Case report

Rare cases of Langerhans cell histiocytosis

Garikapati Sailabala, Dukkipati Kalyani
Department of Pathology, Siddhartha Medical College, Vijayawada, Andhra Pradesh, India.

Article history
Received 10 May 2020
Revised 05 August 2020
Accepted 19 August 2020
Online 10 January 2021
Print 31 January 2021

Abstract
Langerhans cell histiocytosis (LCH) is a group of disorders characterized by proliferation of cells of mononuclear phagocytic system. In this study rare cases of Langerhans cell histiocytosis (LCH) were diagnosed. These patients had bony defects, proptosis, bilateral cervical lymphadenopathy in one case. The second case had cheek swelling, hepatosplenomegaly, skull and cheek swellings along with proptosis. The characteristic Langerhans cells were present on cytology for both cases. Hence these cases were diagnosed in both cases as Langerhans cell histiocytosis (LCH) based on clinical, radiological and cytological features.

Key words: Bony defects, Exophthalmos, Histiocytes, Langerhans cells

DOI: 10.5455/jmas.106193

Corresponding author
Dukkipati Kalyani
Associate Professor,
Department of Pathology,
Siddhartha Medical College,
Vijayawada, Andhra Pradesh, India.
Phone: +91-9573837493
Email: dukkipati29@gmail.com

Langerhans cell histiocytosis (LCH) is characterized by accumulation of dendritic cells. Any organ or system can be affected. Most frequently involved are skeleton (80%), skin (33%) and pituitary (25%)1. Other organs involved are reticuloendothelial system, lungs, lymphnodes and central nervous system, etc.

Clinically, it is self limiting to rapidly progressive disease. Treatment varies depending on disease extent and severity at onset. Hence after diagnosis is confirmed, clinical and diagnostic work up is important. We come across this group of disorders rarely.

Case report
Two pediatric cases were attended in the OPD. The cases were investigated based on the clinical features. The investigations done were radiological (Skull x ray, CT brain and Orbit) and pathological examination (FNAC). The slides were stained with hematoxylin and eosin and cytological features were assessed.

The case details were as follows. First case was of 5 year old male child presented to the OPD with fever since 8 months, proptosis since 1 year and loss of appetite. There was a history of head injury to the right supra-orbital region 18 months back. No H/o previous surgeries and significant family history. He attained milestones according to age. On examination he had pallor, proptosis, bilateral cervical lymphadenopathy and no organomegaly (Fig 1). The case was provisionally diagnosed as an orbital tumor. Eye examination was done. Fundus and optic disc vessels were normal in both eyes. Right sided axial proptosis was present. A-scan of right eye shows axial length 21.69 mm. CT scan of brain and orbit was advised.
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The second case is a 2 year old male child presented with fever since 1 year, swelling left shoulder since 3 months and swelling left cheek with proptosis since 10 days (Fig 3). He also had loss of appetite, anemia and massive hepatosplenomegaly (Fig 3). X-ray findings revealed multilocular osteolytic lesions in the right scapula and skull suggestive of multiple secondaries (Fig 3) and the case was provisionally diagnosis as neuroblastoma with secondaries.

CT scan brain and orbit revealed multiple osteolytic areas noted in ethmoidal bone, orbital plate of right frontal bone, bilateral parietal bones, right frontal bone, left temporal bones, anterior part of ethmoid right frontal bone. Small soft tissue component measuring 3.5 x 1.6 cm was noted in the scalp in right frontal region adjacent to the bone destruction. Posterior fossa structures including 4th ventricle, supratentorial structures and cisternal spaces were normal. Right superior rectus muscle was bulky with mild proptosis of right eyeball. Rest of the extra-ocular muscles was normal (Fig 2). The radiological features were suggestive of secondaries or Langerhans cell histiocytosis. Ultrasound abdomen was normal.

There was a clinical suspicion of myeloma as the patient had multiple osteolytic lesions in skull. The peripheral smear showed normal counts except anemia (Hb: 9 g/dl). WBC and platelet counts were normal. There were no abnormal cells and no evidence of myeloma in the smear. ESR was normal 5 mm/1hr. Other biochemical investigations were normal. HbsAg, HCV and HIV negative. On examination patient had bilateral cervical lymphadenopathy.

Fine needle aspiration was done from cervical lymph nodes (in first case) and scapular and cheek swellings (in second case). Smears were stained with hematoxylin and eosin. Cytology revealed highly cellular smears with large polygonal cells with abundant eosinophilic cytoplasm, oval nuclei with fine chromatin, longitudinal grooves and inconspicuous nucleoli. No mitotic figures seen. Many multinucleated giant cells and eosinophils were seen. Foci of necrosis was also seen (Fig 4).
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Discussion

LCH is a clonal and neoplastic proliferation of pathological Langerhans cells. The annual incidence is about 5 cases per 1 million population mostly seen in children and in males\(^5\) The synonyms Eosinophilic granuloma, Histiocytosis X, Langerhans cell granulomatosis are obsolete now. Apart from the commonest sites of involvement skull, rib, mandible, femur, scapula and vertebrae, it also involves orbit as orbital lesions that leads to proptosis. Nodal involvement may be sole manifestation of disease or associated with systemic disease. It can be single bone involvement (Monostotic) or Multiple bones involved with variable skin involvement (Polyostotic) – skull (calvarium), femur, ribs, pelvis and mandible. It can be also multiple organs involvement (Disseminated)\(^6\).

Based on clinical classification by European Histiocyte Society it is divided into Single system LCH (SS-LCH - One organ/system involved) which can be unifocal or multifocal and Multisystem LCH (MS-LCH - Two or more organs/systems involved) which is again sub-grouped into with or without risk organ (bone marrow, liver or lung) involvement. 50% of cases involve the pituitary stalk, often leading to Diabetes insipidus. The known clinical syndromes are associated with LCH are Hand schuller Christian syndrome (Triad of multiple osteolytic lesions, exophthalmos and Diabetes insipidus) and Letterer-Siwe disease (Wide dissemination of disease involving many organs seen in children below 2 years). The most common mutations are activating valine to glutamate substitution at residue 600 in BRAF, which is present in 55% to 60% of cases and others are TP53, RAS and tyrosine kinase MET.

Few differential diagnoses were considered in our cases and were excluded based on the following features.

1. Metastasis as no markedly pleomorphic cells or mitotic figures was seen.
2. Rosai Dorfman syndrome/ Sinus histiocytosis with massive lymphadenopathy as no emperipolesis is seen.
3. Hodgkin lymphoma as no characteristic Reed Sternberg cells were seen.
4. Non-Hodgkin lymphoma as no monomorphic population were seen.
5. Multiple myeloma is seen exclusively in patients above 40 years.

Similar cases were reported previously in the literature. In the study done by Patne et al\(^5\), lymphnode involvement in LCH presents with adjacent bone lesions were seen in one third patients. The lymphnode involvement can occur either as a part of systemic disease or as an isolated manifestations. Similarly, in our study, one case had bilateral cervical lymphadenopathy apart from skull lesions and proptosis. This was confirmed as LCH based on cytological features.

In the study done by Hang et al\(^6\), they demonstrated that FNA was diagnostic of LCH in 31 of 37 patients (84%) based on its characteristic cytomorphology. In the studies done by Kakkar et al\(^7\), Kumar et al\(^8\) and Handa et al\(^9\), 85% of cases of LCH involving lymphnodes can be diagnosed by FNA cytology. Lee et al\(^10\) in their studies concluded that when accompanied by classic clinical presentation, LCH can be easily diagnosed in a FNA smear because of the presence of characteristic Langerhan cells and eosinophils and FNA can serve as a valuable method of a case of LCH. In a study done by Kumar et al\(^8\), reported a case of LCH on fine needle aspiration cytology and proved that FNA can be used to establish the extent of disease or recurrence of LCH. They also stated that the cytologic features of LCH are highly characteristic to suggest a diagnosis in an appropriate clinical setting with classical radiological findings. The main differential diagnoses considered to be are Rosai Dorfman disease (SHML), Lymphoma, Ewing’s sarcoma (if the bones of the extremities and vertebrae are involved), Metastases and Reactive histiocytosis.

Apart from the routine hematological tests and complete urine examination, skeletal survey and
chest x-ray to rule out bone and lung involvement. Assessment of endocrine function and bone marrow biopsy should be performed wherever indicated. Pathological diagnosis is made by FNAC and tissue biopsy. This can be confirmed by Electron microscopy for presence of Birbeck granules and immunohistochemistry for the markers S100 (nuclear and cytoplasmic), CD-1a, Langerin (membrane). 99% survival will be seen in unifocal disease whereas 66% mortality in young children with multisystem involvement, unresponsive to therapy. The involvement of bone marrow, liver or lung is the high risk factor. Usually the management includes surgery, chemotherapy and radiotherapy. Prognosis is different in relation to the extension of the disease.

Conclusion

To conclude the present cases highlight the importance of FNA in the diagnosis of LCH as they were with usual clinical presentation like bony defects (punched out lesions of skull and scapula), proptosis, cervical lymphadenopathy and hepatosplenomegaly as well as typical cytomorphic features.

LCH can be definitely diagnosed on FNA based on its characteristics cytology and specific immunohistochemical markers. The cytomorphic 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.

Acknowledgments: None

Conflict of interest: None

References