Histiocytosis X in a 27-year-old woman[1]

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Erythematous, scaling plaques, which were unresponsive to topical steroids, developed on the scalp and perineum in a 27-year-old woman. Light and electron microscopy and immunohistochemistry confirmed the clinical diagnosis of histiocytosis X.

Index terms: Histiocytosis X • Skin, diseases
Cleve Clin Q 50:197–200, Summer 1983

Histiocytosis X is a rare syndrome characterized by abnormal proliferation of histiocytes, and ranges from a benign, focal, self-limited disease to an aggressive, widely disseminated, and fatal disorder. Histiocytosis X is presently considered to comprise three often overlapping entities: Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma.[1] We report a case in which the clinical diagnosis of histiocytosis X was confirmed by light and electron microscopy and immunohistochemistry in a 27-year-old woman.

Case report

A 27-year-old white woman with a two-year history of amenorrhea, galactorrhea, weakness, cold intolerance, polydipsia, and polyuria presented in November 1980 with a pruritic, scaling eruption of the scalp and perineum of one month duration. She had previously appeared to be in good health and had given birth to two healthy children. There was no familial or personal history of skin disease.

Physical examination revealed confluent thick, scaling, erythematous, crusted plaques on the scalp and perineum (*Fig. 1*). The mucosal surfaces were normal, and there was no lymphadenopathy or hepatosplenomegaly. Visual field testing was within normal limits.

A complete blood count and differential, platelet count, sodium, potassium, chloride, CO_2, blood urea nitrogen (BUN), creatinine, total protein, albumin, calcium, phosphate, cholesterol, glucose, uric acid, total bilirubin, alkaline phosphatase, creatine phosphokinase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase were all within normal limits. Serum thyroxine was 4.5 μg/dl (normal, 5.2-13.3 μg/dl), serum prolactin, 26.7 ng/ml (normal in women, 10.2±4.7 ng/ml), and fasting cortisol level, 13 μg/dl (normal, 15.9±5.0 μg/dl). The patient regularly excreted large volumes of hyposmolar urine (121 mOsm/kg [normal, 40-1400 mOsm/kg]) and a specific gravity of 1.003. The ratio of urine to plasma osmolarity was 0.42 (normal, 1.0-1.1). Sector computed tomography (CT) of the sella turcica revealed a 9-mm suprasellar nodule. Bone-marrow biopsy and aspiration, bone scans, and abdominal CT scans were negative or normal, and the biopsy of the suprasellar mass revealed only fibrosis and chronic inflammation. The diagnosis was partial pituitary insufficiency and diabetes insipidus. Biopsy of the perineal plaques revealed chronic nonspecific inflammation, and the skin disease was believed to be compatible with seborrheic dermatitis.

Despite lengthy treatment with topical corticosteroids, bland emollients, and antiseborrheic shampoos, the patient's skin disease worsened. In November 1981, skin biopsy revealed a patchy, polymorphous upper dermal infiltrate (*Fig. 2*), characterized by numerous large mononuclear cells with pale cytoplasm and irregularly folded nuclei (*Fig. 3*). Ultrastructural examination revealed large dermal histiocytes containing numerous intracytoplasmic Langerhans' cell (Birbeck) granules (*Fig. 4*). Immunohistochemical staining of cryostat-frozen tissue sections with the use of a modified avidin-biotin complex technique[2] showed that these cells were histiocytes. The cytoplasm of the large mononuclear cells contained HLA-Dr (Ia), OKM_1 (*Fig. 5*), and muramidase (lysozyme). Most cells did not stain with T_3 monoclonal antibody or polyclonal light-chain antibodies.

Administration of 10 mg of topical nitrogen mustard diluted in 50 ml of water and electron-beam therapy to

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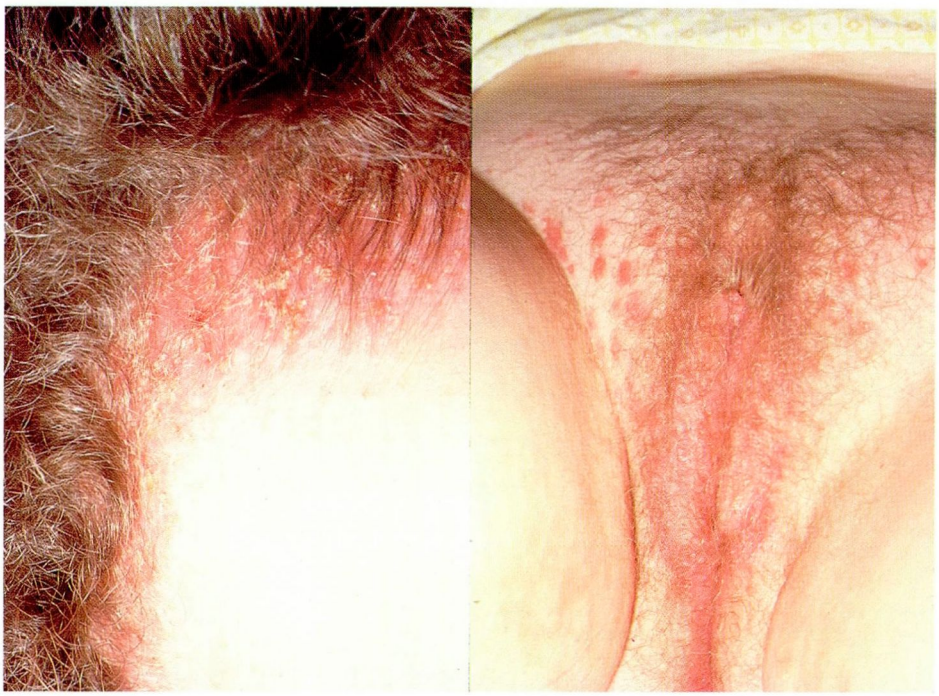
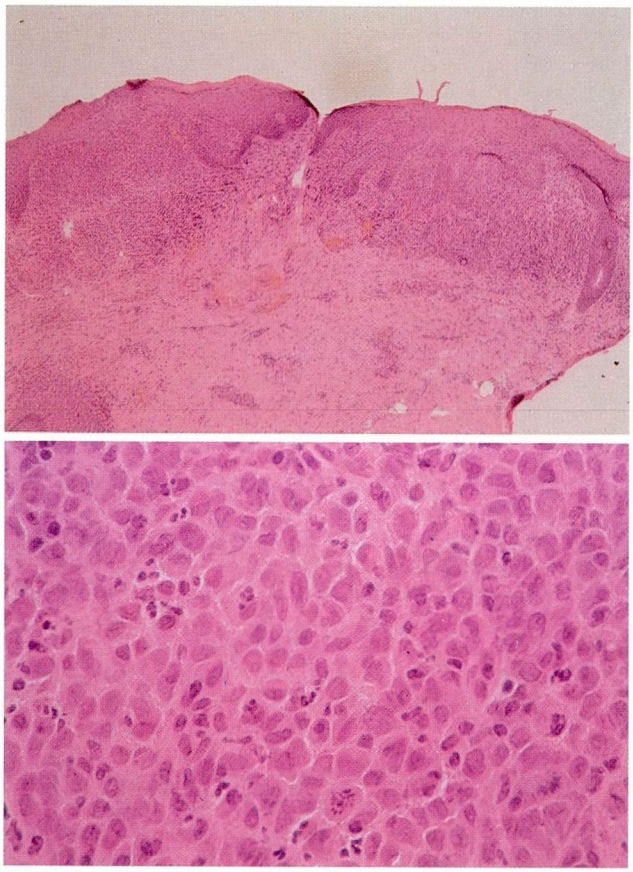


Figure 1.A. Thick, crusted erythematous plaques can be seen in the scalp and along frontal hairline.

B. Perineal lesions similar to the scalp lesions seen in *Figure 1A.*



selected sites resulted in marked clearing of most of the skin lesions. Hormonal therapy with levothyroxine sodium, cortisone acetate, vasopressin, medroxyprogesterone acetate, and bromocriptine resulted in significant control of her endocrine disease.

Discussion

Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma were grouped together by Lichtenstein under the designation of histiocytosis X,[3] based on the common histopathologic finding of abnormal proliferation of histiocytes characterized ultrastructurally by Langerhans' cell (Birbeck) granules.[4] The clinical manifestations of these disorders are extremely variable and almost any organ system may be affected, with the reticuloendothelial, osseous, cutaneous, hematopoietic, and pulmonary systems most commonly involved.[5] Although the fundamental cause of the disorder is still unknown, recent studies have suggested that patients with histiocytosis X may have an altered

Figure 2. Skin biopsy reveals a patchy, polymorphous upper dermal inflammatory infiltrate (hematoxylin and eosin, ×40).

Figure 3. At higher power, numerous large mononuclear cells with pale cytoplasm and irregularly folded nuclei are seen (hematoxylin and eosin, ×400).

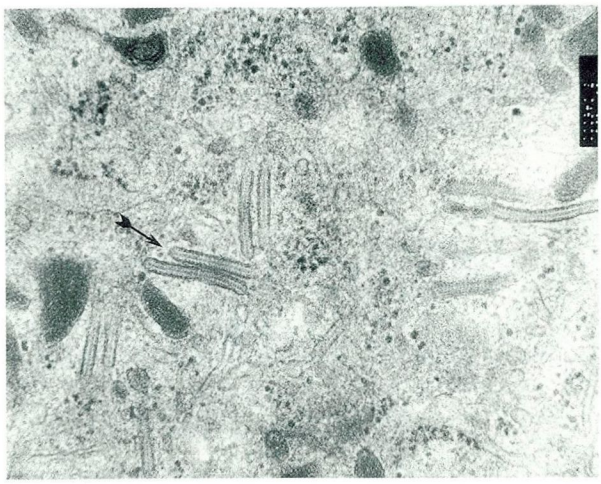


Figure 4. Electron micrograph of the large mononuclear cells demonstrates numerous intracytoplasmic Langerhans' cell (Birbeck) granules (arrow) (×46,000).

immunologic function characterized in part by a deficiency of T suppressor cells.[6]

Letterer-Siwe disease (acute disseminated histiocytosis X) occurs primarily in children less than two years of age; it is characterized by diffuse and rapidly progressive reticuloendothelial, osseous, hematopoietic, and pulmonary involvement. It is fatal in approximately 70% of cases.[7] Skin disease is common and includes widespread scaling papules and vesicles, hemorrhagic crusted erosions and plaques, petechia, and purpura.[8]

Hand-Schüller-Christian disease (chronic progressive histiocytosis X) was originally defined by the triad of skull defects, exophthalmos, and diabetes insipidus.[9] Its peak incidence is between the ages of two and five years. This is a chronic, slowly progressive form of histiocytosis X characterized by systemic involvement similar to but less aggressive than Letterer-Siwe disease and fatal in 30% to 70% of cases.[1] Cutaneous manifestations include general bronze pigmentation, purpura, papules and pustules, mucosal erosions and ulcerations, and seborrhealike eczema.[8]

Eosinophilic granuloma (benign localized histiocytosis X) affects both adults and children and was originally considered to be a benign form of histiocytosis X localized to bone.[10,11] It is currently believed to represent localized, generally self-limited disease in any location and carries a good prognosis.[7] Cutaneous lesions include scaling papules and plaques, often associated with secondary ulceration and crusting.[8]

Various methods have been used to treat histiocytosis X, depending on the form and severity of the disease. These include local surgery, systemic and topical corticosteroids, radiation therapy, topical nitrogen mustard,[12,13] and systemic chemotherapy, most commonly involving vinblastine, vincristine, 6-mercaptopurine, methotrexate, cyclophosphamide, and chlorambucil[14]; more recently, immunotherapy with thymic extract has given promising results.[6]

Although individual patients may have clinically distinct features that allow grouping into one of the traditional categories, transitional cases are not uncommon,[7] so that precise classification is often difficult, as emphasized by the present case. Although the association of vulvar eosinophilic granuloma and diabetes insipidus has been reported,[15,16] intertriginous granulomatous ulcerations and seborrhealike lesions are common in adults with Hand-Schüller-Christian disease.[7] It is unclear whether our patient's con-

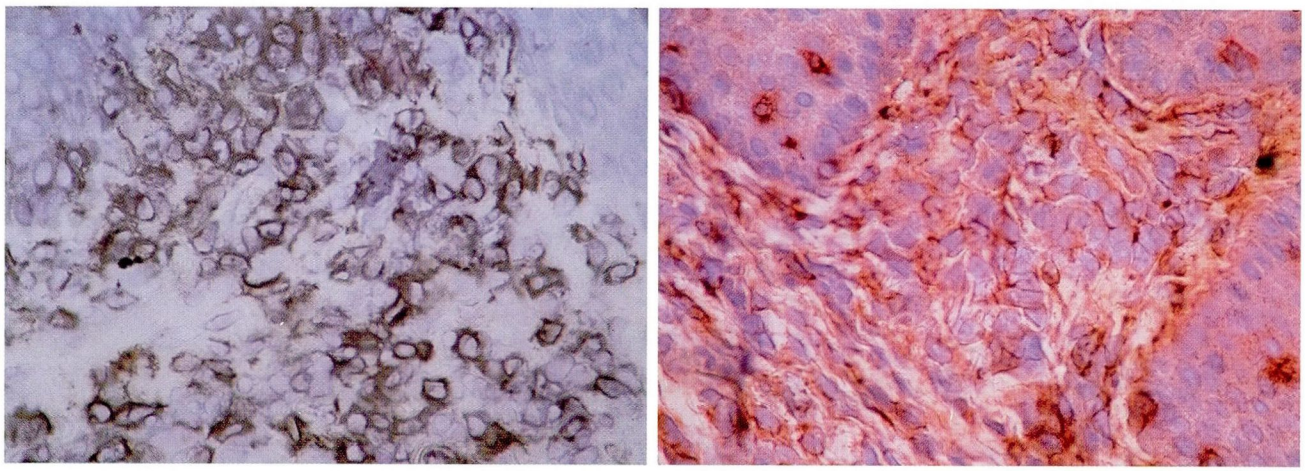


Figure 5. Positive immunostaining with monoclonal antibody differentiates antigens Ia (left) and OKM_1 (right) (frozen sections; counterstained with hematoxylin and eosin, ×400).

dition is a variant of either Hand-Schüller-Christian disease or eosinophilic granuloma, or an overlap of both.

Histiocytosis X comprises an extremely variable spectrum of disease ranging from benign and localized to lethal and disseminated. Although skin disease may be a prominent feature of histiocytosis X, it is frequently difficult to diagnose as such because its relatively benign and nonspecific character often suggests seborrheic dermatitis, eczema, intertrigo, or dermatophytosis. When such skin conditions do not respond to appropriate treatment, histiocytosis X must be considered. Light and electron microscopy and immunohistochemistry can be valuable in confirming the diagnosis.[17]

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