International Journal of Dermatology

Report

Idiopathic histiocytoid Sweet syndrome: a case report with clinical and histopathological considerations

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Funding: None.

Conflict of interest: The authors have no conflict of interest.

doi: 10.1111/ijd.14159

Abstract

Background Histiocytoid Sweet syndrome is characterized by a predominant neutrophilic dermal infiltrate. Usual clinical differential diagnosis includes erythema multiforme, drug eruption, and erythema nodosum. Histiocytoid Sweet syndrome is considered an uncommon histopathological variant of the disease.

Methods We evaluated clinical, histopathological, and immunohistochemical findings of a case categorized as idiopathic histiocytoid Sweet syndrome in which clinical-epidemiological data raised the possibilities of Sweet syndrome, leprosy, and drug reaction.

Results Positive reaction to myeloperoxidase (MPO) in histiocytoid cells of the dermal infiltrate, response to oral corticosteroids, clinical and laboratory investigation, and absence of cutaneous lesions or clinical complaints within 1 year of follow-up are consistent with the diagnosis of idiopathic histiocytoid Sweet syndrome. CD68 (PG-M1) and CD15 positive cells were also present among dermal cells.

Conclusions Epidemiological data are relevant while considering a clinical differential diagnosis of Sweet syndrome that can be further expanded, from a histopathological point of view, when dealing with the histiocytoid variant since neutrophils, macrophages, and immature myelomonocytic cells with histiocytoid morphology are present. The significance of the MPO positive mononuclear dermal cells are not completely established.

Introduction

Sweet syndrome or "acute febrile neutrophilic dermatosis" was first described in 1964 by Robert Sweet through the observation of a group of young women that presented with erythematous and painful papules, plaques, and nodules associated with fever and neutrophilia.[1] The pathogenesis of the condition is still unknown, but it has been classified into three subtypes according to the etiology: idiopathic, drug-induced, or associated with malignancies, mainly of hematologic origin.[2] Diagnosis is based on clinical and histopathologic criteria, and usual histopathological findings include a variably dense dermal infiltrate largely composed of mature neutrophils, together with edema of the papillary dermis.[3] Systemic corticosteroid therapy is the standard treatment, usually with a good response.[2]

In 2005, Requena *et al.* studied a series of patients with typical cutaneous lesions of Sweet syndrome in which histopathology demonstrated an infiltrate mostly composed of histiocytoid mononuclear cells that showed a monocytic-histiocytic immunoprofile with intense myeloperoxidase (MPO) reactivity. The authors named the condition histiocytoid Sweet syndrome, considered to be a histopathological variant of Sweet syndrome.[4]

This report aims to describe a case of idiopathic histiocytoid Sweet syndrome in which clinical-epidemiological data raised the possibilities of Sweet syndrome, leprosy, and drug reaction. We further argue about the significance of MPO positivity found on histiocytoid mononuclear dermal cells.

Case Report

A 60-year-old woman, resident of Rio de Janeiro, Brazil, came to our health primary attention unit with a 1-week history of

sudden onset of painful and erythematous plaques and nodules, initially located in hands, which later progressed to trunk and arms (Fig. 1). She denied fever or signs and symptoms of upper respiratory or gastrointestinal tract infections. Her medical history included hypertension treated with atenolol and hydrochlorothiazide. Clinical diagnostic hypothesis included Sweet syndrome, multibacillary leprosy and/or leprosy reaction, and drug eruption. Laboratory investigation found normal blood cell counts and normal routine biochemical tests, including evaluation for kidney and liver function. Serology for hepatitis B and C, HIV, and syphilis were negative. Anti-streptolysin O test was normal. C-reactive protein level was 2.92 mg/dl (normal, 0.8 mg/dl). Chest x-ray, parasitological examination, and urinalysis added no other remarkable information.

Histopathological examination of a biopsy taken from the arm showed edema of papillary dermis together with a perivascular and band-like inflammatory infiltrate located at the uppermost part of reticular dermis composed mostly of histiocytoid cells. Neutrophils with nuclear fragmentation (leukocytoclasis), lymphocytes, and occasional eosinophils were also present. Histiocytoid cells, lymphocytes, and occasional eosinophils were also present. Mononuclear histiocytoid cells exhibited mostly oval or elongated, inconspicuous nucleoli and scant slightly eosinophilic cytoplasm (Fig. 2). Fibrinoid necrosis of vascular wall and granuloma were not seen. Parasites were not detected with periodic acid-Schiff (PAS) Wade, and silver special stains. Immunohistochemical study was performed to better characterize the cells. Immunostaining revealed $CD68^+$ cells composing most of the dermal infiltrate, followed by MPO^+ and $CD15^+$ cells. Those three immunophenotypic groups of cells accumulated around superficial vessels and surrounding dermis, spreading to the papillary dermis, especially adjacent to the area of edema (Fig. 3). Besides similar tissue location, $CD68^+$ cells presented a wider distribution, also occupying the interstitial space in the upper reticular dermis, and $CD15^+$ cells, outnumbered by $CD68^+$ and MPO^+ cells, could be focally found unattended by other cell types. Positive reaction for CD68 and MPO antibodies was observed on part of the cells with a histiocytic morphology: a moderate amount of cytoplasm and round, oval, or elongated nuclei. In addition, MPO positive reaction was observed in a few polymorphonuclear cells. $CD15^+$ cells displayed a polymorphonuclear leukocyte or a mononuclear cell morphology. $CD34^+$ cells were not detected in the lesional infiltrate. The histopathological diagnosis was histiocytoid Sweet syndrome.

Significant clinical improvement of the lesions was observed within 72 hours of treatment with prednisone 1 mg/kg/day. The dose was gradually reduced and, after 1 year of follow-up, the patient was free of cutaneous lesions and had no other clinical complaints.

Discussion

Sweet syndrome is included in the group of diseases called neutrophilic dermatoses, and its usual histopathology shows edema of the papillary dermis with an underlying band-like infiltrate mostly composed of mature neutrophils with leukocytoclasis, without vasculitis. Density and distribution of neutrophils in the dermal tissue may vary, and other cell types can compose dermal infiltrate. Lymphocytes, eosinophils, and particularly a histiocytic component have been described, opening the spectrum of histopathological features in Sweet syndrome, with implications regarding differential diagnosis.[3]

Histiocytoid Sweet syndrome is considered to be a histopathological variant of the Sweet syndrome characterized by an infiltrate mostly composed of histiocytoid cells, which are actually immature myeloid cells, in particular precursors of neutrophils. The condition was described in 2005 by Requena *et al.*, who reported a series of 41 patients with typical cutaneous lesions of Sweet syndrome, in which histopathology revealed an infiltrate mostly composed of histiocytoid mononuclear cells.[4] The presumed nature of the cells was based on immunophenotypic profile, with the striking finding of MPO immunoreactivity for most cells with a histiocytic appearance.

Following the study of Requena *et al.*,[4] single case reports or small case series of histiocytoid Sweet syndrome were described, and review of literature was recently presented.[5] Then, histiocytoid Sweet syndrome was diagnosed in distinct clinical or histopathological settings and has been associated

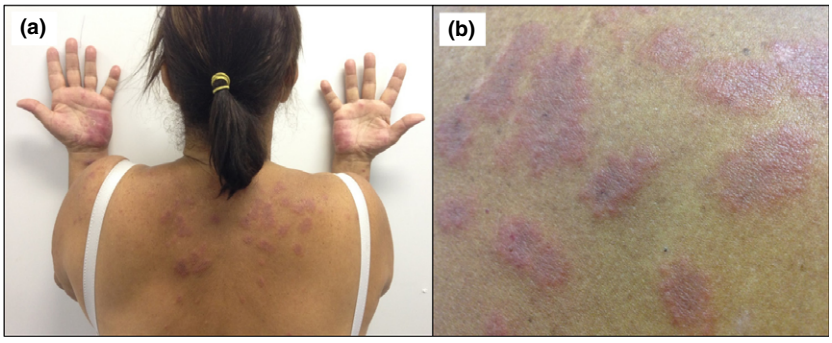

Figure 1 Erythematous plaques on back and palms (a). Detail of the erythematous plaques on back with small vesicles (b)

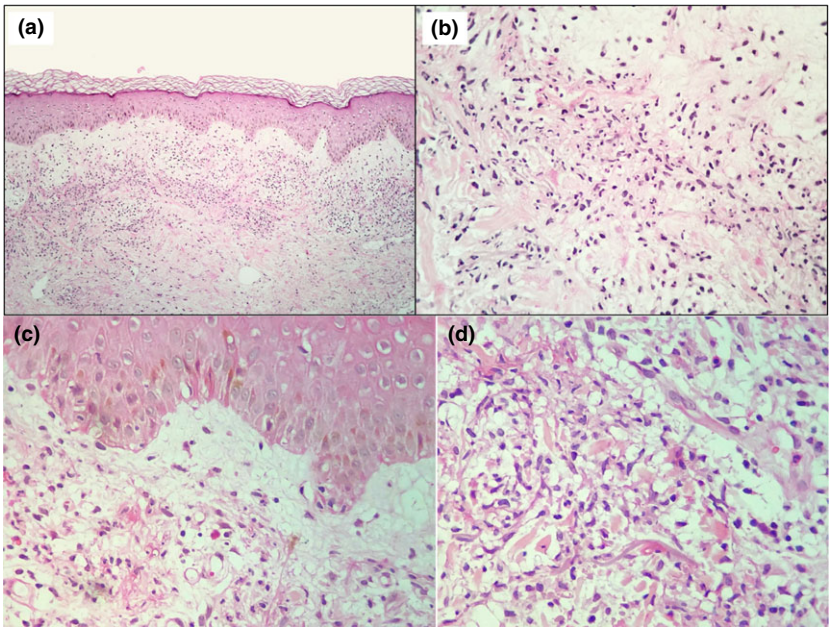

Figure 2 Hyperkeratosis, acanthosis, edema of the papillary dermis, perivascular and confluent inflammatory infiltrate (a – H&E, ×10), comprising neutrophils and mononuclear histiocytoid cells, with leukocytoclasia (b – H&E, ×40). Detail of the papillary dermis with edema, mononuclear histiocytoid and polymophonuclear cells, and leukocytoclasis (c – H&E, ×40) and of the dermal infiltrate with predominant mononuclear histiocytoid cells (d – H&E, ×40)

with hematologic diseases, autoimmune diseases, inflammatory bowel disease, infections, pregnancy, and the use of systemic drugs.[5] In our case, all screening tests performed before treatment were normal, and the patient remained stable and without any sign of illness a year after the initial diagnosis. Thus, it was not possible to identify an etiologic factor, and we considered the idiopathic form of the disease.[6,7]

Histiocytoid Sweet syndrome is a histologic diagnosis and requires clinical correlation in order to exclude other entities, including leukemia cutis and histiocyte-rich dermatosis.[8] Initial clinical exam considered differential diagnosis with leprosy and drug eruption. Along with dermatological evaluation of the lesions in this particular case, epidemiological data impose leprosy as a possible diagnosis since lesions are pleomorphic, and early diagnosis assists in disrupting the transmission cycle. Brazil is the second country with the highest number of new cases of leprosy, corresponding to 13% of the worldwide rate.[9] Multiple erythematous plaques can describe a clinical picture of multibacillary or type II reactional leprosy in which bacilli are numerous or easily found. Bacilli were not detected in Wade stained sections in our patient. On the other hand, histopathology can promptly diagnose multibacillary or type II reactional leprosy that clinically mimics Sweet syndrome.[10] Similar lesions can still represent reaction to drugs.[2] Maintenance of the antihypertensive drugs by the patient, complete resolution, and normal laboratory exams after 1 year of follow-up make secondary histiocytoid Sweet syndrome implausible.

From medical reports,[5,6,11–17] histopathological data describe a cellular infiltrate mainly composed of histiocytoid mononuclear cells expressing macrophage markers together with MPO positivity; CD15, when investigated, was variably reactive. Immunostaining of our case is in accordance with those findings. Mononuclear histiocytoid cells were seen on H&E stain and prompted to immunostaining investigation. However, Delabie *et al*., while describing the presence of numerous histiocytes in patients with typical lesions of Sweet syndrome, emphasized that the small size of these cells could mimic neutrophils.[18]

Positive reaction for MPO together with morphology of the histiocytoid cells give support to the interpretation that they are immature myeloid cells with the hypothesis of their granulocytic nature.[5,6,11,13,16] It should be emphasized that while MPO activity is most pronounced in immature granulocytes, it is discernible in monocytes and in a subset of monocytic neoplasms.[12] Our finding that CD68 (PG-M1) and MPO were not expressed in all of the histiocytoid cells together with some distinction on their tissue location and morphology is coherent with the imputed specificities for the antibodies applied.[15,19,20] We found that dermal cell infiltrate was mostly composed of macrophages (CD68/PG-M1$^+$ cells), followed by a distinct population of immature mononuclear myeloid cells (MPO$^+$/mostly; CD15$^+$/few cells) and by a third population of cells that correspond to mature neutrophils (polymorphonuclear CD15$^+$ cells). Although histiocytoid cells in histiocytoid Sweet syndrome were shown to express markers specific of the macrophage/monocyte lineage, myeloid lineage

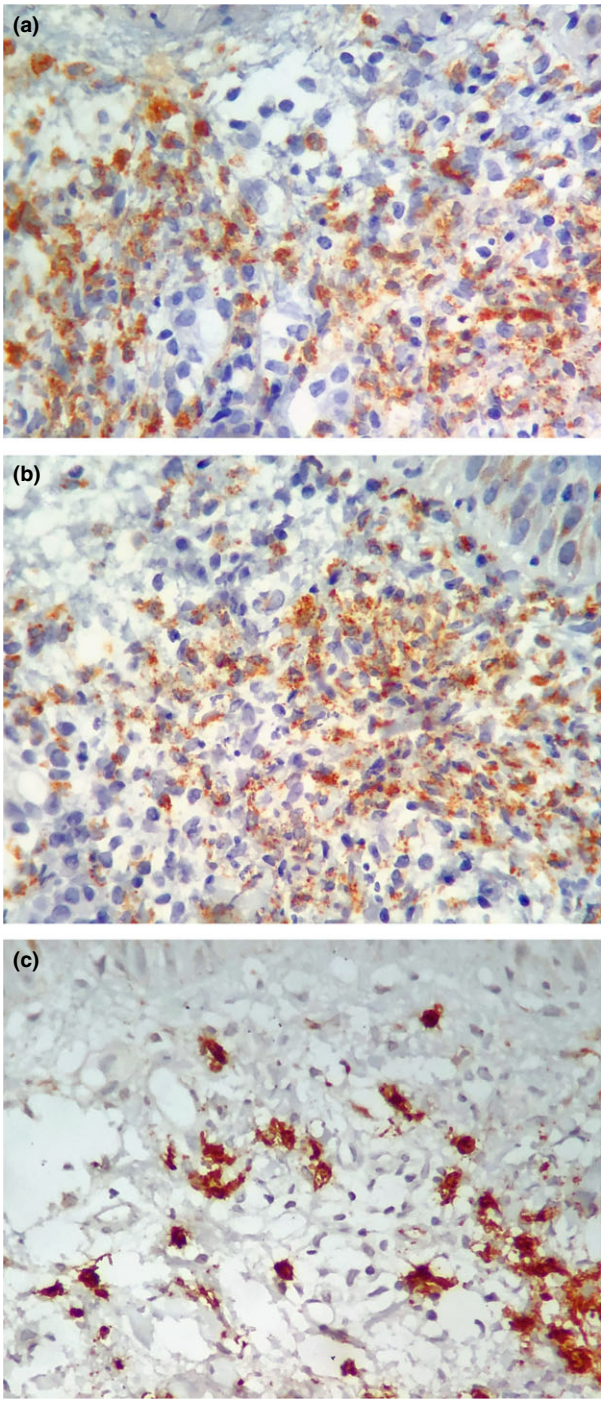

Figure 3 Immunostain positive reaction for MPO (a) and CD68 (b) in some of the mononuclear histiocytoid dermal cells. $CD15^+$ cells have a polymophonuclear and mononuclear cell morphology (c – H&E, ×40)

and finally of both,[17] and because there is overlap between the immunophenotypic characteristics of myeloid and monocytic cells, it seems established that the dermal infiltrate of cutaneous lesions of histiocytoid Sweet syndrome is composed mostly of MPO^+ immature myelomonocytic cells with histiocytoid morphology.[21] Interestingly our case showed a predominance of $CD68^+$ cells. On the other hand, we question whether the only presence of histiocytoid MPO^+ cells, in varied proportion among inflammatory dermal infiltrate, is sufficient enough to qualify a histological variant of the disease since their finding would suit in the context of recruitment of cells for a neutrophil-mediated inflammatory response and may be present in other neutrophilic rich dermatoses.[22]

Histiocytoid Sweet syndrome has the same expected response to conventional treatment and prognosis as classic Sweet syndrome. Oral corticosteroids are the first-line treatment, and lesions tend to disappear in the first month, as it occurred with our patient.[2,5,17]

Comments and Conclusion

Clinical-pathological correlation is important while dealing with mononuclear-neutrophil rich dermatosis. We describe a case of idiopathic histiocytoid Sweet syndrome in which clinical-epidemiological data raised the possibilities of Sweet syndrome, leprosy, and drug reaction. Characteristic MPO^+ histiocytoid mononuclear cells were present though CD68/PG-$M1^+$ cells appeared predominant in the dermal infiltrate.

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