Langerhans cell histiocytosis in children diagnosed by fine-needle aspiration

ABSTRACT
Background: Langerhans cell histiocytosis (LCH) is a rare intricate pediatric neoplasm with varied clinical manifestations and multiple treatment modalities.

Aim: To study the cytological features of LCH and the differential diagnoses on fine-needle aspiration (FNA).

Materials and Methods: FNA was performed using a 23-gauge needle fitted to a 10 mL syringe mounted on syringe holder. LCH was diagnosed on FNA smears in seven cases confined to the head and neck region, which included three cases of lymphadenopathy, three cases of scalp swelling, and one case of orbital swelling.

Results: The age of the patients ranged from 25 days to 11 years and male-to-female ratio was 1:1.3. Clinically, the diagnoses suggested were tuberculosis, inflammatory lesion, abscess, and malignancy. The cytologic findings included high cellularity, isolated Langerhans cells (LCs) with prominent nuclear indentation, grooves and abundant vacuolated cytoplasm, multinucleated giant cells, eosinophils, and lymphocytes. Areas of necrosis were noted in one case. Histopathology, along with positive S-100 immunohistochemistry, confirmed the diagnosis of LCH.

Conclusions: LCH is a rare disease occurring predominantly in children and can be diagnosed with ease on FNA cytology by the presence of characteristic Langerhans cells. The S-100 positivity aids in suggesting a diagnosis of LCH.

Key words: Cytology; fine-needle aspiration (FNA); Langerhans cell histiocytosis (LCH)

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease affecting predominantly children and young adults but can be found in any age group. The disorder is characterized by abnormal, clonal proliferation and accumulation of antigen-presenting dendritic cells, the Langerhans cells (LCs), associated with immunosurveillance and immune regulation. The peculiar cytomorphological, immunohistochemical, immunophenotypic, ultrastructural, and functional properties of these cells allow them to be identified amid various cells of the monocyte-macrophage lineage.

The disease has a variable clinical presentation and outcome. The spectrum ranges from unifocal disease with excellent survival to multifocal disease with single system or multisystem involvement associated with poor prognosis. The skin, bone, lymph node, lungs, liver, spleen, thymus, and central nervous system may be involved. The varied disease manifestations mandate different treatment modalities, which range from minimal therapy to aggressive multidrug chemotherapeutic regimens.

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The present study was undertaken to study the cytomorphological features of LCH, along with the differential diagnoses so that a rapid and accurate diagnosis on fine-needle aspirates can be made.

Materials and Methods

Seven cases of LCH diagnosed on fine-needle aspiration (FNA) over a period of 10 years (2004-2013) were retrieved from the archives. The clinical data from the cytology forms and case files of the patients were collected. The clinical parameters including the age, sex, and signs and symptoms with emphasis on the type of lesions were evaluated. FNA was performed by the cytopathologist using 23-gauge needle fitted to a 10 mL disposable syringe mounted on syringe holder. One to two passes were taken. The smears were air-dried for May-Grünwald-Giemsa (MGG) and wet-fixed in 95% alcohol for hematoxylin and eosin (H and E) and Papanicolaou staining. Histopathology and S-100 immunohistochemistry were available in all the cases.

Results

The age of the patients ranged from 25 days to 11 years and the male-to-female ratio was 1:1.3. All the seven cases were confined to the head and neck region, which included three cases of lymphadenopathy, three cases of scalp swelling, and one case of orbital swelling as shown in Table 1. Clinically, the diagnoses suggested were tuberculosis, abscess, and malignancy in cases with enlarged lymph nodes. The scalp swelling was thought to be tuberculosis in one case and this patient also had cervical lymphadenopathy. The clinical possibility of a retrobulbar inflammatory lesion was kept in the case with orbital swelling.

Cytologic findings

The cytological findings are summarized in Table 1. The cytologic smears in all the cases were cellular showing isolated LCs with low nuclear: cytoplasmic ratio, many having large, pale, bland ovoid vesicular “coffee-bean” nuclei with grooves and indentations, along with ample eosinophilic granular cytoplasm [Figures 1a-c]. Binucleated and multinucleated cells were also seen. Mitoses were occasionally seen. Also seen were eosinophils and lymphocytes. Charcot-Leyden crystals were not seen. Areas of necrosis were seen in one case and staining for acid-fast bacilli done in this case was negative (case 2). On cytology, the diagnosis rendered was LCH in all the cases.

Histologic findings

Histopathologic confirmation was performed in all the cases. Paraffin sections showed sheets and islands of dense mixed infiltrate composed of LCs, eosinophils, and lymphocytes [Figure 1d]. In all the cases, immunohistochemistry for S-100 antibody showed nuclear and cytoplasmic staining in LCs [Figure 1d].

Discussion

The estimated annual incidence of LCH ranges from 0.5 to 5.4 cases per million.[2,4] The disparate group of diseases with variable nomenclatures — histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian syndrome, Hashimoto-Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, Type II histiocytosis, and nonlipid reticuloendotheliosis are now collectively referred to as LCH.[5] These in fact are different presentations of the same disorder, the LCH.

The clonal proliferation of the antigen presenting dendritic cells, the Langerhans cells, supports neoplastic nature of LCH.[4] For a long time, it was debatable as to whether LCH represents a reactive or neoplastic process.[4] The exact pathogenesis of the disease is, however, unknown.[7] It may be a viral infection induced or a defect in T cell macrophage interaction and/or a cytokine-mediated process, involving...
interplay of tumor necrosis factor, interleukin 11, and leukemia inhibitory factor.\(^2\)

The clinical presentation in LCH is varied. It can be a solitary lesion to multifocal unisystem to multisystem lesions.\(^{1,8}\) The unifocal disease usually involves the skeleton. The multifocal unisystem disease almost always occurs in the bone usually involving the skull, spine, pelvis, ribs, and mandible in more than half of the cases.\(^4\) Systemic LCH commonly affects children under 2 years of age. The multifocal multisystem disease involves multiple organs — the bone, liver, spleen, hematopoietic system, skin, and lymph node. Isolated lymph node involvement is rare as seen in one of our cases.

Lytic lesions in the skull bones having a punched out appearance was seen in one case. The differential diagnoses of skull lesions clinically include Ewing’s sarcoma, non-Hodgkin lymphoma, and osteomyelitis.\(^{4,9}\) Ewing’s sarcoma and non-Hodgkin lymphoma are characterized by a monotonous population of malignant small round cells.\(^4\) In acute osteomyelitis, there is a neutrophilic predominance while chronic osteomyelitis shows numerous plasma cells and lymphocytes.

The cytological smears in LCH are almost always cellular, composed of sheets and scattered LCs with interspersed polymorphous population of eosinophils, neutrophils, lymphocytes, plasma cells, and multinucleated giant cells.\(^{10,11}\) In FNA, the cellularity of the smears and proportion of various cells correlate with the stages of lesions in LCH.\(^{12}\) Early lesions show good cellularity with a preponderance of LCs or eosinophils. Older lesions notably show macrophages with foamy cytoplasm and sparse LCs. Further, with increasing duration fibrosis sets in; the LCs and eosinophils become an occasional finding. The cytologic differential diagnoses of LCH include dermatopathic lymphadenitis, parasitic infection, Kimura’s disease, cat-scratch disease, sinus histiocytosis with massive lymphadenopathy, and hyperplastic lymph nodes.\(^{1,13}\)

The cytomorphological features in the presence of relevant clinical and radiological findings are sufficient for reaching a correct diagnosis and ancillary studies are not mandatory in all the cases. In diagnostic difficulties, ancillary techniques such as immunostaining and electron microscopy are of help. LCs show positivity for S-100, CD1a, and langerin immunostains.\(^{1,4}\) The Birbeck granules — pentalaminar structures with prominent central cross striations seen on electron microscopy is the ultrastructural hallmark, which is present in 2-69% of the cases.\(^{14}\)

**Conclusion**

To conclude, FNA procedure, which is rapid, quick, and easy may be helpful in the early identification of LCH patients.
so that appropriate therapeutic measures are instituted. A high index of suspicion, awareness of cytological features of LCH, and the diagnostic pitfalls hold the key to an accurate diagnosis.

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Conflicts of interest
There are no conflicts of interest.

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