89% neutrophils (18,111 cells/mm^3). Pediatric rheumatology was consulted for further evaluation and concluded that he fulfilled diagnostic criteria for Sweet's syndrome based on his mucocutaneous features, skin biopsy, fever, elevated inflammatory markers (erythrocyte sedimentation rate of 33 mm/h and C-reactive protein of 21.5 mg/dL), and leukocytosis with neutrophilia (Fig. 4) [12].

The patient's extensive mucocutaneous lesions were steroid-responsive, however, he would flare with any attempts to taper. He was trialed on various immunomodulator therapies, including colchicine, anakinra, dapsone, and cyclosporine, with inadequate control. Ultimately, his disease became controlled and quiescent on intravenous tocilizumab (interleukin-6 antagonist) 10 mg/kg/dose every 2 weeks in combination with oral lenalidomide 10 mg daily. He was also successfully tapered off all systemic steroids. Follow up direct laryngoscopy and bronchoscopy showed persistent subglottic and tracheal narrowing which was treated endoscopically once quiescent (Fig. 5).

At the time of presentation, the patient had normal immunoglobulin levels for age and normal complement levels. He did have non-protective diphtheria and tetanus titers (diphtheria IgG 0.050 IU/mL, tetanus IgG 0.09 IU/mL), but he initially demonstrated an appropriate response to booster vaccination (Table 1). Over a 15-month span, he had a decline in serum immunoglobulin levels and vaccine responses. In parallel, he developed significant infections including recurrent and chronic upper and lower respiratory tract infections, and several episodes of otitis media requiring tympanostomy tube placement. At 12 years of age, he was admitted to the hospital for pneumonia. During this admission, he was evaluated by pediatric allergy/immunology for an immunodeficiency. He was found to have hypogammaglobulinemia: IgG 290 mg/dL (600–1700 mg/dL), IgM < 25 mg/dL (35–290 mg/dL), and IgA 16 mg/dL (40–400 mg/dL). He also had poor and unsustained responses to pneumococcal conjugate and polysaccharide vaccines. Tetanus antibody titers were also declining, being previously protective at 0.49 IU/mL several years prior and non-protective at 0.05 IU/mL at 12 years of age. Other immunodeficiency states were excluded, as evidenced by normal complement levels, neutrophil oxidative burst, and quantitation of B, T, and NK cell populations. Plasma

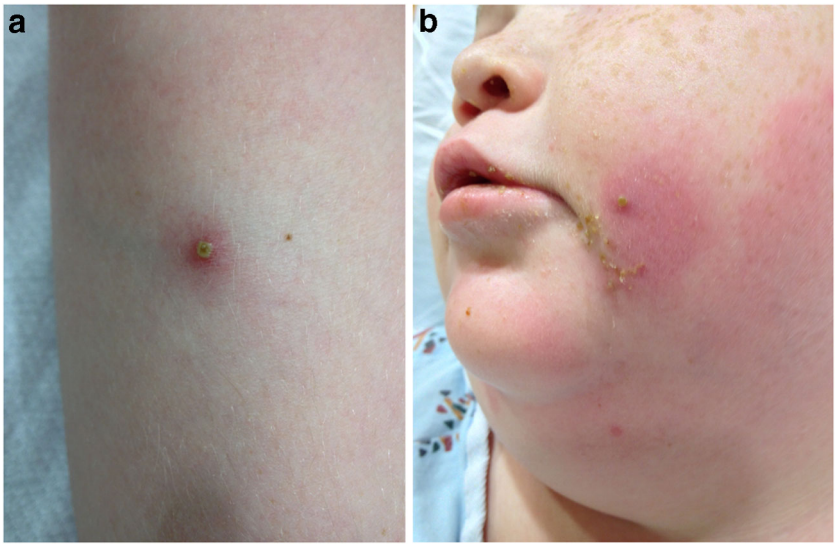

Fig. 1 Cutaneous findings. **a** The patient developed several erythematous papules and plaques, with some central, nodular crusting to his extremities (shin shown here). **b** He was also noted to have facial lesions

adenosine deaminase 2 (ADA2) activity was measured, which was normal—ruling out deficiency of ADA2 (DAD2). Based on his clinical history, immunoglobulin levels being greater than two standard deviations below the mean, and poor vaccine responses, he was diagnosed with CVID.

While admitted, he received a dose of IV immunoglobulin replacement (400 mg/kg/dose). He was subsequently transitioned to subcutaneous immunoglobulin replacement. His total IgG improved to 828 mg/dL approximately 2 months following initiation of therapy. He also clinically improved with a reduced frequency of upper respiratory tract infections and increased energy and appetite. Over the subsequent months, he was successfully weaned off of lenalidomide followed by tocilizumab without any recurrence in his Sweet's syndrome. More than a year after his CVID diagnosis, his total IgG remains stable at 810 mg/dL.

Discussion and Literature Review

Our patient exemplifies the heterogeneity of immune dysregulation seen in CVID. CVID is more than an immune deficiency, and there is a myriad of inflammatory clinical manifestations that can be seen in individuals affected by CVID. In our patient's case, he had a severe, refractory form of neutrophilic dermatosis. There are limited case reports and studies regarding the presence of comorbid immunodeficiencies in Sweet's syndrome. In this review, we will further discuss

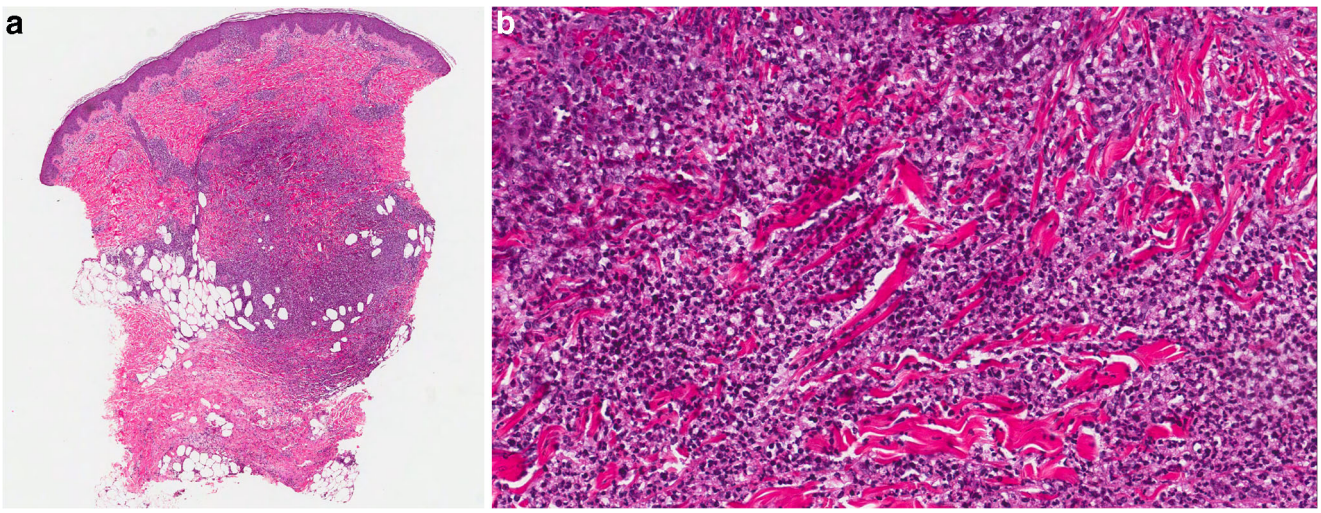

Fig. 2 Dermatopathology slides. Courtesy of Paul B. Googe, MD, Department of Dermatology, University of North Carolina, Chapel Hill, NC. **a** Punch biopsy of the patient's skin showed a dense accumulation of cells in the lower dermis and upper subcutaneous fat. **b** Neutrophils filled interstitial spaces and formed confluent sheets, characteristic of a neutrophilic dermatosis, with no malignant cells or macrophages noted

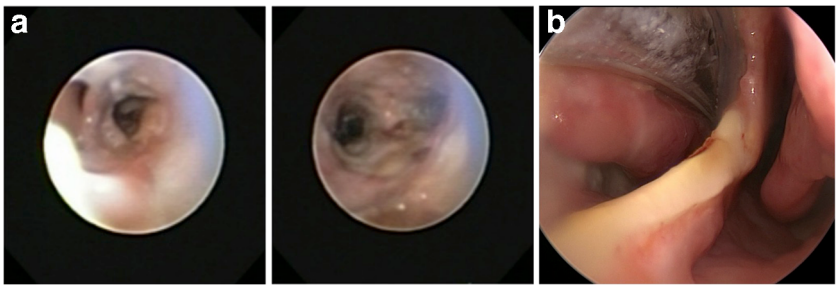

Fig. 3 Airway evaluation. Courtesy of Carlton J. Zdanski, MD, Department of Otolaryngology, University of North Carolina, Chapel Hill, NC. Direct laryngoscopy showed diffuse epithelial sloughing and perforation of the nasal septum

Sweet's syndrome and reported immunodeficiencies, as well as proposed mechanisms of immune dysregulation in CVID.

Sweet's Syndrome (SS)

Sweet's syndrome (SS) is a clinical syndrome characterized by fevers, neutrophilia of the blood and dermis, and tender erythematous skin lesions that are generally responsive to steroids [13]. The condition was first described by Dr. Robert Douglas Sweet in 1964 as acute febrile neutrophilic dermatosis and later given the eponym of "Sweet's syndrome." At the time, Dr. Sweet reported eight cases of an acute inflammatory skin rash associated with fever and leukocytosis. All of the patients were female and had acute infections (upper respiratory and gastrointestinal) [14]. In children, viral infections often precede the presentation of SS [15, 16]. Since then, multiple classification schemes have been developed regarding the etiology and diagnostic criteria for SS [12].

SS occurs in three major clinical settings: idiopathic (classic) Sweet's syndrome, malignancy-associated, or drug-induced [12, 13]. For the purposes of this literature review, we will focus on idiopathic (classic) Sweet's syndrome, which is most relevant to our patient's case. SS has no racial predilection and is reported worldwide. Classic/idiopathic Sweet's syndrome tends to affect adult women; however, it also affects males, and there are pediatric and young adult cases [12]. Idiopathic SS represents the majority of cases, and it can present with a variety of medical conditions. Better known associations include infections, inflammatory bowel disease, and pregnancy. Lesser known and not well-established associations include HIV and tuberculosis infections, primary immunodeficiency, rheumatoid arthritis (RA), sarcoidosis, autoimmune thyroid disease, systemic lupus erythematosus (SLE), polychondritis, dermatomyositis, and Behcet's syndrome [5, 12]. In a retrospective chart review of 77 tertiary care referrals with SS, 41 (53%) of cases were classic/idiopathic SS, 27 (35%) malignancy-associated, and 9 (12%) drug-induced. Within this cohort, seven patients had concomitant autoimmune disease including Crohn's disease, RA, SLE, Hashimoto's thyroiditis, relapsing polychondritis, and erythema nodosum [17].

Diagnosis of SS

Specific diagnostic criteria exist for both idiopathic and drug-induced SS [12, 18]. The diagnostic criteria for both entities

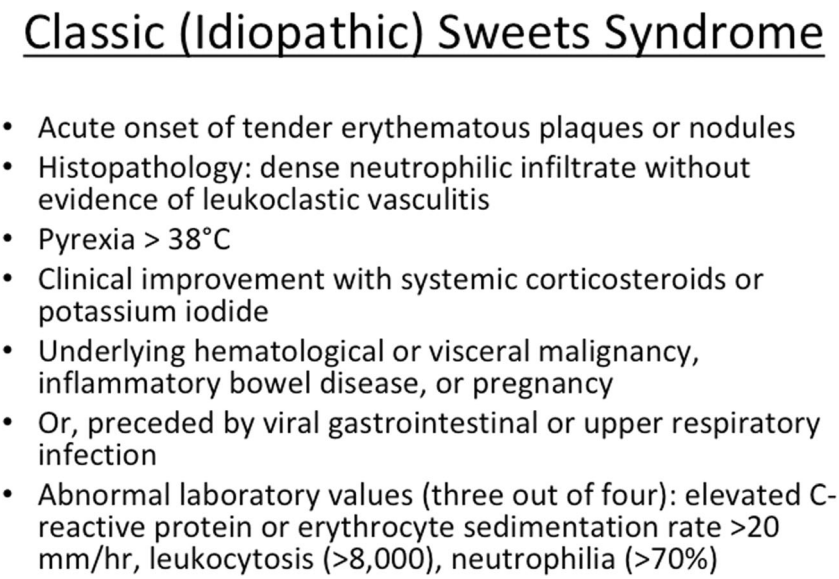

Fig. 4 Summary of the diagnostic criteria for Idiopathic Sweet's Syndrome (SS). Figure adapted from Cohen et al. *Orphanet Rare Disease* 2007 [12]. Open Access license: https://creativecommons.org/licenses/by/4.0/

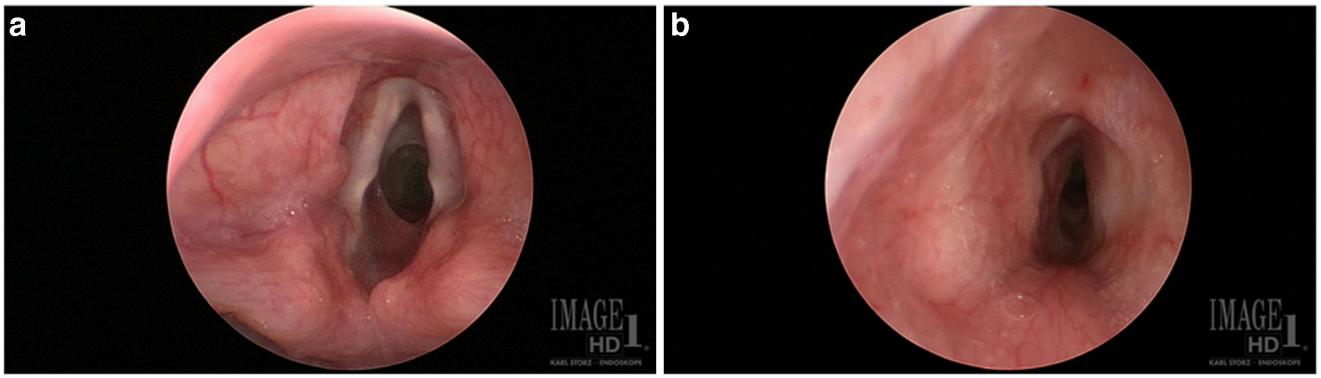

Fig. 5 Airway evaluation. Courtesy of Carlton J. Zdanski, MD, Department of Otolaryngology, University of North Carolina, Chapel Hill, NC. **a** and **b** Laryngoscopy post treatment demonstrated mature scarring of the trachea and narrowing

are similar; however, the diagnosis of drug-induced SS requires a temporal relationship with the offending drug and development of clinical symptoms. In order to diagnose idiopathic (classic) SS, the following major criteria must be met: a clinical history of abrupt onset of painful erythematous plaques and nodules and histological evidence of a dense neutrophilic infiltrate, with no evidence of leukocytoclastic vasculitis. Two out of four minor criteria must also be met, which include (1) pyrexia (> 38 °C); (2) association with underlying hematoproliferative disorder/malignancy, solid tumor, pregnancy, inflammatory disorder, or preceding respiratory or gastrointestinal infection; (3) excellent response to steroids or potassium iodide; and (4) laboratory abnormalities (ESR > 20 mm/h, elevated CRP, leukocytosis of 8000 cells/μL with > 70% neutrophils) (Fig. 4) [12, 13, 18]. In addition, an age-appropriate evaluation for malignancy (specified by the American Cancer Society) should be pursued as newly diagnosed SS could be the initial presentation of an undiagnosed malignancy [13]. Accordingly, in adults, this may include a serum protein electrophoresis with immunofixation to evaluate for myeloproliferative disorders. Screening for autoimmune conditions should be pursued if clinical presentation supports this evaluation. In some reports, a baseline antinuclear antibody screen is recommended [19].

The evaluation for extracutaneous manifestations may include additional serum studies such as hepatic function panels, BUN/Cr, urinalysis, and appropriate organ-specific imaging (i.e., chest radiography or computerized tomography, brain imaging) [13]. Skin biopsies, of course, are necessary for the diagnosis of SS. Equally important, careful review of a patient's medications is necessary to identify any potential drugs that have previously been implicated in the development of SS [13].

Table 1 Serum immunoglobulins

	Date of measurement			
	11/2013	4/2015	7/2016	9/2016
IgG (600–1700 mg/dL)	702	536	290	828[a]
IgM (35–290 mg/dL)	124	36	< 25	< 25
IgA (40–400 mg/dL)	83	108	16	8.5

[a] Following initiation of immunoglobulin replacement

Pathogenesis of SS

Sweet's syndrome is a type of neutrophilic dermatosis. The neutrophilic dermatoses are a large and heterogeneous group of cutaneous inflammatory disorders characterized by the accumulation of neutrophils in the skin. Neutrophilic infiltrates can also involve the internal organs. SS primarily involves dermal infiltrates, in comparison to the superficial infiltrates seen in aseptic pustolosis of the folds (APF) and acute generalized exanthematic pustulosis (AGEP), or deep infiltrates seen in pyoderma gangrenosum or hidradenitis suppurativa [20]. The etiology is unclear and not well understood. Some proposed mechanisms include a hypersensitivity reaction to a tumor, bacteria, or virus that leads to the production of neutrophil-activating cytokines. The ultimate result is an increase in neutrophil production and infiltrate formation [10, 15, 21]. Some argue that the steroid-responsive nature of this condition supports this hypothesis [12].

Immune dysregulation secondary to overexpression of pro-inflammatory cytokines, circulating autoantibodies, immune complexes, dermal dendrocytes, and leukotactic mechanisms have been hypothesized as potential causes [13]. For example, increased expression of IL-8, neutrophil chemotactic factor, has been identified in tissue samples of SS patients. Similarly, overexpression was noted for IL-1, IL-1 receptor, CXCL 1/2/3, and CXCL13 in SS patients compared to controls. However, the expression of these inflammatory effectors was lower when compared to samples from patients with pyoderma gangrenosum [22]. Immunohistochemical methods have also demonstrated elevation of TNF-α, IL-8, IL-17,

metalloproteinases (MMP-2, MMP-9), and vascular endothelial growth factor in SS tissue samples when compared to controls. This elevation in inflammatory cytokines and effector proteins was also noted in tissue samples from patients with amicrobial pustulosis of the folds and pyoderma gangrenosum [23]. Another study demonstrated elevated T_H1 cytokines (IL-1, L-2, IFN-γ) and normal T_H2 cytokines (IL-4) in the serum of SS patients [24].

Granulocyte-stimulating factor (G-CSF) also has a unique role in the pathogenesis of Sweet's syndrome. Kawakami et al. reported that G-CSF promotes neutrophilia by suppressing apoptosis. Serum levels of G-CSF were studied in patients with active Sweet's syndrome and active Behcet's disease (BD). The levels were compared against healthy controls and subjects with inactive SS and BD. Patients with active SS had increased serum levels of G-CSF and higher rates of neutrophil apoptosis when compared to those with inactive disease. Neutrophil apoptosis was suppressed when the neutrophils were cultured in autologous serum. Based on these results, the study authors proposed that G-CSF may suppress neutrophil apoptosis which could account for the pathogenesis of SS [25]. Interestingly, exogenous G-CSF is a frequently cited cause of drug-induced SS [26].

Needless to say, SS develops from immune dysregulation that promotes a highly inflammatory state that can affect the skin and several other organ systems. Lastly, genetic susceptibility could play a role in the development of SS. SS has been noted to occur more frequently with HLA-Bw58, HLA-B8, and HLA-Cw7 subtypes [7, 27]. In another study, SS was reported in a Japanese female infant with non-B54 HLA subtypes [28]. As many have concluded, the development of SS is multifactorial and likely cannot be isolated to a specific cause [12, 13].

Cutaneous Manifestations

The cutaneous findings associated with SS include the acute development of painful inflammatory skin lesions. The morphology can vary from erythematous papules, plaques, nodules, vesicles, and pustules. Pseudovesicular appearances can be attributed to dermal edema [3••, 7, 12, 13]. The lesions can also appear target-like, similar to erythema multiforme. SS lesions vary in size, with an asymmetric distribution and facial, neck, upper trunk, and upper extremity predominance [3••, 12]. Like pyoderma gangrenosum, pathergy (development of lesions at sites of trauma) can occur [12]. Rapid resolution with systemic steroids also suggests a SS diagnosis. Equally important, a clinical history of preceding fever and leukocytosis will assist in making this diagnosis [3••, 12, 13]. Histologically, a dense infiltration of mature neutrophils in the dermis is noted. Leukocytoclastic vasculitis and infection must be ruled out [3••, 7, 12].

Extracutaneous Manifestations

Numerous extracutaneous findings have been reported in SS patients, including bone, central nervous system, renal, intestinal, hepatic, ocular, pulmonary, cardiac, and muscular involvement [12]. The oral mucosal effects of SS are more commonly associated with hematological disorders and less often seen in idiopathic/classic SS. Oral ulcers secondary to SS are also steroid-responsive [12, 13]. The pulmonary manifestations of SS are very diverse, including neutrophilic inflammation of the bronchi, the appearance of red-bordered bronchial pustules, sterile pleural effusions with neutrophilia, and progressive pharyngeal mucosal infiltration with edema. Corticosteroid-responsive pulmonary infiltrates have also been reported [12]. In our patient's case, his initial bronchoalveolar lavage showed prominent neutrophilia. He was also noted upon presentation to have tracheal stenosis that subsequently required multiple balloon dilations. Musculoskeletal manifestations of SS include arthralgias and varying types of arthritis [19, 29].

Management

Systemic corticosteroids are the treatment of choice for Sweet's syndrome. Steroids are considered first line with a recommended dose of 0.5–1 mg/kg/day. This is typical dosing for most neutrophilic dermatoses [3••, 13, 19]. Clinical response typically occurs within days to weeks of initiation. Patients will most likely require a taper over the course of 4–6 weeks [12]. For prolonged corticosteroid therapy, the American College of Rheumatology advises calcium and vitamin D supplementation. In addition to oral administration, IV methylprednisolone pulses, topical clobetasol propionate, and intralesional triamcinolone injections have been reported as potential therapeutic options [13, 16, 19]. Other first-line therapies include colchicine and potassium iodide (KI). Colchicine decreases neutrophil chemotaxis and degranulation [19, 30]. KI works in a similar fashion as dapsone, by inhibiting neutrophil myeloperoxidase and chemotaxis [19, 31, 32].

Second- and third-line therapies are considered steroid-sparing agents. Dapsone was first reported in the mid-1980s as a possible therapeutic agent for Sweet's syndrome. It can be used as a monotherapy or as a steroid-sparing agent [19]. Anti-TNF antagonists have shown efficacy in SS patients with comorbid autoimmune diseases, such as inflammatory bowel disease and arthritis. Other reported therapies for SS include cyclosporine, non-steroid anti-inflammatory drugs, azathioprine, anakinra, thalidomide, and methotrexate. Antimicrobials have also been reported, including

doxycycline and metronidazole. Overall, evidence supporting their use is limited to case reports [19]. Our patient's SS was refractory to prolonged systemic and topical corticosteroids. Given the refractory nature and extent of his disease with critical airway involvement, additional immunomodulator therapy was required. He did not adequately respond to colchicine, anakinra, dapsone, and cyclosporine. Our case is the first reporting the effective and safe use of IV tocilizumab in combination with lenalidomide for refractory SS with extracutaneous manifestations.

SS-related lesions may resolve without therapeutic intervention; however, they may persist for weeks to months. In malignancy-associated SS, treatment and resolution of the underlying cancer may lead to resolution of SS lesions as well. Similarly, in drug-induced SS, discontinuation of the offending agent may stop the cutaneous disease. There is the risk of recurrence despite treatment. The extracutaneous manifestations and associated co-morbidities (i.e., IBD, thyroid disease) may warrant disease-specific therapies [12]. The presence of an immunodeficiency can complicate the management of an inflammatory disease process that requires immunosuppression.

In the following sections, we will review reported cases of immunodeficiency occurring in SS patients and their management [4–6, 9–11, 33, 34]. We will then discuss common variable immunodeficiency (CVID) as it relates to our patient and proposed mechanisms of autoimmunity in CVID patients.

Immunodeficiencies Reported with Sweet's Syndrome

SS occurring with an immunodeficiency in pediatric patients is rare. As previously discussed, the validity of the association between SS and primary or secondary immunodeficiencies is not well established [12]. Well-known cutaneous manifestations of primary immunodeficiencies do exist, such as erythroderma in Omenn syndrome/SCID, chronic mucocutaneous candidiasis in Th17 cell defects, and noninfectious granulomas in chronic granulomatous disease (CGD) [8]. Sweet's syndrome is not necessarily pathognomonic for an immunodeficiency [5, 16]. In a literature review of early-infancy onset SS, Gray et al. reported 20 cases of SS occurring during the first 6 months of life. Of those 20 cases, four involved immunodeficiencies including humoral defects (2), CGD (1), and HIV infection (1). Pre-malignant states and autoimmune diseases were also reported. The study authors concluded that SS could be the harbinger of a serious systemic illness in a young child [5].

SS and T Cell Lymphopenia

Lipp et al. reported a case of persistent SS occurring in a young child with $CD3^+$ T cell lymphopenia and reduced lymphocyte proliferation to candida and tetanus toxoid. This patient had protective antibody responses to diphtheria, tetanus, and pneumococcal immunization. Adenosine deaminase level was within normal limits, ruling out severe combined immunodeficiency [4]. This patient also had refractory SS skin lesions to glucocorticoids, dapsone, and indomethacin. However, this patient improved with vancomycin, suggesting that the child's SS was a hypersensitivity reaction to an opportunistic infection or due to immune dysregulation following infection predisposed this patient to the development of SS [4]. SS has also been documented in association with secondary T cell lymphopenia due to HIV in children and adults [4, 33, 34].

SS and Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is an immunodeficiency characterized by a defect in nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase, the enzyme responsible for phagocyte respiratory burst. Defects in oxidative metabolism impair intracellular microbe killing. CGD manifests as recurrent pyogenic bacterial and fungal infections as well as granuloma formation. CGD patients are more susceptible to infections with *Staphylococcal auerus*, *Burkholderia cepacia*, *Serratia marcescens*, *Aspergillus* species, and *Nocardia* [11]. CGD is rare and is estimated to occur in 1/200,000 live births [2, 10]. Cases of SS occurring in CGD patients have been reported [9–11]. The mechanistic relationship between the neutrophil dysfunction seen in CGD and proliferation related to SS is not well characterized and warrants further study [11].

Sweet's syndrome was reported as the initial presentation of CGD in a toddler male with a history of congenital syphilis, alopecia, and recurrent sinopulmonary infections. Following the abrupt onset of persistent fever, papulopustular skin lesions, and lymphadenopathy that were unresponsive to antibiotics and prednisolone, the skin lesions were biopsied. Punch biopsy revealed mixed neutrophilic and granulomatous infiltrates. His presentation, limited improvement with steroids, and histologic findings prompted his providers to evaluate for an immunodeficiency. In this patient's case, a diagnosis of CGD was confirmed with an abnormal nitroblue trazolium dye test (NBT), reduced superoxide production (DHR 123 fluorescence assay), and *CYBB* missense mutation on the X-chromosome. Dapsone was added to his treatment regimen, resulting in resolution of skin lesions and hair regrowth. Interestingly, dapsone inhibits myeloperoxidase activity which suppresses neutrophil activity. This suppression has two-fold effects: reducing neutrophil-mediated tissue damage secondary to SS and mitigating the chronic inflammation secondary to CGD [10].

Another case report described the development of SS in a toddler with an established CGD diagnosis. During the treatment of *MSSA* necrotizing granulomatous lymphadenitis, the

child developed persistent fevers and diffuse papulopustular and vesicular lesions. This patient also had pathergy, which has been noted in other cases of SS affecting males with X-linked and autosomal recessive CGD. Reported infections and co-morbidities included granulomatous colitis, inguinal lymphadenitis, invasive aspergillosis *Staphylococcal aureus* and *Klebsiella pneumoniae* infections [5, 6, 9, 11].

SS and Hypogammaglobulinemia

In a literature review of early-onset SS, Gray et al. reported a case of biopsy-proven SS in a young infant with hypogammaglobulinemia. This patient's symptom complex included fevers, hepatosplenomegaly, diffuse erythematous plaques and nodules, anemia, and neutrophilia. Bone marrow biopsy revealed tri-lineage dysplasia, and further immune evaluation demonstrated profound hypogammaglobulinemia and reduced peripheral and bone marrow B cells (specifically $CD19^+$, $CD10^+$, $CD34^-$). He had normal Bruton tyrosine kinase gene analysis. The patient was ultimately diagnosed with primary myelodysplastic syndrome and hypogammaglobulinemia. He was ultimately managed with mycophenolate mofetil and immunoglobulin replacement [5].

SS and Common Variable Immunodeficiency (CVID)

Similar to our patient, CVID was previously reported once in a 17-year-old male with childhood SS (diagnosed during infancy), that was marginally responsive to oral corticosteroids. At diagnosis, the patient had a normal immunological evaluation, including normal immunoglobulins, $CD4^+$ T cell count, T cell functional assays, complement levels, and NBT test. During early childhood, he developed frequent lower respiratory tract infections and gastroenteritis, prompting a further workup. Consistent with CVID, he had low IgG, undetectable IgM, and absent antibody responses to pneumococcal and tetanus antigens. He was ultimately managed with immunoglobulin replacement and dapsone, but skin lesions often recurred with dapsone drug holidays. As with our patient, the frequency of infections decreased and skin symptoms improved with IVIG [35].

A similar case of hypogammaglobulinemia and SS that was effectively treated with IVIG has been reported. As in the previous case, there was a dramatic improvement in skin lesions within 48 h of starting IVIG (1 g/kg). The patient was maintained on immunoglobulin replacement and dapsone. Several months later, the patient continued to have smaller SS lesions compared to presentation [7]. Indeed, the diagnosis of Sweet's syndrome in a pediatric patient may herald that other features of immune dysfunction are present. Given that reports of CVID occurring in SS patients are exceedingly rare, we will review CVID as a disease and possible mechanisms to account for concurrent autoimmunity in CVID patients [35].

Common Variable Immunodeficiency (CVID)

CVID is a humoral immunodeficiency that affects up to 1:10,000 to 50,000 individuals in North America and Europe. The majority of patients are diagnosed between 20 and 40 years of age. Peaks in CVID diagnoses occur in childhood and during the third decade of life. Males are generally affected equally as females; however, there is emerging evidence of a male predominance [1, 36–38]. Some estimate that 20% of CVID diagnoses are made under the age of 3. This is quite controversial as making a diagnosis of CVID in children under 4 can be complicated by possible immaturity of the immune system (i.e., transient hypogammaglobulinemia of infancy) [36].

Diagnosis of CVID

Our patient was diagnosed with CVID in accordance with the European Society for Immunodeficiency (ESID) and Pan American Group for Immunodeficiency (PAGID) (1999) diagnostic criteria for CVID [1, 38]. In addition to hypogammaglobulinemia, impaired specific antibody responses, +/− reduction in B cell populations, and the absence of other immunodeficiencies are hallmarks of making this diagnosis [2]. Our patient had notable hypogammaglobulinemia with IgG, IgM, and IgA all two standard deviations below the mean for patient's age. He also demonstrated poor and unsustained responses to pneumococcal conjugate and polysaccharide vaccines [2, 36]. The ESID/PAGID criteria also require exclusion of other systemic causes of hypogammaglobulinemia, including iatrogenic causes, malignancy, protein loss, or hypercatabolism [38]. Accordingly, other primary and secondary immunodeficiencies were ruled out in our case, such as complement deficiencies, combined cellular and humoral immunodeficiencies, neutrophil defects, and human immunodeficiency virus (HIV) (Table 2) [1].

Clinical Presentation of CVID

The presentation of CVID is variable, which may contribute to delays in diagnosis. Some reports suggest up to a 6–7-year delay [36]. Noninfectious, inflammatory, or autoimmune diagnoses could be the initial manifestation of CVID. As a result, patients may first present to different subspecialists, such as gastroenterology, pulmonology, and rheumatology, all before evaluation with an allergist-immunologist. In one review, this is estimated to be up to 20% CVID patients [36, 38, 39]. Hallmark infections of CVID include frequent sinopulmonary infections, particularly pneumonia. However, patients with CVID may present with other inflammatory or autoimmune co-morbidities. For this

Table 2 Additional immunological workup

	Results (reference value)
Diphtheria IgG titer (IU/mL)	0.48 (> 0.15)
Tetanus IgG titer (IU/mL)	0.05 (> 0.15)
Pneumococcal titers for PCV13 serotypes	Protective to 2/12 serotypes (> 70%)
Absolute lymphocyte count (cells/mcL)	400 (1900–3700)
Absolute CD3 count (cells/mcL)	1411 (1000–2200)
Absolute CD4 count (cells/mcL)	794 (530–1300)
Absolute CD8 count (cells/mcL)	600 (330–920)
Absolute CD19 count (cells/mcL)	159 (110–570)
Absolute CD 16/56 count (cells/mcL)	194 (70–480)
C3 complement (mg/dL)	113 (88–171)
C4 complement (mg/dL)	8.8 (15–48)
Neutrophil oxidative burst	Normal
HIV antibody/antigen	Nonreactive

reason, some argue that CVID exists as two major phenotypes: predominantly infectious versus inflammatory [36]. This can complicate management of CVID; which includes prompt treatment of infections and immunoglobulin replacement when indicated, as treatment of autoimmune and inflammatory conditions may require systemic immunosuppression [36, 39].

Pathogenesis of CVID

The exact etiology of CVID remains unclear, although there is agreement that intrinsic B cell defects leading to low IgG or IgM production despite adequate signaling causes hypogammaglobulinemia. There is a failure of B cell differentiation into switched memory B cells and plasma cells. During maturation, B cells circulate between the bone marrow, lymph nodes, and splenic follicles. They either undergo apoptosis or activation by antigens. Derangements in this process can result in a reduction in plasma cells [1, 38]. Some proposed mechanisms include altered calcium signaling, alterations in toll-like receptor signaling (TLR7 and TLR9), impaired upregulation of activation markers, defects in early B cell development, and abnormalities in T cell signaling (i.e., CD40 ligand) [1]. Multiple genetic defects have been identified by sequencing techniques including defects affecting the B cell antigen receptor complex (CD19, 81, 21), CD20, B cell activating factor receptor (BAFF-R), inducible co-stimulator (ICOS), and transmembrane activator calcium-modulator and cyclophilin ligand interactor (TACI). Only 15% of CVID patients are currently estimated to have these specific defects [40–47]. In one study, in vitro assays of serum from CVID patients demonstrated decreased IL-12 production from dendritic cells in the presence of LPS, TNF-α, and CD40L. Similarly, affected patients had impaired antigen presentation. The study authors concluded that attenuated T cell stimulation may account for poor antibody responses to vaccines [48]. Suffice it to say, there is no single defect responsible for CVID, partially accounting for the variable presentation of immune dysregulation among patients [1].

Comorbidities

CVID is associated with several noninfectious comorbidities. There is no consensus regarding the clinical monitoring for these conditions [1, 36, 39]. Hepatic complications include biliary disease and nodular regenerative hyperplasia, which is an aggressive form of liver disease. Transaminases and ultrasound might be useful for screening and surveillance. Other gastrointestinal morbidities such as enteropathy, inflammatory bowel disease, gastritis, and pernicious anemia can also occur in CVID. CVID patients are also at risk for pulmonary disease, including bronchiectasis, interstitial lung disease, asthma, and a rarer entity called granulomatous lymphocytic interstitial lung disease (GLILD). Serial pulmonary imaging (i.e., radiography or computerized tomography) and spirometry are recommended. Equally important, pulmonary physiotherapy is highly advised for CVID patients with known lung disease as this can mitigate infection risk and further disease-related damage [1].

Autoimmune cytopenias and malignancy can also occur in CVID. Monitoring CBC/differential and obtaining a serum lactic acid dehydrogenase level should be done when indicated [1, 36, 39]. Noninfectious comorbidities are treated on problem-specific basis. This often includes immunosuppressive therapies, which may heighten an immunodeficient patient's risk for infection [1].

CVID and Autoimmunity

As previously mentioned, autoimmunity is a common manifestation of immune dysregulation seen in CVID. Gathmann et al. reviewed the clinical and immunological features of 2200 CVID patients enrolled in the European Society for Immunodeficiencies Database. Among the 902 subjects for which they had access to clinical information, the most common clinical features included pneumonia (32%), autoimmunity (29%), splenomegaly (26%), and bronchiectasis (23%) [37]. In a smaller American cohort of 473 CVID patients, up to 68% of the patients had documented noninfectious manifestations of CVID, including hematologic-oncologic comorbidities, organ-specific autoimmunity, pulmonary disease (chronic lung disease, bronchiectasis), and gastrointestinal disorders (inflammatory disease, malabsorption) [39]. Individuals with

noninfectious complications had an 11-fold greater mortality risk compared to those without (hazard ratio 10.95, $p < 0.0001$). A majority of the risk was attributable to lymphoma, liver disease, functional/structural pulmonary disease, and gastrointestinal disorders, and not necessarily with autoimmunity [39]. In a more recent literature review, Azizi et al. summarized multiple CVID cohort studies and reported an estimated 30% (21–42%) of CVID patients being affected by autoimmune disease. They reported the most common complications were autoimmune cytopenias (idiopathic thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia), followed by systemic and organ-specific autoimmune diseases [49].

The proposed mechanisms for autoimmunity in CVID are vast. Autoimmunity is a failure of self-tolerance. Underlying potential mechanisms include defects in T regulatory cell development and function, B cell defects, dendritic cell defects, and exaggerated responses to tissue injury following infection [49]. Altered CD21 expression has also been proposed as a possible mechanism for breakdown in self-tolerance. Increased $CD21^{low}$ B cell populations have been reported in patients with CVID and CVID with idiopathic thrombocytopenic purpura [38]. Other proposed mechanisms include increased IFN-γ expression, increased circulating ILCs, and known CVID-related mutations, such as *TACI* defects leading to increased autoimmunity rates [50]. It is important to note that these mechanisms are not necessarily mutually exclusive.

Management

Prevention and management of infections are paramount in the care of CVID patients. Immunoglobulin replacement is necessary for the treatment of hypogammaglobulinemia and impaired specific antibody responses. Antimicrobial prophylaxis may also be indicated. IVIG may have other therapeutic benefits in CVID. For those patients with autoimmune diseases, IVIG may alleviate the immune dysregulation. Suggested mechanisms include Fc receptor blockade, down-regulation of B cells via the FcγRIIB receptor, modulation of macrophages and dendritic cells, and activation of regulatory T cells [49]. Treatment with other immunomodulators may also be required in the management of inflammatory and autoimmune comorbidities associated with CVID. Immunomodulators must be used judiciously and cautiously given their potential for increasing infection risk.

Conclusions

Sweet's syndrome is characterized by immune dysregulation resulting in serum and skin neutrophilia. Reports of co-morbid immunodeficiencies with SS are rare. Of the known cases, chronic granulomatous disease, hypogammaglobulinemia, T cell lymphopenia, and CVID have been reported in patients with Sweet's syndrome [1, 4, 5, 9–11, 35]. Our patient had idiopathic Sweet's that was refractory to traditional therapies and gradually developed waning humoral immunity. Following his diagnosis of CVID and initiation of immunoglobulin replacement, the frequency of clinical infections decreased. SS-related skin lesions also improved. In our patient's case, an autoimmune disorder possibly predated the development of an immunodeficiency. CVID confers an increased risk for autoimmunity and malignancy. The mechanisms for autoimmunity in CVID patients are vast and not well characterized [37, 49].

Most importantly, our patient's case highlights the importance of obtaining a baseline immune evaluation in patients with autoimmune disorders. We were able to trend immunoglobulin levels and vaccine titers, which allowed for a timely diagnosis and initiation of therapy. For baseline evaluations, we recommend a complete blood count and differential, quantitative immunoglobulins, vaccine responses to diphtheria, tetanus, and pneumococcal antigens. Immune surveillance may prove useful should the patient develop increased frequency of clinical infections and allow for prompt diagnosis and initiation of prophylactic antimicrobials or immunoglobulin replacement if indicated. In the case of CVID, this may result in reduced morbidity and mortality secondary to infectious and non-infectious complications.

However, it is evident that further study to understand the pathogenesis of hypogammaglobulinemia in SS patient is necessary. By characterizing the exact mechanisms responsible for hypogammaglobulinemia, this may allow for identification of potential biomarkers predictive of the development of immunodeficiency in this patient population. A major barrier for this type of work is the lack of a sizable patient cohort with SS and CVID to participate in prospective studies. One possible solution would be the development of SS patient registries. Until then, clinical monitoring of humoral immunity will be necessary to capture and promptly treat SS patients with evolving immunodeficiencies.

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Compliance with Ethical Standards

Conflict of Interest Drs. Cook, Googe, Wu, Zdanski, and Burkhart declare that they have no conflicts of interest.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from individual(s) discussed in this case report.

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