Histiocytoid Sweet syndrome: Report of two cases and review of the literature

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ABSTRACT

Histiocytoid Sweet syndrome (SS) is a rare inflammatory disease that has recently been described as a variant of classic SS. Histopathologically, histiocytoid SS is characterized by papillary dermal edema with infiltration of histiocyte-like cells into the upper dermis. These microscopic features may be similar to those of leukemia cutis, which involves infiltration of malignant blasts into the dermis. However, the treatment and clinical prognosis of these two conditions are quite different. Here, we report the case of two Taiwanese patients with histiocytoid SS. Interestingly, one of the patients had a history of myelodysplastic syndrome and was initially considered to have ongoing leukemic transformation with concomitant leukemia cutis. Finally, the patient was diagnosed with histiocytoid SS based on histological findings, and both patients were successfully treated with low-dose oral corticosteroids.

Introduction

Histiocytoid Sweet syndrome (SS) was first described by Requena et al in 2005 and was considered to be a histological variant of acute febrile neutrophilic dermatosis. In contrast to classic SS, the dermal infiltrate of inflammatory cells in histiocytoid SS consists of histiocytoid cells, which are considered to be immature myeloid cells. Here, we report the case of two Taiwanese patients with histiocytoid SS and review the relevant literature.

Case presentations

Patient 1

A 49-year-old Taiwanese male presented in 2008 with recurrent tender skin rashes on his chest and abdomen; the lesions spontaneously resolved without any treatment. One year later, he experienced painful swelling of the foot joints bilaterally and came to our hospital for examination and finally was diagnosed with unclassified myelodysplastic syndrome (MDS). Six months later, the same rashes recurred, and the patient was referred to our dermatological department as the hematologist suspected that the MDS had transformed to a leukemic state with leukemia cutis. On physical examination, tender erythematous papules were found to be diffusely scattered over the chest, abdomen, back, and upper limbs (Figure 1A and 1B). In addition, fever and leukopenia (3.24 × 10⁹/L) were noted.

Skin biopsy from a papule revealed a dense cellular infiltrate beneath the papillary dermal edema and mild perivascular infiltration (Figure 2A). Cells were composed of many seemingly atypical mononuclear cells, which contained large, reniform nuclei with scanty eosinophilic cytoplasm (Figure 2A; inset). Additionally, sparse polymorphonuclear cells, histiocytes, and CD4-positive reactive lymphocytes were scattered in the dermis. The atypical mononuclear cells were strongly positive for lysozyme (Figure 2B), myeloperoxidase (MPO) (Figure 2C), and CD68 (KP1) (Figure 2D). Staining with CD2, CD15, CD34, CD56 and CD117 for blasts showed negative results. Chest and abdominal computed tomography revealed that the patient’s lymph nodes and visceral organs such as the liver and spleen were normal. Except for the physiological uptake, positron emission tomography did not show any abnormal uptake. No myeloid blasts were observed by cytological examination of peripheral blood and bone marrow.

Finally, based on these findings, histiocytoid SS was diagnosed. The lesions resolved gradually over a 14-day tapered-dose course of oral prednisolone. The patient was regularly followed up in our
outpatient department for 15 months. Throughout the follow-up period, the skin lesions showed improvement and recurred less frequently under low-dose prednisolone treatment (5 mg/day) when required.

**Patient 2**
A 55-year-old Taiwanese female with an unremarkable medical history presented with fever as well as tender and mildly pruritic...
erythematous to violaceous papulonodules on the abdomen and all four limbs, which had persisted for about 1 week (Figure 1C). Some lesions had a transparent, vesicle-like appearance, giving rise to “an illusion of vesiculation” (Figure 1D). Laboratory examination revealed peripheral neutrophilia without blasts in the blood, and an elevated erythrocyte sedimentation rate and C-reactive protein level. Histopathological analysis showed tense papillary dermal edema with infiltration of histiocytoid cells (Figure 3A). Immunohistochemical assessment revealed the same results as those observed in Patient 1 (Figure 3B–D). The physical examination did not show palpable lymph nodes. The chest X-ray and abdominal sonography showed no signs of hilar lymphadenopathy and hepatosplenomegaly. Based on these findings, the patient was diagnosed with histiocytoid SS. The cutaneous lesions subsided with systemic administration of methylprednisolone 40 mg/day for 1 week. At the 12-month follow-up after cessation of oral corticosteroids, the patient was still free of cutaneous lesions.

Discussion

SS is a well-recognized inflammatory dermatosis characterized by dermal infiltration of polymorphonuclear leukocytes. In the present two cases, the clinical picture of both patients was consistent with SS. However, microscopic findings in both patients differed from those of typical SS as the dermal infiltrate was composed of mononuclear cells with histiocytoid morphology. In addition, leukopenia was seen in one of our patients, which has been shown rarely to occur in combination with histiocytoid SS.2 Both our patients were regularly followed up in our outpatient department for more than 1 year after the diagnosis of histiocytoid SS; the general condition of both patients was good throughout follow-up, without evidence of leukemic transformation or other visceral malignancy.

In 2005, Requena et al first described a series of 41 patients with SS with dermal infiltration of histiocytoid cells, which manifested as large, twisted, basophilic vesicular nuclei with scant eosinophilic cytoplasm.1 In addition, immunostaining results of histiocytoid-like cells were found to be strongly positive for CD68 (KP1), lysozyme, and MPO. The CD68 stain tests for both myeloid and monocytic/histiocytic lineage; however, PGM1 is more selective for monocytes/histiocytes. In histiocytoid SS, immature cells are strongly stained with KP1.1 Other specific indicators for discriminating cells of myeloid lineage include neutrophil elastase, T-cell intracellular antigen-1, and MPO. Nevertheless, the most reliable marker for distinguishing myeloid cells from monocytes/histiocytes is MPO, which is the major component of primary granules in myeloid cells, including early and mature forms. Requena et al considered that the observed cells with histiocytic appearance were immature myeloid cells from the bone marrow in the early acute stage, and therefore defined the described condition as a histiocytoid variant of SS.

The significance of histiocytoid SS is its association with other medical conditions such as diabetes mellitus and internal malignancy. In the report of 41 patients, six cases of histiocytoid SS were associated with malignant neoplasms and four with hematological malignancies.1 Although the mechanism of migration of immature myeloid cells to the skin is well documented in myelogenous leukemia,3 the pathogenesis of histiocytoid SS is still not clear. Granulocyte colony-stimulating factor is known to promote the maturation of myeloid cells, and recent studies have shown that this factor may play an important role in the pathogenesis of SS.4 However, the levels of granulocyte-colony stimulating factor observed in histiocytoid SS may be too low to stimulate neutrophil maturation.1 In addition, CXCL8-producing T-cells, which may secrete granulocyte/macrophage colony-stimulating factor and interleukin-8 to attract immature granulocytes, may also influence neutrophilic skin inflammation.5 These possible underlying mechanisms need to be assessed in further studies.

Figure 3 Biopsy specimen from patient 2. (A) Inflammatory cellular infiltrate with severe papillary dermal edema (hematoxylin and eosin, 100 x). Inset: inflammatory infiltrate composed of histiocyte-like cells (hematoxylin and eosin, 400 x). (B) Strong immunoreactivity for lysozyme (lysozyme stain, 200 x). (C) Strong immunoreactivity for myeloperoxidase (myeloperoxidase stain, 200 x). (D) Positive immunostaining for CD68 (KP1; 200 x).
Medication-induced histiocytoid SS has also been reported. Murase et al described the case of a 69-year-old man with multiple myeloma treated with bortezomib, who developed histiocytoid SS. In addition, Wu et al reported the case of a patient with sinusitis treated with trimethoprim-sulfamethoxasole (TMP-SMX), who subsequently developed severe leukopenia with histiocytoid SS; the authors proposed that TMP-SMX may have arrested idiosyncratic granulocytic maturation, thereby inducing histiocytoid SS.

Generally, histiocytoid SS needs to be differentiated from several cutaneous dermatoses characterized by the infiltration of abundant histiocytes, including interstitial granuloma annulare and interstitial granulomatous dermatitis with arthritis. More importantly, in patients with MDS, leukemia cutis always should be considered before establishing the diagnosis of SS. Leukemia cutis is clinically identifiable by the infiltration of neoplastic leukocytes (immature myeloid or lymphoid cells) into the skin. In MDS patients, leukemic transformation to myeloid leukemia has previously been reported, and leukemia cutis may be observed before, concomitant with, or after this leukemic change.

Clinically, myeloid leukemia cutis presents as erythematous or violaceous papuloplaques and nodules on the face, trunk, or extremities. On histological examination, diffuse infiltration of malignant blasts with prominent nuclei is observed beneath an uninvolved grenz zone, which may involve periadnexal, perivascular, and/or perineural areas. Most cells reveal positive immunohistochemical findings for CD68 (KP1), lysozyme, and MPO. In addition, peripheral blood examination or bone marrow aspiration will also show leukemic cells, and patients with leukemia cutis usually have an unfavorable disease course. However, in histiocytoid SS, leukemic cells are absent in peripheral blood tests, as well as in the bone marrow, and the lesions resolve dramatically with systemic corticosteroid use, as is the case in classic SS.

Spencer et al reported the case of a patient with histiocytoid SS associated with Crohn's disease who responded well to dapsone therapy. Both of our patients were successfully treated with systemic corticosteroid administration; however, the first patient, who had underlying MDS, experienced recurrent eruptions after cessation of oral prednisolone. Hence, therapy focusing on the underlying disease in patients with histiocytoid SS associated with malignancy may prevent recurrent cutaneous lesions. Recently, a case of histiocytoid SS associated with MDS was reportedly successfully treated by allogeneic stem cell transplantation, which may be the treatment of choice for histiocytoid SS accompanied with hematologic malignancy.

In conclusion, we have reported two cases of histiocytoid SS that were diagnosed histologically. Because the prognosis and biological behavior of histiocytoid SS does not differ from that of classic SS, we propose that classic SS and histiocytoid SS may be part of a spectrum of the same disease. The diagnosis of histiocytoid SS should be a diagnosis of exclusion, and clinicopathological correlation is essential.

References