

LANGERHANS CELLS HISTIOCYTOSIS IN ONE FAMILY

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Abstract- Histiocytosis of Langerhans cells (class 1 histiocytosis) consists of a range of clinical manifestations, including bone eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe disease. These syndromes represent a spectrum of severity and prognosis of an underlying disorder which is usually sporadic. This report describes three cases in one family, who developed the disease a few years after their brother was discovered to have histiocytosis. All three patients had the same clinical manifestations. They had hyperthermia, eczematous rash, swelling in skull, hand and foot. Radiological data included lytic areas in the skull and fourth metacarpal. Serology for Epstein-Barr infection was negative. Infiltration of abnormal Langerhans cell histiocytes was demonstrated upon bone biopsy. Chemotherapy was administered. One case (male) died after a year of chemotherapy. In another case (female) chemotherapy was unsuccessful, but T-cell suppressor (cyclosporin) induced remission. In the third case (female), chemotherapy was successful.

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INTRODUCTION

The distinct syndromes of eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe disease are not easily distinguished from each other, either by pathologic or clinical findings. Recognizing this problem, Lichtenstein proposed the unifying term of histiocytosis X in 1953. Langerhans cell histiocytosis (LCH) later replaced histiocytosis X as the inclusive term for these disorders (1). The estimated incidence is in the range of 0.5 per 100,000/year in children younger than 15 years (1,2), and it has been reported in monozygotic twins and in familial pattern (3). The etiology is unknown, modern investigators suggest an atypical immunologic reaction or autoimmunity (1). The signs and symptoms of LCH vary considerably, depending on which organs are infiltrated by

Langerhans cells. Bone, skin, teeth, gingival tissue, ear, endocrine organ, lung, liver, spleen, lymph node and bone marrow can all become involved (2), associated with bone lytic lesions, seborrheic dermatitis, dental anomalies, gingivostomatitis, otitis media, diabetes insipidus, and hepatosplenomegaly. The diagnosis may be suspected by examination of formalin-fixed tissue by light microscopy (1,4), which reveals reactive infiltration of immature Langerhans cells. Flow cytometry does not reveal evidence of DNA aneuploidy (2). Either the demonstration of Birbeck granular pattern by electron microscopy, or T6/leu 6 (CD 1) membrane immunologic marker on fresh or frozen material is required for confirmation of the diagnosis. S-100 protein (cell surface antigens) can be demonstrated on formalin-fixed tissue (1,4,5).

Case 1

A 2 year-old boy was admitted because of fever, loss of appetite, swelling of face and legs, periorbital echymosis, chronic otitis, and hepatosplenomegaly. X-ray revealed lytic areas in the right tibia and fibula, left ulna and radius. The disease was defined as a multi-system disease and rapidly progressive

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(Letterer-Siwe disease, stage III). Bone biopsy showed trabecular bone with a lytic tumor composed of fibroblasts, many foamy histiocytes, (some multinucleated) and infiltration of lymphocytes and neutrophils but no eosinophils. Chemotherapy was administered, but the patient died one year later (Fig. 1).

Case 2

Two years after the death of case 1, his 3 year-old sister was admitted to the Children's Hospital, because of fever, facial swelling and eczematoid rash, chronic otitis media, and fracture of the second cervical vertebra. X-ray showed lytic areas in skull and finger. Skin biopsy demonstrated, heavy infiltration of Langerhans histiocytes with lymphomononuclear cells, plasma cells, eosinophils and neutrophils which involved the overlying epidermis (Letterer-Siwe disease, stage III). She underwent chemotherapy (vinblastine 6mg/m², prednisone 40mg/m², vp 16 100mg/m²) over a 6-month period. Because of unfavorable response to initial treatment, she received radiotherapy and cyclosporin and was subsequently well (Fig. 2 and 3). The lesion healed without complication.



Fig. 1. Eczematoid ulcer in case 1



Fig. 2. Eczematoid ulcer in case 2

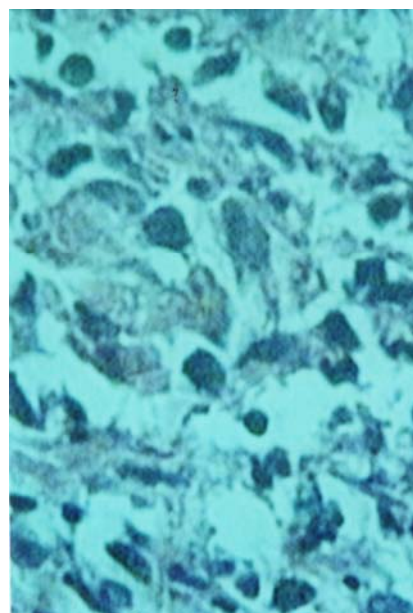


Fig. 3. Case 2: skin biopsy.

Case 3

The third child of this family was fourteen months of age at the time of admission, presenting with swelling of the entire body and exophthalmos. X-ray showed lytic areas in the skull and fourth metacarpal of right hand, with no evidence of marginal sclerosis or periosteal reaction. Biopsy of the lesions revealed fibroconnective tissue and bone. There were aggregates of histiocytes with grooved nucleoli and dentation of nuclei, and most of the cytoplasm was eosinophilic. Also, there were multi-nucleated giant cells, lymphocytes, plasma cells, polymorphonuclears and foci of necrosis (LCH). She was diagnosed with Hand-Schüller-Christian syndrome, stage II. Serology for Epstein Barr virus (EBV) infection was negative, and the level of serum IgG antibody to cytomegalovirus was elevated (Fig. 4)



Fig. 4. Case 3: lytic lesion in fourth metacarpal

DISCUSSION

LCH is a class I histiocytosis characterized by the presence of the pathologic Langerhans cell infiltration of skin and bone and in its most severe form is manifested by multifocal infiltration of organs. (3,6).

In 1986 Letter-Siwe disease was reported in two brothers, 15 and 11 months old. A similar clinical picture was manifested by hyperthermia, hepatosplenomegaly, moderate lymphadenopathy and cutaneous changes in one of the brothers (7). In 1995 Hesslis et al reported a 10 month-old girl who presented with pyrexia, hepatosplenomegaly, an eczematous skin rash, thrombocytopenia and marked elevation of serum IgG and IgM antibody levels to cytomegalovirus (8). In 1999 Arico et al reported nine families that had more than one affected relative, five with LCH in siblings or cousins. Clinical features were similar in patients (9). Baliko et al in 2000 reported two different manifestations of Langerhans cell histiocytosis, the first occurring as a solitary rib eosinophilic granuloma in 2 years old girl, and the second as an eosinophilic granuloma of the lung of her mother (10). In 2001 Arico et al reported a new family in which LCH had been diagnosed in two generations. (6) Familial clustering of histiocytosis X disease is very rare and raises the possibility of inherited mutations that promote emergence of clonal Langerhans cells (10). The chemotactic response of the neutrophils in these patients was depressed. Studies of immunoglobulin level and complement titers of patients showed no

consistent abnormalities (11). However, in contrast to normal Langerhans cells, the cells of LCH also express leukocyte adhesion molecules, such as CD 11 and CD14, typically expressed in greater density on phagocytic histiocytes (4). The etiology is unknown, although viral infection has been proposed as a potential etiologic factor (2). A virus could theoretically activate histiocytes and also impair immune regulation by disabling suppressor T cells, resulting in an amplified and uncontrolled response to the primary infection (4). HHV-6, a recently described member of the human herpes virus family, has been associated with atypical or malignant lymphocytic processes, an immune disorder (12). Based on these observations, we suspected that human herpes virus (HHV-6) may play a role in the pathogenesis of LCH (6). Lesional tissue of 30 patients with LCH was examined for presence of HHV-6 by using the polymerase chain reaction HHV-6 DNA was detected in lesions of 14 of 30 patients with LCH (47%) (12). Although the presence of a virus alone does not establish a crucial role, in the disease, it supports the possibility of an etiologic relationship (12). This report describes histiocytosis in one family, which was diagnosed with bone biopsy and treated by chemotherapy. At the time of writing, two of the patients are alive and well. In addition to family reported in our study, we performed search for presence of cells showing chromosomal or chromatid breaks, structural rearrangements, or polyploidy. A viral etiology in families with LCH, can not be ruled out and should be further investigated.

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