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Case Report

Pathology Section

Langerhans Cell Histiocytosis without Eosinophilia and Lytic Lesions of Bone: A Rare Disease with Unusual Presentation

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ABSTRACT

Langerhans Cell Histiocytosis (LCH) is a disease of abnormal clonal proliferation of langerhans cell of the bone marrow derived monocyte-macrophage lineage. Cells with characteristic coffee bean/grooved/indented nuclei with a background of histiocytes, lymphocytes, eosinophils and other inflammatory cells are seen. Clinical presentation varies from unifocal unisystem to multifocal unisystem to multifocal multisystem. We present a rare case of multisystem LCH involving high risk organs in a two and a half year old child. presented with the chief complaints of fever and red raised maculopapular lesions on trunk, palm, forehead and scalp for one and a half yrs with hepatosplenomegaly. There were no lytic lesions of the bones. Haematological parameters showed anaemia with thrombocytopenia while Bone Marrow Aspirate showed increase in histiocytic cell with some cells showing characteristic coffee bean, cleaved irregularly contoured nuclei. However, eosinophilia was not seen. Sections from the skin lesions showed cells with similar morphology without usually accompanied eosinophilia. The cells were CD1a and S100 positive. So a FINAL DIAGNOSIS of langerhans cell histiocytosis was made. The emphasis here lies on thorough analysis of the clinical presentations, imaging studies and scrupulous histomorphological and immunohistochemical examination, so that early diagnosis and timely intervention is ensured in such cases where the characteristic features like lytic lesions of bone and eosinophilia is not found.

Keywords: Benign, Histopathology, Haematological, Multisystem, Pathogenesis, Prognosis

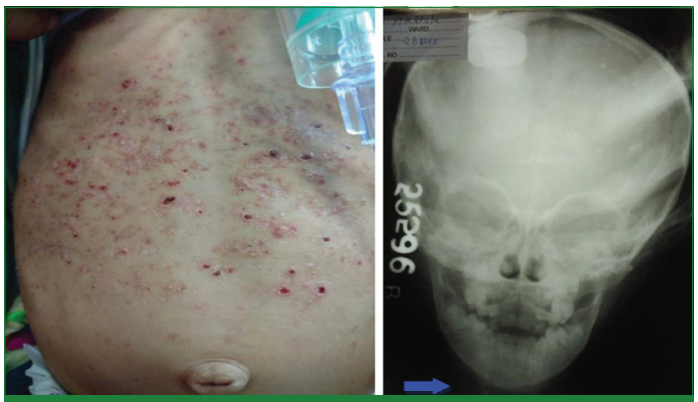
CASE REPORT

A two and a half years old female child presented with chief complaints of fever and red raised maculopapular lesions on trunk, palm, forehead and scalp for one and a half years to the Department of Pathology [Table/Fig-1]. There was no past history of any illness and no significant family history. Vaccination was adequate but anthropometric measurements lagged behind age.

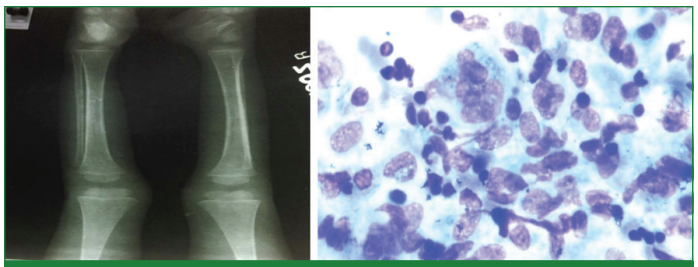
On examination, the patient was very sick, pale and thin built. The patient presented with moderate grade fever with normal vitals. The patient had hepatosplenomegaly. Skin lesions comprised of petechiae and erythematous maculopapular lesions with crusts, plaques and nodules [Table/Fig-1]. Provisional diagnosis of disseminated Kochs, haematological malignancy, haemophagocytic lymphohistiocytosis, storage disorder, infections, and Langerhans Cell Histiocytosis (LCH) were made. Biochemical investigations including liver function tests, kidney function tests and hormonal profile were normal. Plasma fibrinogen, serum ferritin and serum triglyceride were normal thus ruling out Haemophagocytic lymphohistiocytosis. Coagulation profile, widal test, RK39, malaria and viral markers were negative and ruled out infectious etiology. In peripheral smear malarial parasite/rapid malaria antigen testing were also negative. No lytic lesions were seen on X-ray of skull [Table/Fig-2]. Chest X-ray and X-ray limbs were normal [Table/Fig-3].

Haematological parameters showed anaemia with thrombocytopenia with haemoglobin=9 gm/dL amd platelet count=75,000/microlitre. Bone marrow aspiration was performed from the posterior superior iliac crest using jamshidi needle and showed hypercellular particles with normal erythroid, myeloid and megakaryocytic series with increase in histiocytic cells lying in clusters and singly. Cells had moderate to abundant pale blue vacuolated cytoplasm with centric to eccentric nuclei [Table/Fig-4].

Some cells showed characteristic coffee bean, cleaved, irregularly contoured nuclei [Table/Fig-5].

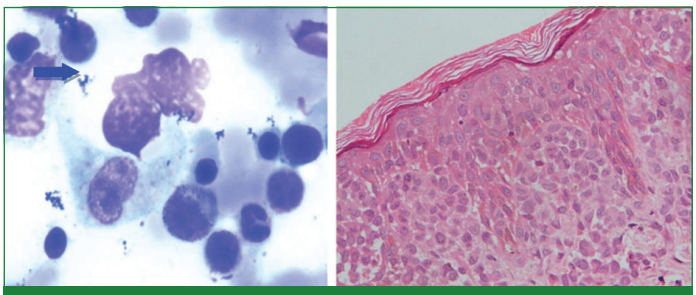


[Table/Fig-1]: Skin lesions on trunk comprising of petechiae and erythematous maculopapular lesions with crusts, plaques and nodules.
[Table/Fig-2]: No lytic lesions seen on X-ray skull. (Images from left to right)

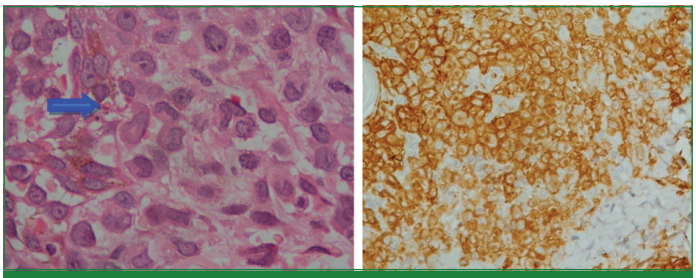


[Table/Fig-3]: No lytic lesions seen on X-ray lower limbs.
[Table/Fig-4]: Cells having moderate to abundant, pale blue vacuolated cytoplasm with centric to eccentric, round to oval nuclei with fine chromatin along with few binucleated to multinucleated cells (arrow). (40X, Leishman stain). (Images from left to right)

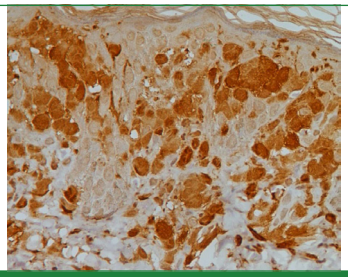
Binucleated to multinucleated cells were also seen. Acid Fast Bacilli was negative. However, eosinophilia was not seen. An impression of LCH was made. Skin biopsy was done from one of the lesions on the trunk. Sections from skin lesions showed infiltration and destruction of epidermis and dermis by sheets of similar cells having coffee bean nuclei [Table/Fig-6,7]. These cells were CD1a and S100 positive [Table/Fig-8,9].



[Table/Fig-5]: Cells with nuclei showing characteristic coffee bean, cleaved irregularly contoured nuclei. [marked by blue arrow, 100(X), Leishman stain].
[Table/Fig-6]: Sections from skin lesions showed infiltration and destruction of epidermis and dermis by sheets of histiocytic cells and cells cleaved nuclei (20X, H&E stain). (Images from left to right)



[Table/Fig-7]: Sections from skin lesions showing histiocytic cells with coffee bean cleaved nuclei (marked by arrow). (40X, H&E stain). **[Table/Fig-8]:** On immunohistochemistry, the cells show CD1a positivity(40X). (Images from left to right)



[Table/Fig-9]: On immunohistochemistry, the cells show S100 positivity (40X).

Final diagnosis of LCH was made on skin histology. The patient was planned for chemotherapy comprising of vinblastine (6 mg/m^2) and etoposide weekly for six weeks with daily prednisolone (40 mg/m^2), followed by maintenance therapy of 12 cycles with same drugs at intervals of three weeks and daily six mercaptopurine. The patient showed improvement within a month of treatment, but was later lost to follow-up.

DISCUSSION

The LCH is a group of rare disorders characterised by proliferation of langerhans cells in single or multiple organs. Langerhans cells are bone marrow derived dendritic cells normally residing in the skin and lymph nodes [1]. They act as Antigen Presenting Cells (APC) to T-lymphocytes and play key role in immunopathological reactions taking place at cutaneous and/or mucosal levels [1]. The pathogenesis of Langerhans cell histiocytosis is still unclear. Whether LCH is a reactive process due to immune dysregulation or a neoplastic disorder, is yet to be answered [2].

The incidence is approximately 2-9 per million per year in children and is even rarer in adults(1-2 cases/million). The median age is 3.8 years ranging from two months to 13.7 years [3,4]. The clinical presentation of LCH is very heterogeneous ranging from a single-system involvement, generally benign, to a multisystem life-threatening disease. Most common sites involved are bone (80-100% of cases), skin (33%), pituitary gland (25%), lung, liver, spleen (15%) each, lymph node (5-10%), Bone Marrow (BM) (2-7.5%), Central nervous system (2-4% excluding pituitary cases). Involvement of BM is very unusual [5]. BM involvement can be suspected in patients with a multisystem form of LCH and single or multilineage cytopenia. Study by Galluzo et al show that multisystem involvement usually occurs in infants [6] and more common in males presenting poor prognosis. BM involvement is usually associated with multisystem LCH and associated with poor prognosis [5,6]. This case belongs to the multisystem disease type with risk organ involvement [7,8].

On morphology, cells with characteristic coffee bean/grooved/indented nuclei with a background of histiocytes, lymphocytes, eosinophils and other inflammatory cells are seen. CD1a, CD207 (langerin) positivity is diagnostic on immunohistochemistry [8]. However, in this case Langerin postivity or confirm mutation in proto-oncogene BRAF-V600E could not be showed or demonstration of birbeck granules was not done due to unavailability of these ancillary aids [8].

Eosinophilia is an important feature of LCH. The probable pathogenesis for this is C-C Motif Ligand 11 (CCL-11)/eotaxin-1 expression in LCH cells which may attract eosinophilic infiltration [9]. Janin et al found an evidence for release of three cationic proteins and subsequent uptake in macrophages in the immunopathological study of eosinophils in eosinophilic granuloma of bone [10].

However, in this case there was absence of usually accompanied eosinophilia both in the BM as well as skin lesions. Infact, in the skin lesions, eosinophils were hardly seen. Whether it was due to defect in eosinophilc response to stimuli, is yet to be understood. An exhaustive search of the literature has revealed only a single case of LCH without eosinophils [11]. Y Kawabata et al., had suggested an intimate relationship between the preceding degranulation of dead eosinophils in necrosis and various kinds of tissue destruction both in non pulmonary and pulmonary LCH [12]. Thus, cases with absence of eosinophilia might have better prognosis which is yet to be determined [12]. However, in this case the expected prognosis was poor due to multisystem involvement by the disease. The patient initially responded to chemotherapy, but the exact prognosis could not be assessed as the patient was lost to follow-up.

This case was unusual in one more aspect, that it involved bone marrow without any bone lesion. Review of literature shows only limited number of cases without bone involvement in LCH [13-15].

CONCLUSION(S)

In this case, the patient lacked the characteristic eosinophilia and lytic lesions of bone. Thus, high index of suspicion and awareness of characterictic features of LCH (i.e. coffee bean or grooved nuclei) and CD1a positivity is essential to reach the correct and timely diagnosis.

REFERENCES

[1] Lombardi T, Hauser C, Budtz-Jörgensen E. Langerhans' cells: structure, function and role in oral pathological conditions. J Oral PatholMed. 1993;22(5):193-202.
[2] Badalian V G, Vergilio JA, Fleming M, Rollins BJ. Pathogenesis of Langerhans cell histiocytosis, Annu. Rev. Pathol. 2013;8:1-20
[3] Zinn DJ, Chakraborty R, Allen CE. Langerhans Cell Histiocytosis: Emerging Insights and Clinical Implications. Oncology (Williston Park). 2016 Feb;30(2):122-32, 139.
[4] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H.WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed. Lyon, France: International Agency for Research on Cancer,;2008, 358–360.
[5] Minkov M, Grois N, Heitger A, Ulrike Pötschger, T Westermeier, Helmut Gadner et al. Response to initial treatment of multisystem Langerhans cell histiocytosis: an important prognostic indicator, Med. Pediatr. Oncol. 2002;39(6):581–585.
[6] Galluzzo ML, Braier J, Rosenzweig SD, Garcia de Davila MT, Rosso D, Bone marrow findings at diagnosis in patients with multisystem langerhans cell histiocytosis, Pediatr. Dev. Pathol. 2010;13(2): 101–106.
[7] Abla O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: current concepts and treatments. Cancer Treat Rev. 2010;36:354–59
[8] Jezierska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M. Langerhans cell histiocytosis in children - a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. Postepy Dermatol Alergol. 2018;35(1):6-17.
[9] Cho YA1, Yoon HJ, Hong SD, Lee JI, Hong SP. Hypothetical pathogenesis of eosinophilic infiltration in Langerhans cell histiocytosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Dec;116(6):734-42.

[10] Janin A, Torpier G, Capron M, Courtin P and Gosselin B:Immunopathological study of eosinophils in eosinophilic granuloma of bone: evidence for release of three cationic proteins and subsequent uptake in macrophages. Virchows Arch A Pathol Anat Histopathol. 1992;421:255-61.
[11] Papasozomenos SC et al, Hypothalamic Langerhans cell histiocytosis with no eosinophils, Clin Neuropathol, 1999 Sep- Oct; 18(5): 260-4.
[12] Kawabata Y, Tomichi N, Tanino MA, Ogura T, Kawamoto M, Fukushima Yet al. The role of eosinophils in necrosis mainly in single-system Langerhans cell histiocytosis. J Histol Histopathol. 2021; 8:1.
[13] Manfredi M, Corradi D, Vescovi P et al, Langerhans cell histiocytosis: A Clinical case without bone involvement, Journal periodontol 2005, 76(1): 143-147.
[14] Cleveland DB, Goldberg KM, Greenspan JS, Seitz TE, Miller AS. Langerhans' cell histiocytosis, Report of three cases with unusual oral soft tissue involvement, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:541–548
[15] Milian MA, Bagan JV, Jimenez Y, Perez A, Scully C, Antoniades D, Langerhans cell histiocytosis restricted to oral mucosa, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:76-79.

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