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Sinus Histiocytosis (Rosai-Dorfman Disease) Clinically Limited to the Skin

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Sinus histiocytosis with massive lymphadenopathy (SHML) is an idiopathic proliferation of unique histiocytes that have vesicular nuclei and voluminous pale cytoplasm, often with emperipolesis. Pure cutaneous involvement is very rare. We describe a patient with SHML limited to the skin whose lesion has spontaneously regressed. A 35-year-old Korean male visited the Department of Dermatology due to facial rash for 2 months. A 3 × 3.5 cm-sized well-demarcated dark erythematous non-tender plaque was noted on the right cheek. Skin biopsy showed dense, nodular infiltrates of histiocytes with abundant cytoplasm and vesicular nuclei rimmed by lymphoplasma cell aggregates throughout the upper and mid-dermis. The histiocytes were immunohistochemically positive for S-100 protein and CD68, but negative for CD1a. Laboratory tests and a thorough physical examination revealed no abnormalities. These findings suggested that this was a case of SHML clinically limited to the skin. The skin lesion was initially resistant to steroid therapy, but began to regress 10 months after the onset without further treatment. ***Key words: sinus histiocytosis; skin.***

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Sinus histiocytosis with massive lymphadenopathy (SHML) was first described by Rosai & Dorfman (1) in 1969. The prototype patient was a black child or adolescent with persistent fever, prominent cervical lymphadenopathy and associated haematological and immunological abnormalities. At first, massive lymphadenopathy was regarded as a hallmark of SHML, but experience with larger numbers of patients has shown that lymphadenopathy is occasionally lacking. Involvement of extranodal sites (skeleton (2), salivary gland (3), central nervous system (4), eyes (5), upper respiratory tracts (3, 6) and skin (7, 8)) have been documented in approximately 30% of affected individuals. Cutaneous infiltrates have been noted in 10%, but sinus histiocytosis limited to the skin is very rare (9). We describe a patient with sinus histiocytosis limited to the skin, whose skin lesion has been regressed spontaneously.

CASE REPORT

A 35-year-old Korean male visited the Department of Dermatology, Yonsei University College of Medicine due to facial rash for 2 months. Examination revealed a 3 × 3.5 cm-sized, well-demarcated, dark erythematous non-tender plaque on the right cheek without any lymphadenopathy (Fig. 1A). There was no fever, malaise, fatigue, weight loss or other general symptoms. CBC, urinalysis, VDRL, antinuclear antibody, liver function test, immunoelectrophoresis, Coombs test, abdominal ultrasonogram and whole body bone scan were all negative or within normal limits. IgG antibody for Epstein-Barr (EB) virus nuclear antigen was positive, but IgG and IgM antibodies for EB virus early antigen were negative. PPD skin test with 5 TU was positive, but with 1 TU it was negative.

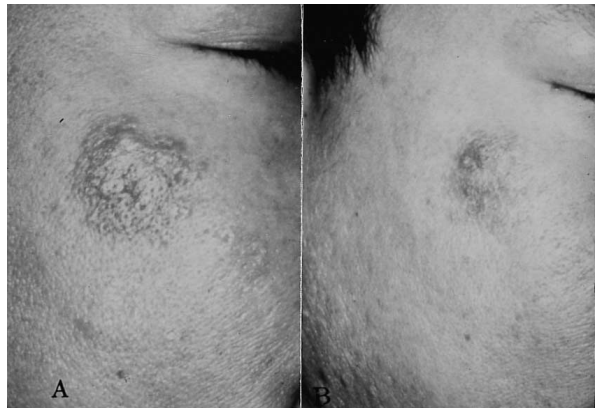

Fig. 1. (A) A 3 × 3.5 cm-sized, well-demarcated, dark erythematous non-tender plaque on the right cheek. (B) The size of the plaque on the right cheek decreased to a 0.3 × 0.5 cm-sized papule with surrounding erythema of 2.8 × 2.3 cm size 18 months after development of the lesion.

Skin biopsy demonstrated dense, nodular infiltrates of histiocytes with an abundant, ill-defined border of cytoplasm and vesicular nuclei throughout the upper and mid-dermis. Abundant plasma cells and lymphocyte infiltrations were observed at the periphery of the lesion (Fig. 2). Emperipolesis of lymphocytes was also found, but was not prominent. Immunohistochemically, histiocytes were positive for S-100 protein (Dako, Carpinteria, CA, USA) (Fig. 3) and CD 68 (KP1 and PGM1, Dako) but negative for CD1a (Immutech, France) and CD 30 (Dako). The patient had previously received treatments with dapsone for 2 months at local clinic without improvement before

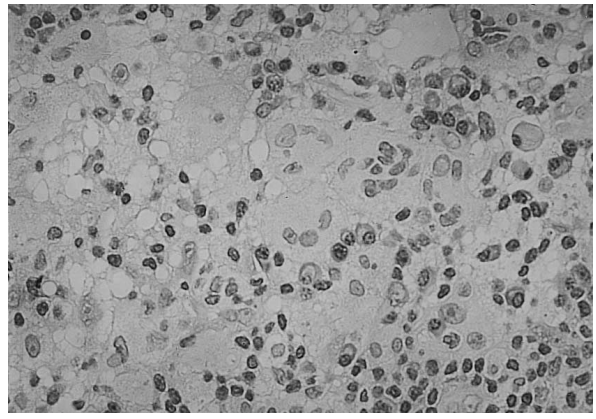

Fig. 2. Histiocytes with abundant, ill-defined borders of cytoplasm and vesicular nuclei (H & E × 400).

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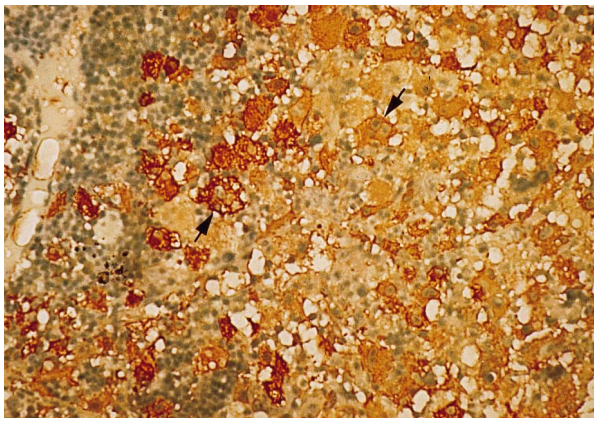

Fig. 3. Infiltrated histiocytes showing diffuse and strong positivity for S-100 protein and some of them showing intracytoplasmic emperipolesis of lymphocytes (arrow) (Immunohistochemical stain, $\times 400$).

coming to our department. Thus, we started administration of systemic steroids for 2 months, which also showed no effect. Then we simply observed the patient for 14 months without any further treatment. The size of the plaque on the right cheek started to decrease 10 months after its onset. Now it was a mere 0.3×0.5 cm-sized papule with surrounding erythema of 2.8×2.3 cm size (Fig. 1B). Systemic symptoms were not observed during the 18 months of follow-up. Follow-up studies, including CBC, liver function test, immunoelectrophoresis, abdominal ultrasonograph and antibodies for EB virus, were within normal limits or negative.

DISCUSSION

SHML is a well-established clinicopathological entity usually developed in children or young adults (10). The clinical spectrum includes nodal and extranodal disease. Extranodal infiltrates, which occur in approximately 40% of patients (11), have been documented in almost any organ, but the most common sites of involvement appear to be the orbits, skin, upper respiratory tract and bone. Those patients may have fever or weight loss, and less commonly tonsillitis, nasal discharge or nasal obstruction. Cutaneous lesions usually consist of solitary or multiple papules or nodules of a xanthomatous or erythematous hue ranging in size up to 4 cm (8).

The laboratory findings are non-specific but hypergammaglobulinaemia (usually polyclonal), as well as elevated antibody titres to EB virus, have been found in a considerable proportion of patients, suggesting an impaired immune response to an infectious agent or antigen (12). Our patient had IgG antibody for EB virus nuclear antigen, but IgG and IgM antibodies for EB virus early antigen were negative. Thus, our patient did not show any significantly abnormal laboratory findings.

The definitive diagnosis of SHML has always been based on histopathological features. Foucar et al. (9) considered emperipolesis and S-100 protein expression by histiocytes with feathery border to be the main findings allowing a firm diagnosis of SHML. In extranodal SHML, the morphological features recapitulate to those of nodal disease. However, accompanying fibrosis with vascular proliferation and less prominent emperipolesis can make the diagnosis difficult. Chu & LeBoit (13) have also stressed the histological features of cutaneous SHML; the characteristic histiocytes admixed with other inflammatory cells, emperipolesis, and thick-walled venules surrounded by cuffs of plasma cells, especially at the periphery of lesions. Our case also showed prominent infiltration of the characteristic histiocytes with feathery border, emperipolesis, numerous plasma cell infiltrations and lymphoid aggregation.

The differential diagnoses of cutaneous SHML include reticulohistiocytoma cutis, malignant histiocytosis, hemophagocytic syndrome, Langerhans' cell histiocytosis (14) and CD30(+) T-cell lymphoma. Although S-100 protein expression (13) and leukophagocytosis (15) have been rarely reported in reticulohistiocytoma cutis, the cytoplasm of the proliferative histiocytes has a characteristic ground-glass appearance with well-defined cell membranes and contains abundant PAS-positive, diastase-resistant material. In addition, plasma cells are infrequent in contrast to SHML (13). Malignant histiocytosis (16) shows pleomorphic nuclei and frequent mitotic figures, but SHML lacks pleomorphism. Haemophagocytic syndrome usually exhibits lobular panniculitis and the histiocytes do not express S-100 protein. Phagocytosis is exceptional in Langerhans' cell histiocytosis (17) while the histiocytes show characteristic grooved nuclei and eosinophils are commonly associated. Although some nuclei with prominent nucleoli are seen in our case, we can rule out the possibility of CD 30(+) pleomorphic T-cell lymphoma due to negative results of CD30. Benign-appearing histiocytes exhibiting leukophagocytosis can be seen in erythema elevatum diutinum (18), Sweet's syndrome (19) and infectious disease. The clinical features of our case and the lack of leukocytoclastic vasculitis and/or dermal neutrophilic infiltration with nuclear dust excluded these diseases.

S-100 protein is expressed in various tissue, melanocytes, nerves, eccrine glands and Langerhans' cells (20, 21). Among the histiocytoses, Langerhans' cell histiocytosis, indeterminated cell histiocytosis, congenital self-healing reticulohistiocytosis and SHML show S-100 protein-positive histiocytes (20). Among them, SHML usually does not express CD1a in contrast to the others (14). CD68 (KP1 and PGM1) is a macrophage marker and dendritic lineage histiocytes do not usually express this molecule. So the histological findings, as well as the immunophenotype (S-100 protein+, CD68+, CD1a−), fit well with the diagnosis of SHML.

SHML usually shows a benign clinical course, and an ideal therapeutic option other than excision has not yet been established. In some patients, the disease may be persistent and progressive and associated immunological and haematological abnormalities have been reported to be an unfavourable sign predicting poor prognosis (22). The clinical course of the reported pure cutaneous form of SHML is variable. Some cases are persistent while others are self-healed, but there have been no fatal cases. Our patient did not show any abnormalities of immune function and no sign of systemic involvement was detected. The lesion did not have any response to dapsone and systemic corticosteroid treatment. Therefore, we have followed the patient without further treatment. Fortunately, his skin lesion has decreased in size to 0.3×0.5 cm 18 months after onset of the disease even without any specific treatment. However, frequent physical examination and laboratory studies seem most appropriate at this juncture until complete clearance is realized.

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