



Solitary Lymph Node Involvement by Langerhans Cell Histiocytosis: Cytomorphologic Diagnosis and Pitfalls on Fine Needle Aspiration Cytology

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease and when confined to lymph node, it is even rarer. Lymph node involvement in LCH can be seen as a component of the systemic form or it may be the initial and sometimes exclusive manifestation of the disease [1]. We present a case of LCH confined to the lymph node diagnosed initially by fine needle aspiration cytology (FNAC) in a 7 year old girl. Highly cellular smears showed fair number of large histiocytic cells (Langerhans cells) showing round to oval vesicular nuclei with irregular folded and grooved nuclei with abundant, pale blue cytoplasm admixed with numerous neutrophils, lymphocytes, macrophages, multinucleated giant cells and tingible body macrophages suggesting the diagnosis of LCH. This was confirmed on histopathological and immunohistochemical study of the excised lymph node. The highly characteristic common and rare cytological features are highlighted with focus on differential diagnosis and causes of pitfalls.

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disease arising from clonal proliferation of Langerhans cells, which are abnormal cells derived from bone marrow that migrate from skin to lymph node. LCH is considered a neoplasm of the mononuclear phagocytic immunoregulatory system of unknown etiology. This disease is characterized by clonal proliferation of a special kind of histiocyte of the antigen-presenting dendritic type called the Langerhans cell (LC).^[1,2] It affects predominantly children and young adults, but it can be found in any age group. LCH remains a complex disease with a wide array of presentations and clinical courses. Approximately two-thirds of children with LCH have single-system disease that most commonly affects bone, but that can also involve skin, lymph nodes or the central nervous system.^[3]

Case Report

A seven year old girl presented to surgical oncology OPD with multiple bilateral cervical lymphadenopathy for approximately 20 days. The lymph nodes were non tender, mobile and varying in size from 1 to 2 cm. The patient had no history of fever or weight loss. The liver and spleen were not palpable. Her complete blood counts and urine microscopy were unremarkable. The patient was referred for FNAC.

FNAC from lymph node yielded white aspirate and smears were stained with Giemsa and Haematoxylin & Eosin. Highly cellular smears showed numerous atypical histiocytes as the predominant cell type scattered singly and in loosely cohesive clusters. A fair number of these cells showed round to oval vesicular nuclei with irregular folded and grooved nuclei (coffee bean appearance) with abundant, pale blue cytoplasm. Admixed polymorphous population of numerous neutrophils, lymphocytes, macrophages, multinucleated giant cells and tingible body macrophages was seen. Few binucleate and multinucleate forms were also encountered. (Fig. 1) A diagnosis of LCH was suggested and histopathological and immunohistochemical confirmation was advised.

Multiple x-rays of whole body (including cervical spine, knee joint with leg, humerus with forearm, pelvis with thigh, skull), ultrasound abdomen and CECT chest and abdomen were done to rule out any other systemic involvement. Excision biopsy of the cervical lymph node was also done which on histopathology (Fig. 2) showed partial effacement of lymphnode architecture with sheets of histiocytes (langerhans cells) admixed with eosinophils, neutrophils and giant cells. These langerhans cells have eosinophilic to clear cytoplasm and contain oval to grooved nuclei.

was referred to as histiocytosis X and had three variants: eosinophilic granuloma, Hand-Schuller-Christian disease

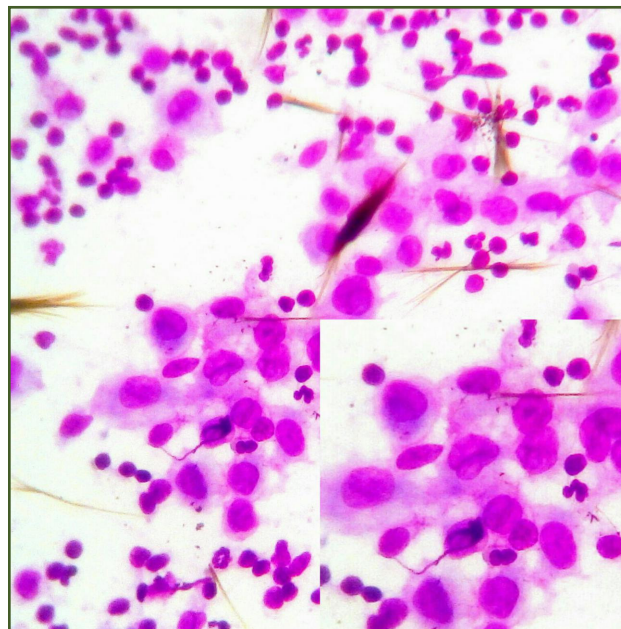


Fig. 1: Cytomicrograph showing cluster of langerhans cells with oval vesicular to irregularly folded and grooved nuclei (coffee bean appearance) with abundant, pale blue cytoplasm in background of neutrophils, lymphocytes and eosinophils (400x, Giemsa stain). Inset (600x, Giemsa stain).

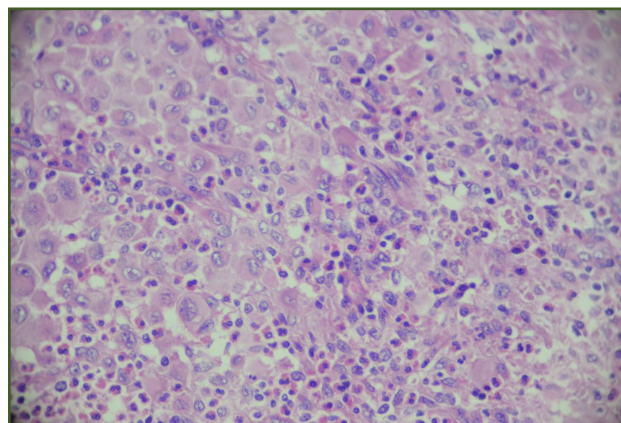


Fig. 2: Histomorphological picture showing sheets of histiocytes (langerhans cells) admixed with eosinophils, neutrophils and giant cells. These langerhans cells have eosinophilic to clear cytoplasm and contain oval to grooved nuclei. (600x, H&E stain).

nuclei. These cells were CD68, S-100 and CD1A positive, confirming the diagnosis of LCH in cervical lymph node.

Discussion

LCH is a rare disease with an estimated annual incidence of 0.5-5.4 cases per million^[1] In the past, the disorder

and Letterer-Siwe syndrome. These three conditions are believed to represent different expressions of the same disorder, now collectively known as LCH.^[1,4] LCH shows no age bar and affects patients from the neonatal period to adulthood, although it appears to be more common in children aged 0-15 years. There is no significant gender difference.^[2,4]

A controversial debate exists on the origin of LCH, whether this is a reactive or neoplastic process.^[3] The disease is characterized by a clonal proliferation of the antigen-presenting dendritic cell called the Langerhans cell (LC).^[2,3,4] The proliferation may be induced by a viral infection, a defect in T cell macrophage interaction, and/or a cytokine-driven process mediated by tumor necrosis factor, interleukin 11, and leukemia inhibitory factor.^[4] LCH remains a versatile mimicker and diagnosis is often difficult and delayed. The course of the disease varies from spontaneous resolution to a progressive multisystem disorder with organ dysfunction and potential life threatening complications.^[2] The clinical spectrum of LCH varies from having a single system disease (solitary unifocal and multifocal unisystem) to multifocal multisystem disease. The single system commonly affects bone but can also involve skin, lymph node or central nervous system.^[1-7]

Traditionally, the diagnosis of LCH is based on hematologic and histologic criteria and cytology closely reflects histomorphology. Ancillary studies may not be always necessary for diagnosis in appropriate setting. The cytological features of LCH include high cellularity composed of sheets and singly scattered LCs admixed with polymorphous population of numerous eosinophils, neutrophils, lymphocytes, plasma cells, multinucleated giant cells, and macrophages. The key to the diagnosis is to identify the LC through its characteristic features, namely, nuclear grooves (with a coffee bean appearance) and nuclear pseudoinclusions as seen in our case. They show variable degree of pleomorphism and mitotic activity. Sometimes, the LCs are few and nuclear grooves may not be very prominent or lack cytoplasmic processes. Ancillary studies such as immunohistochemistry and ultrastructural study aid the diagnosis in such cases.^[1,2,4]

Charcot-Leyden crystals are crystalloids containing eosinophil membrane protein formed from rupture of eosinophil's granules. Charcot-Leyden crystals singly and in bunches within the macrophages, giant cells, and extracellularly have also been described in cases of LCH. They indicate tissue eosinophilia and may help in drawing attention to the LCH diagnosis.^[4] Degree of eosinophil

infiltration varies in different areas of LCH lesion and different organs, thus their number can vary from scant to abundant in cytology smears. Their presence can help attract attention to the diagnosis.^[4] In our case, predominantly LCs and reactive histiocytes were seen in lymph node smears and eosinophils were scant. Touton type of giant cells have also been described in association with LCH in cytological smears of lymph node.^[7] However, we did not encounter such feature in our case. The diagnosis may be missed due to lack of familiarity with its cytological features among pathologists or due to the lack of characteristic cytological findings resulting from a sampling error.

The common differential diagnoses in a lymph node should include all those conditions with localized aggregates of LCs such as those observed in association with Dermatopathic lymphadenitis (DL), parasitic infection, Kimura's disease, hypersensitivity reactions, cat-scratch disease, sinus histiocytosis with massive lymphadenopathy (SHML), and hyperplastic lymph node.^[1,4] Dermatopathic lymphadenitis (DL) can be excluded by the absence of pigment in the histiocytes. SHML involves primarily the cervical nodes, but its histiocytes are morphologically quite different from those of LCH. In SHML, the histiocytes have abundant cytoplasm, exhibiting emperipolesis and prominent nucleoli. In addition, in SHML, the histiocytes are S-100 protein (+), lysozyme (-), and CD1a (-), whereas, LCs show positivity for S-100, PNA (peanut agglutinin), MHC class II, CD1a and langerin (CD207). Our case showed positivity for S-100 protein and CD1a.

In addition, on rare occasions, LCH can be seen associated with a variety of malignant neoplasms in the same node, i.e., malignant lymphoma or metastatic neoplasms.^[8] Other neoplastic conditions with eosinophilic infiltration and nuclear grooving such as Hodgkin's disease (HD), malignant melanoma, papillary thyroid carcinoma, malignant histiocytosis (MH), and other tumor cells with nuclear groovings should be considered in differential diagnosis and ruled out. Malignancies are easily excluded when no malignant cells with obvious cytologic atypia are present.^[1]

On electron microscopy, Birbeck granules are distinctive ultrastructural hallmark. However, it is time consuming and costly and not considered essential for the diagnosis as suggested by other authors.^[2,4] FNA can be a useful diagnostic modality for primary diagnosis as well as to evaluate the extent of the disease or recurrence of LCH. Patients with apparently restricted LCH need careful staging of their disease to ensure that the lesions are not part of a more extensive process.

Conclusion

To conclude, the present case highlights the role of FNA in the diagnosis of LCH with discussion of differential diagnosis and pitfalls. A high index of suspicion, awareness of characteristic cytological features of LCH, and its differential diagnoses is necessary. This can obviate the need of biopsy, immunohistochemistry and electron microscopy. Immunocytochemistry, if available, can be performed on cytology smears and cell block.

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Competing Interests

None

Reference

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