Infantile histiocytoid Sweet syndrome without an underlying systemic association

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INTRODUCTION

Sweet syndrome, also referred to as acute febrile neutrophilic dermatosis, was first reported in 1964 by Dr Robert Douglas Sweet.[1] The entity is characterized clinically by an abrupt cutaneous eruption of painful erythematous nodules and plaques accompanied by fever and leukocytosis.[2] On histopathologic examination, prominent papillary dermal edema and a dense dermal infiltrate of neutrophils are classic.[3]

In 2005, Requena et al[4] described a variant termed "histiocytoid Sweet syndrome" (HSS). HSS, although clinically indistinguishable from its classic counterpart, demonstrates an inflammatory infiltrate composed of myeloperoxidase (MPO)-positive immature mononuclear cells with a histiocytoid morphology rather than neutrophils.[2,4,5] These immature mononuclear cells simulate histiocytes both in appearance and with CD68 staining.[2,5] Therefore, MPO staining is necessary to confirm that these cells are neutrophil precursors and not true histiocytes.[5]

Sweet syndrome has been associated with underlying systemic diseases of infectious, inflammatory, autoimmune, and neoplastic nature.[3] Children account for only 5% to 8% of all cases worldwide.[6] HSS in the pediatric population is even more rare, with only 5 cases previously reported, none of which were in an infant without an underlying association.[2,7-9]

Abbreviations used:

HSS: histiocytoid Sweet syndrome
MPO: myeloperoxidase

CASE REPORT

An 11-month-old otherwise healthy Caucasian boy presented with a 3-month history of relapsing fevers ranging from 37.7 °C to 38.6 °C accompanied by irritability and a tender skin eruption that recurred in crops every 5 to 6 days. The patient's mother denied associated lethargy, arthralgias, myalgias, edema, or conjunctival injection. He was not taking any medications and was achieving his growth and developmental milestones. The patient had 3 siblings, all of whom were healthy and without recent illness.

Multiple fixed erythematous-to-violaceous nodules and plaques, some with dusky centers and several pink patches, were present on the face and extremities (Fig 1). The lesions were somewhat indurated but without vesicular, bullous, or pustular change. There was no lymphadenopathy or mucosal involvement. A lesional biopsy revealed mild papillary dermal edema and an infiltrate of $CD68^{+}$ mononuclear cells interspersed between collagen bundles in the upper half portion of the dermis (Figs 2 and 3). The cells failed to stain with S100 protein, and CD1a. MPO positivity confirmed immature cells of myeloid lineage (Fig 4). A preliminary diagnosis of HSS was made.

The patient was referred to the departments of pediatric hematology/oncology, rheumatology, and infectious disease for further evaluation. A complete blood cell count, peripheral blood smear, and

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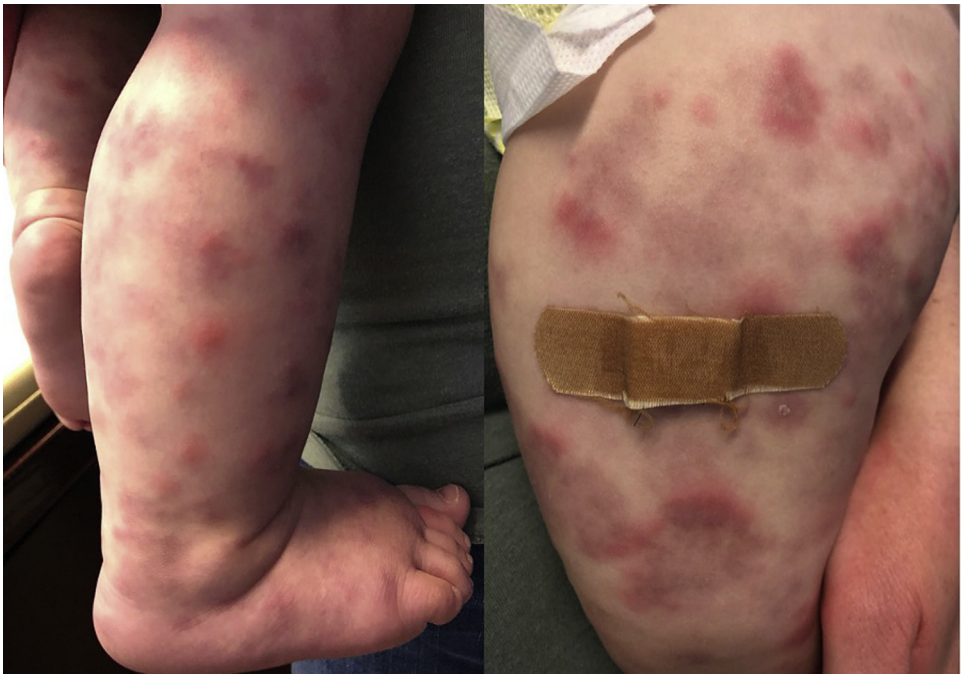

Fig 1. Clinical images on the day of in-office examination. Several scattered erythematous-to-violaceous nodules and plaques over the lower extremities.

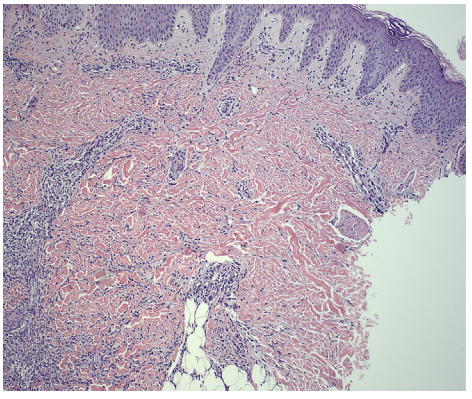

Fig 2. Histopathology of lesional tissue. Mild papillary dermal edema and a diffuse and interstitial infiltrate were noted in the mid-to-papillary dermis. There was no evidence of hemorrhage, leukocytoclasia, eosinophilia, or pustule formation in the biopsy specimen. (Hematoxylin-eosin stain.)

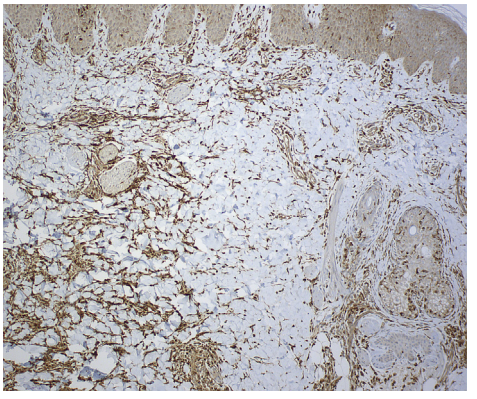

Fig 3. Mononuclear cells interspersed between collagen bundles. (CD68 stain.)

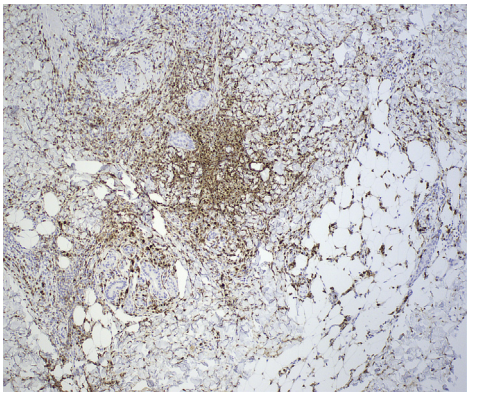

Fig 4. Reactivity of the dermal infiltrate confirming immature cells of myeloid lineage. (Myeloperoxidase stain.)

lymphocyte T cell, B cell, and natural cell panel were unremarkable. An extensive workup found no underlying associations. The patient achieved clearance with a 6-week course of oral prednisolone solution at a dose of 2.0 mg/kg/d, which was tapered gradually. With the child's excellent response to treatment, he met the established criteria for Sweet syndrome and was diagnosed with the histiocytoid variant. Over the past 14 months, no sequelae have been noted, and the patient continues to receive close monitoring by his pediatrician.

DISCUSSION

Pediatric Sweet syndrome is rare, accounting for an estimated 5% to 8% of all Sweet syndrome cases.[6] Pediatric HSS is a histopathologic variant that is even more uncommon, with only 5 previous cases documented and all infantile cases having an identifiable underlying systemic association.[2,7-9]

A diagnosis of Sweet syndrome requires both major criteria and at least 2 minor criteria.[10] The major criteria are as follows: (1) abrupt onset of painful and well-demarcated erythematous or violaceous papules or nodules and (2) dermis with neutrophilic infiltration without leukocytoclastic vasculitis. The minor criteria are as follows: (1) preceded by a respiratory infection, gastrointestinal infection, or vaccination, or associated with an autoimmune disease, underlying hematologic or visceral malignancy, or pregnancy; (2) periods of malaise and fever of >38 °C; (3) excellent response to treatment with systemic corticosteroids or potassium iodine; and (4) 3 of the following 4 abnormal laboratory workup values: erythrocyte sedimentation rate of >20 mm/h, positive C-reactive protein, leukocytosis >8000, or neutrophils >70%.[10] Because our patient's inflammatory infiltrate was composed of MPO^+ neutrophil precursors resembling histiocytes, he met both major criteria and 2 of the 4 minor criteria (malaise with high-grade fevers and rapid clearance with corticosteroid treatment), supporting our final diagnosis.

Although many cases may be idiopathic and the exact etiology is unknown, Sweet syndrome has been postulated to be a hypersensitivity reaction to bacterial, viral, or tumor antigens in response to inappropriate secretion of cytokines such as granulocyte-colony–stimulating factor and interleukin 1.[3,6] Halpern et al[6] reported that children with Sweet syndrome over 3 years of age were more likely to have an associated hematologic malignancy, whereas finding no predilection for either sex, whereas children under 3 with Sweet syndrome were predominantly male and had no associated malignancy. Preceding infection and underlying hematologic malignancy are the most common associated findings with Sweet syndrome in children.[2,6-9]

In the pediatric population, Sweet syndrome has an atypical or largely variable clinical presentation compared with the more predictable adult skin eruption.[6,10] Patients may exhibit pathergy and cutaneous findings reportedly ranging from pustules, vesicles, and bullae to oral ulcerations and atrophic scars.[2,6-9] Considering the variability in morphology, the clinical differential diagnosis is broad and includes reactive granulomatous disease, acute hemorrhagic edema of infancy, leukemia cutis, and Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis), each associated with its own unusual risks.

Biopsy is the gold standard for diagnosis and is necessary to confirm HSS. Characteristically, HSS demonstrates a diffuse and interstitial infiltrate concentrated in the mid-to-papillary dermis composed of mononuclear cells that possess large, slightly eccentric, elongated nuclei and eosinophilic cytoplasm, resembling histiocytes.[2] CD68 staining supports the diagnosis but is a relatively nonspecific marker and can be positive in true histiocytic disease. Therefore, the most striking immunohistochemical finding, which is mandatory for diagnosis, is the reactivity to MPO in these cells, confirming that they are immature myeloid cells, specifically neutrophil precursors with a histiocytoid appearance.[2,7]

Before initiation of therapy, at minimum a complete blood cell count is indicated to investigate patients with Sweet syndrome for underlying hematologic malignancy.[10] Anemia and thrombocytosis have been reported in 94% and 50% of associated cases, respectively.[10] Subspecialty referrals should also be considered. Systemic corticosteroids are the treatment of choice for Sweet syndrome, and resolution of symptoms is rapid and characteristic.[2,6,10] In children, the recommended dose is 2.0 mg/kg/d of prednisolone, followed by a tapering dose.[2,6,10] Although improvement is typically seen, recurrences have been reported in 20% to 30% of patients, particularly during the taper.[2,6,10]

If left untreated, the cutaneous symptoms of uncomplicated Sweet syndrome typically self-resolve over several months, but secondary complications must be considered when determining the need for therapy. HSS has been associated with postinflammatory scarring, acquired cutis laxa, cardiovascular compromise, epiglottitis, gastrointestinal bleeding, and skin necrosis.[6] Of these, cardiovascular sequelae, which include pericarditis, vessel dilation, valve disease, and myocardial infarction are the most severe and associated with the highest risk of mortality in the pediatric population.[6]

Sweet syndrome may herald an underlying hematologic cancer or systemic disease in a child. Promptly obtaining a skin biopsy is paramount to confirm a diagnosis of Sweet syndrome, since early surveillance for underlying associations is critical. Myeloperoxidase staining is essential for detecting the rare histiocytoid variant of Sweet syndrome.

Conflicts of interest

None disclosed.

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