Case Report

Langerhan Cell Histiocytosis- A Case Report

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Introduction

Langerhan cell histiocytosis (LCH), previously known as histiocytosis X, is a reactive proliferative disease of unknown pathogenesis characterized by proliferation of Langerhans’ cells. The clinical spectrum of LCH includes one end, an acute fulminant, disseminated disease in infants called Letterer-Siwe disease and, on the other end, solitary or few, indolent and chronic, lesions of bone or other organs called eosinophilic granulomas. The intermediate Hand-Schuller-Christian disease is characterized by multifocal, chronic involvement and classically presents as the triad of diabetes insipidus, proptosis, and lytic bone lesions in older children and adults. A congenital self-healing form called Hashimoto-Pritzker disease has also been described.

We report here a case of Letterer-Siwe disease in an infant involving skin, liver and spleen. The disease was picked on Fine Needle Aspiration Cytology (FNAC) of liver and spleen. The skin biopsy later also revealed Langerhan cell infiltrate. This case also emphasizes upon the use of oil immersion lens in difficult cases on cytologic smears as in this case the diagnosis was made on 1000 magnification that clearly showed the cytoplasmic processes of Langerhan cells.

Case Report

A 9 months old boy presented to pediatrics department in September 2004 with fever and pallor for 15 days, progressively increasing abdominal distension for 1 month and rash on scalp and abdomen since 5 months. There was history of fits at the age of 5 months. He was a product of non-consanguineous marriage. Rest of the siblings were alive and healthy. On examination he was a sick looking pale child with maculopapular rash on abdomen, soles, palms, scalp, postauricular area, cheek and concha with sparing of chest, limbs and back. (Fig1) There was hepatosplenomegaly. The differential diagnosis included anemia, seborrheic dermatitis, storage disease or infectious disease. Laboratory investigations revealed pancytopenia with Hb count of 1.9 gm/dl, WBC count 2500/mm³ and platelet count of 40000/mm³. Bone marrow aspiration and biopsy were performed which showed hypercellular marrow with erythroid hyperplasia and moderate degree of fibrosis. There was no evidence of lymphoma, leukemia or any abnormal cells in bone marrow. FNAC of liver and spleen were performed with 23 gauge needle using stab technique from 3 different areas. The smears were fixed with 95% ethanol and stained with hematoxylin and eosin. Skin biopsy specimen was fixed in 10% buffered formalin, routinely processed and embedded in paraffin. The sections were stained with hematoxylin and eosin and a diagnosis of Langerhan cell Histiocytosis was made on FNAC of liver and spleen. Skin biopsy also revealed same picture. He was given injection Vincristine but unfortunately he succumbed to his disease.

Pathologic Findings

FNAC of liver and spleen revealed a hypercellular smear composed of large number of cells having deeply indented nuclei and abundant acidophilic cytoplasm. There was a background of lymphocytes and red blood cells. Examination under oil immersion lens using xylene revealed long cytoplasmic processes in cells. (Fig. 2) Scattered hepatocytes were also present. The characteristic cytoplasmic processes and nuclear grooves led to diagnosis of Langerhan cell Histiocytosis. Meanwhile we also received skin biopsy of patient which confirmed our diagnosis. There was epidermal atrophy, spongiosis and scab formation. Dermis was heavily infiltrated by histiocytes having granular cytoplasm and grooved nuclei. (Fig 3)
Discussion

In 1868, Paul Langerhans discovered the epidermal dendritic cells that now bear his name. The ultrastructural hallmark of the Langerhan cell, the Birbeck granule, was described a century later. The term Langerhan cell histiocytosis is generally preferred to the older term, histiocytosis X. This new name emphasizes the histogenesis of the condition by specifying the type of lesional cell and removes the connotation of the unknown (X) because its cellular basis has now been clarified. The working group of the Histiocyte Society has divided histiocytic disorders into 3 different groups: (1) dendritic cell histiocytosis, (2) erythrophagocytic macrophage disorders, and (3) malignant histiocytosis. Langerhan cell histiocytosis belongs to group 1 and encompasses a number of diseases.  

LCH can affect practically every organ. The most common sites are bone, skin, lymph node, ears, bone marrow, lung, and pituitary. Unusual sites including brain, thymus, pancreas, vulva and thyroid have also been reported. Cutaneous lesions are very commonly seen in Letterer-Siwe disease and occur occasionally in the other two forms. LCH of liver may be seen as a solitary isolated finding or as a component of systemic disease while splenic involvement is almost always the expression of systemic disease. A presumptive diagnosis of LHC is given when classic morphologic features are seen in an appropriate clinical setting; a diagnosis is made when the clinical features are seen along with two or more of the following: positivity for S-100, adenosine triphosphatase or alpha D-mannosidase or binding with peanut lectin; a definitive diagnosis is made only if the lesion shows positivity for CD1a or the presence of Birbeck granules on electron microscopy. The clinical course and prognosis of LCH are difficult to predict. The most important parameters are the age of the patient, the number of organs involved and the degree of organ dysfunction. Abnormalities of bone marrow, liver or lungs suggest a poor prognosis. According to some studies, involvement of skin before the age of 2 years is a bad sign. Acute disseminated disease usually occurs in infants. Rarely is it seen in older children and adults. The prognosis generally is serious, particularly if the disease is extensive. The most common manifestations are fever, anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy and pulmonary infiltrates. Osteolytic lesions are not common. Cutaneous lesions are seen in...
80% cases. They are often the first sign of disease and are therefore of considerable diagnostic importance.6

The cutaneous lesions usually consist of petechiae and papules. In some cases, one observes numerous closely set, brownish papules covered with scales or crusts. This type of eruption may be extensive, involving particularly the scalp, face and trunk.6

Minkov et al studied the incidence; clinical patterns, course, and outcome of neonatal Langerhans cell histiocytosis and found out the estimated incidence of neonatal LCH (LCH diagnosed within 28 days after birth) in the population-based registry in Germany to be 1-2/1,000,000. Neonatal LCH is characterized by a clear predominance of multisystem-LCH. Cutaneous changes are the most common initial manifestation in neonates with both single system-LCH and multisystem-LCH. Neonates with multisystem-LCH, especially those with risk organ involvement at diagnosis, have less favorable prognosis compared to infants and older children, and need systemic therapy.6

Although the first clinical description of Langerhans cell histiocytosis was published over a century ago, the etiology and pathogenesis of this enigmatic disorder still remain unknown. Viral, immunological, neoplastic and other pathogenetic mechanisms have been considered, but none has been proven. Arguments supporting the reactive nature of this disorder include the occurrence of spontaneous remissions, the failure to detect aneuploidy, metaphase or karyotypic abnormalities, and the good survival rate in patients without organ dysfunction. On the other hand, the infiltration of organs by aberrant cells, a possible lethal evolution, and the cancer-based modalities of successful treatment are all consistent with a neoplastic process.2 A key feature of a neoplasm is its clonal derivation from a single cell. Clonal CD1a+ histiocytes have now been detected in the lesional tissues in patients affected with LCH.9 Evidence exists for a role of immune dysfunction in the pathogenesis of Langerhan cell histiocytosis by the creation of a permissive immunosurveillance system. Abnormalities of suppressor cell number and function have been documented in several reports. Increased levels of messenger RNA for macrophage colony-stimulating factor and platelet-derived growth factor have been detected in cells from a pulmonary LCH lesion.2 According to Rolland et al LHC is a disease of myeloid precursor cells. They found out that lin(-) HLA-DR(+)CD11c+ precursors of dendritic cells, able to give rise to either Langerhans cells or macrophages, are significantly (p = 0.004) increased in the blood of LCH patients.1 The presumed immunological dysregulation in LCH may affect the expression of cellular adhesion molecules, reflected by the inconsistent expression of CD11a and CD11b and the unexpected expression of CD2. These features may contribute to migration of Langerhan cells to sites in combination with abnormal persistence and proliferation.10 Early hemopoietic cytokines such as FLT3-L (a dendritic cell-mobilizing factor), stem cell factor, and M-CSF maybe relevant in LCH pathogenesis and might be considered as novel therapeutic targets.10 LCH represents a cytokine-driven condition partially mediated by TNF, IL-11, and LIF. These three cytokines are all osteoclastogenic, suggesting a pathogenetic pathway for the osteolytic lesions in LCH. Furthermore, thrombocytosis in LCH may be explained by IL-11 and LIF activity.11 Dina et al studied extent of angiogenic response in LHC and found that vascular endothelial growth factor was expressed in LCH cells and that all multisystem lesions were VEGF producers raise the possibility of using anti-angiogenic drugs to treat these patients.12

Although three kinds of histologic reactions have been described in LCH histiocytosis—proliferative, granulomatous and xanthomatous—only the first two are commonly seen. A relationship exists between the type of histologic reaction and the clinical type of disease. In general, the proliferative reaction with it’s almost purely histiocytic infiltrate is typical of acute disseminated LCH and the granulomatous reaction of chronic focal or multifocal LCH, as the name eosinophilic granuloma suggests. The xanthomatous reaction is seen in Hand-Schüller-Christian disease. The proliferative reaction is encountered in the skin in petechiae, in both hemorrhagic and nonhemorrhagic papules and in scaling and crusting eruptions. It is characterized by the presence of an extensive infiltrate of histiocytes lying close to or involving the epidermis, resulting in ulceration and crusting. Inflammatory cells are also present mostly lymphocytes and eosinophils. Extravasated erythrocytes may also be present. In this stage, cytology is quite distinctive and a touch preparation from an ulcerated or weeping lesion can often provide a rapid diagnosis.9 FNAC of lesion usually yields a richly cellular aspirate. Smears are composed of mixed population of eosinophils, neutrophils, lymphocytes and Langerhans’ histiocytes.
The latter are large to medium sized cells with plentiful cytoplasm and rounded, bean or kidney shaped nuclei. Characteristically, the nuclei are irregular and lobulated or show folded nuclear membranes; so called coffee bean nuclei have been reported to be especially typical. Some of these cells are binucleated or multinucleated. One must be aware, however, of different morphologic patterns of LCHs and of unusual appearances of Langerhan cells, which may lead to diagnostic errors. Electron microscopic demonstration of specific Birbeck granules and immunocytochemistry using CD1 (a) are of value in establishing a reliable diagnosis. Langerin is a recently identified lectin for which antibodies can be used as immunohistochemical markers of Langerhans cells.

In single system disease, Langerhans cell histiocytosis is responsive to local therapy but, in resistant single system disease or in multisystem disease, etoposide is the most effective monochemotherapy. Some patients need maintenance treatment with azathioprine or 6-mercaptopurine with or without methotrexate.

We present here a case of Histiocytosis X with multisystem involvement. The cytomorphicologic pattern of LCHs in fine needle aspiration cytology smears is usually characteristic. The pathognomonic feature of LCH is “Langerhan cell”. Varying numbers of eosinophils, polymorphs and lymphocytes can also be seen. In our case special cytologic feature was presence of cytoplasmic processes seen under oil immersion lens. To the best of our knowledge there is no previous report of such large cytoplasmic processes on FNAC. We recommend the routine examination of sections especially the doubtful ones under oil immersion lens as it greatly helps in diagnosis by making cellular morphology more evident.