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Langerhans Cell Histiocytosis

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We present a case of an 8-month-old boy with purpuric seborrheic papules of his scalp and forehead and multiple, pinkish-yellow, umblicated, varicelliform vesicles on his trunk, palms and soles. The lesions appeared 3 months ago and didn't respond to the antibacterial treatment. Detailed investigation was performed and hepatomegaly was detected. Histopathological investigation of the skin lesions revealed the diagnosis of Langerhans cell histiocytosis, demonstrating abnormal proliferation of histiocytic-like cells. Immunohistochemistry was positive for S100 protein and CD1a. According to the skin manifestations, characteristic histological findings and immunohistochemistry the diagnosis of Letterer-Siwe disease was made. This is a clinical variant of Langerhans cell histiocytosis, which is a rare disease with bad prognosis. The disorder is characterized by neoplastic proliferation of Langerhans cells that involves the skin and other organs and systems, where the microscopic examination and morphological findings are very important for establishing the diagnosis.

Key words: Langerhans cell histiocytosis, Letterer-Siwe disease, Langerhans cells, histopathology, immunohistochemistry.

Introduction

Langerhans cell histiocytosis (LCH), previously referred to as histiocytosis X [11], refers to a spectrum of diseases characterized by the proliferation of pathogenic Langerhans cells and their infiltration of into various organs.

LCH is a rare disease that usually occurs in children. The tumor cells may infiltrate single or multiple organs such as the lungs, lymph nodes, liver, spleen, bone marrow, hypothalamus, pituitary gland, skin, and mucous membrane [13]. Whether LCH is neoplastic or reactive has not yet been determined, however. Current theories suggest a role for environmental, infectious, immunologic, and genetic causes.Viral infection has been suspected as a potential etiologic factor, and a study has suggested the possibility of a relationship between LCH and Epstein-Barr virus [7].

Cutaneous histiocytosis is often the initial manifestation of the disease and classically presents as scaly, erythematous plaques of the scalp, discrete, reddish-brown papules of the trunk with erosions of the groin and intertriginous areas.

The microscopic examination is critical for the diagnosis. The characteristic histological appearance of cutaneous LCH is the collection of large, bland histiocytes with eosinofilic to pale cytoplasm and reniform nuclei in the papillary dermis [5]. Mitoses and pleomorphic cells may be present. Perivascular and epidermal infiltration is not uncom-

mon. A variety of inflammatory cells, including lymphocytes, mast cells, neutrophils, and eosinophils, may be present. Immunohistochemistry plays an important role as a diagnostic tool if S100 and CD1a are positive. Although a positive CD1a immunohistochemical stain in the setting of appropriate histology is usually considered adequate for diagnosis, demonstrating Birbeck granules in the abnormally proliferating Langerhans cells using electron microscopy is another specific diagnostic test.

Material and Methods

An 8-month-old white boy presented with a three-month history of a skin eruption of red papules, some of which coated with squamo-crusts. The lesions were distributed on the head, body, palms and soles. They had not enlarged in size and changed in shape but increased in number. The onset of the eruption was associated with fever and diarrhea. The baby was treated with antibacterial drugs per oral and topical without effect.

He was born without complications and was the first-born child. His mother was healthy young white woman (24-year-old at that time). She denied illness and took no medications during the prenatal period.

The following laboratory investigations including complete blood counts, erythrocyte sedimentation rate (ESR), blood sugar, hepatic and renal function tests, lipid analysis, immunological parameters, HIV, HSV and HBV serology and urinalysis, were performed. Chest-X-rays, ultrasonography of abdomen, X-rays of cranium, femur and pelvis, were done. Skin biopsy of active papules from the body was obtained. For immunohistochemical analysis kids for CD1a and S-100 protein was also performed.

Results

On physical examination the boy was a healthy-appearing, nondysmorphic, smiling baby. Skin lesions were scaly, erythematous, seborrhea-like brown to red papules localized on the forehead, capilitium, palms and soles. An eruption of small nodular lesions that resemble those of healing chicken pox were distributed on the skin of the back and around the umbilicus. Erythematous red plaques and erosions were seen on the intertriginous inguinal folds.

According to pediatricians the baby had normal psychic and physical status. Laboratory investigations revealed an elevated ESR, leucocytosis and hyperlipidemia. Chest-X-rays and X-rays of the bones were not contributory. Abdominal ultrasound found solid hepatomegalia with normal echogenic structures. There was inguinal lymphadenopathy.

Histological findings from the lesion showed cell infiltrate, disposed on the upper derma, penetrated into the epidermis. It consisted of histiocytes with big nuclei, lymphoid cells, eosinophils and isolated giant cells of Touton (Fig. 1). Immunochistochemistry was positive for S-100 protein (Fig. 2) and CD1a (Fig. 3).

On the basis of the skin manifestations, characteristic histological findings and immunohistochemistry the diagnosis of Letterer- Siwe disease, a clinical variant of LCH, was made. Chemotherapy was prescribed.

Discussion

Skin involvement is common in LCH (up to 50% with multisystem disease may initially present with a rash), with the intertriginous zones and lumbosacral areas most commonly

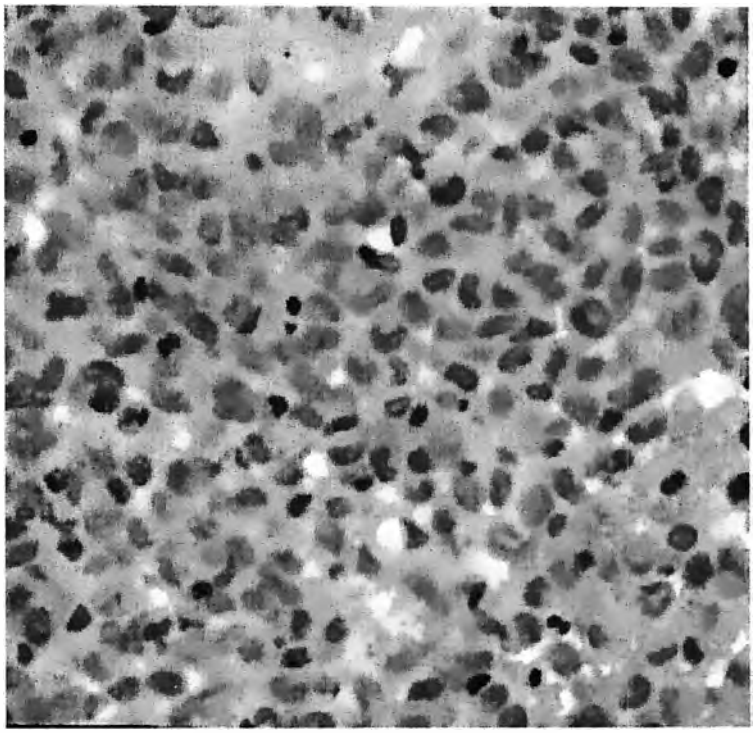

Fig. 1. Histology of skin lesion with H-E staining showing histiocytes and interspersed eosinophils (×400)

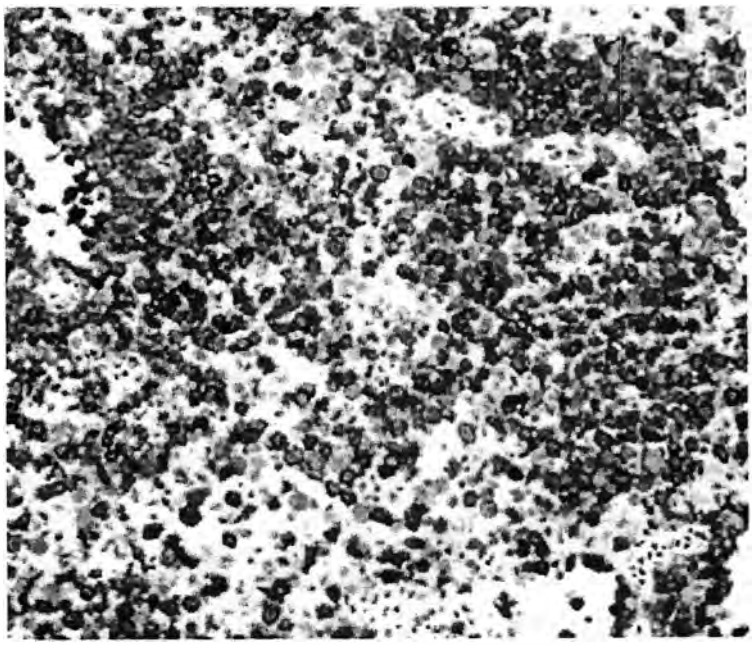

Fig. 2. Immunochistochemistry positive for S100 protein (×300)

Fig. 3. Immunochistochemistry positive for CD1a (×200)

affected [3, 12]. It is usually present in up to 80% of those with multisystem disease and 30% with less extensive multisystem disease [8]. It is reported as the only affected site in about 10% of cases [3]. It is often the first sign of multisystem LCH, and it becomes evident as scaly, erythematous, seborrhea-like brown to red papules [12, 13], presenting in a fashion similar to contact dermatitis [3, 8, 12].

The microscopic examination is very important for the diagnosis [6]. The tissues from LCH lesions contain an abnormal proliferation of histiocytic-like cells. The lesions are locally proliferative and have been shown to demonstrate elevated proliferation rates ranging from 3% to 48%, with the largest indices found in the lymph nodes [8]. Characteristic pathologic morphology of tissue from children with LCH includes large cells with elongated, irregular nuclei, prominent nuclear grooves, folding, and indentation, moderate to abundant cytoplasm, and frequent mitotic figures [1, 10]. Variable numbers of eosinophils are often present. The lesions are also characterized by osteoclast-like multinucleated giant histiocytes with bone destruction, necrosis, hemorrhage, and eosinophilic abscesses [8, 10]. Also, indeterminate cells, interdigitating dendritic cells, macrophages, and T lymphocytes are often found in increased numbers in the lesions [1, 2, 8]. Granulomas may or not be seen, and fibrosis may be seen in later lesions.

The CD1a immunohistochemical stain is a very helpful adjunct to the diagnosis, although a less specific marker of the pathogenic Langerhans cells [4, 8]. A positive CD1a with the described histology in the right clinical setting is often considered adequate for diagnosis. Although S100 is not diagnostic, it is important in the evaluation of histiocytic disorders and identifies a family dendritic of cells that are part of cytological continuum [8].

There are three main clinical subtypes that are encompassed by the term LCH [4, 10]. The first variant is a unifocal variant (single system, single site), and it has been referred to as eosinophilic granuloma. This subtype commonly involves bone (up to 80% of cases), lymph nodes, or lungs as a primary target [1]. Children with localized disease tend to have bone involvement while adults have a greater propensity for lung involvement [9]. Based on a study of 459 pediatric patients (less than 15 years of age), this subtype has been documented to represent 33.3% of cases, with a median age at diagnosis in this group of 2.2 [4].

The second subtype is considered to be multifocal, and it has been referred to as Hand-Schuller-Christian disease. This variant usually affects younger patients and involves several sites in one organ system (single system, multiple sites) [1]. The organ system involved varies from one patient to another. With cranial involvement, it often presents with skull lesions, diabetes insipidus, and exophthalmos. Other bones, the oral cavity, skin, lymph nodes, brain, lungs, and liver represent other organ systems that may be affected in different patients [8]. Multiple foci of disease will be found in the particular organ system affected for a given patient. In a study of pediatric patients, this subtype has been reported to involve 15.1% of cases of children less than 15 years of age, with a median age at diagnosis of 3 [5]. This subtype is fatal in 15% of patients [2].

The third subtype has been referred to as disseminated histiocytosis or Letterer-Siwe disease. It affects multiple sites in multiple organ systems, and is most prevalent in young children and infants [1]. This variant is associated with the worst outcome [1]. Typical manifestations include multisystem involvement of bone and organs and may include persistent fevers, irritability, anorexia, failure to thrive, purpuric rash, superinfection, diarrhea, pancytopenia, and life-threatening sepsis. Pulmonary, hepatic and splenic involvement may occur [9]. Based on a study of pediatric patients, this subtype has been reported to include 51.6% of cases of children less than 15 years old. This form progresses rapidly and is usually fatal [2]. Despite its high prevalence in pediatric LCH patients, this variant represents less than 15% of all cases [8]. Thus, if diagnosed at a younger age, it is more likely that a child will have more serious disease with significant multisystem involvement. It is therefore apparent that young children suffer excess mortality rates from LCH, when compared to patients of other age groups.

The report presented here is a case of Letterer-Siwe disease, which is a clinical variant of LCH. This is a rare disease with bad prognosis. The characteristic skin lesions of papulosquamous eruption, distributed on typical topographic areas–head, trunk and intertriginous folds, were the first sign that directed us to this diagnosis. The acute beginning, fever, diarrhea and hepatomegaly were referred to multisystem involvement. The typical histopathologic findings and positive immunochistocemistry played the main role to establishing the diagnosis.

It is important to make the diagnosis as quickly as possible, because time from presentation to diagnosis is of prognostic importance in patients with LCH.

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