

Unusual presentation and special sites involvement in langerhans cell histiocytosis

Abstract

Introduction: Langerhans Cell Histiocytosis (LCH) is a rare disorder due to accumulation of cells of the mononuclear phagocytic system. It can affect single or multiple organs causing destructive lesions that may lead to aggressive disabilities and adversely affect the quality of life.

Cases: We present two pediatric patients who presented with different head and neck manifestations and were diagnosed as LCH affecting special sites. These two patients have been diagnosed early and successfully treated with chemotherapy without the need of surgical or radiotherapy interventions.

Conclusion: We recommended thorough investigations for children who present with head and neck manifestations in particular; oral, facial or ear lesions if there is a high level of clinical suspicion towards LCH, as early diagnosis and prompt management will certainly improve quality of life and prevent adverse consequences.

Keywords: LCH, hand-schüller-christian disease, letterer-siwe disease, eosinophilic granuloma

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Background

Langerhans Cell Histiocytosis (LCH) occurs due to clonal proliferation of functionally immature, rounded LCH cells together with several inflammatory cells like eosinophils, macrophages, and multinucleated giant cells.¹

The LCH cell has a gene expression profile that resembles a myeloid dendritic cell. Some studies have shown that the *BRAF V600E* mutation can be identified in mononuclear cells in peripheral blood mainly in patients with disseminated disease. These findings have led the clinicians to propose the classification of LCH as a myeloid neoplasm.²

LCH can affect a single organ (single-system) which presents as unifocal or multifocal lesions or can involve multiple (two or more) organs (multisystem). The multisystem affection is further differentiated into high-risk group and low-risk group depending on the organ affected; i.e. liver, spleen and hematopoietic system are considered among the high-risk group and called risk organs. In certain situations, LCH can involve craniofacial bones, vertebrae with significant intraspinal component, ear, eye and oral cavity, these sites are regarded as disease in special sites.³

The clinical spectrum of LCH includes: 1- the classic Hand-Schüller-Christian disease that presents with a triad of diabetes insipidus, proptosis, and multifocal bone lesions, 2- Letterer-Siwe disease; an acute, aggressive disseminated disease, and 3- eosinophilic granuloma which is a solitary or few chronic lesions of bone or other organs.⁴

Prognosis of LCH is closely related to the clinical presentation; patients with unifocal disease generally have an excellent prognosis, however, for disease forms that affect high-risk organs, the mortality rate is around 35% specially in those who do not respond to initial therapy.⁵

Case presentation

Case I

This is an 8-month-old boy previously well, with no known allergies, vaccination is up-to-date and development is normal for his age. Presented with a painful left side facial swelling of 3months duration, the swelling involved the maxillary bone and could be visualized during intraoral examination in the form of ulcerated lesion. There was cervical lymphadenopathy at the same site of the lesion. Other systems review was unremarkable and the child was well, active, chest was clear and there was no organomegaly.

Initial lab works were all within acceptable range including blood counts, electrolytes, renal and liver function tests. There was no history suggestive of diabetes insipidus (DI) and no other history of concern.

Histopathologic examination of involved lesions revealed a diffuse infiltration of histiocytic cells interspaced with lymphocytes and eosinophils. Immunohistochemical analysis showed positivity for CD1a, CD31, and S-100 antigens. Initial work up included bone scan and skeletal survey that showed active bone lesion in inferior maxilla, with no other bones involved. CT scan confirmed the presence of lytic bone lesions at the maxilla, while CT scan of the neck, chest and abdomen was unremarkable (Figure 1). Bone marrow aspirate and biopsy were normal.

The child was diagnosed as LCH, and according to the LCH III trial of the Histiocyte Society, he was considered as having a single system involvement of special site. Having known that Surgical intervention was not feasible and radiotherapy is not recommended for this age group, it was decided to start him on chemotherapy protocol; vinblastine weekly for the first 6 weeks then every 3weeks for 12months with prednisolone 1 month at course I then for 5 days every 3 weeks thereafter.



Figure 1 An axial CT showing a soft tissue mass on the left side with mandibular and maxillary bone destruction.

After initial treatment, bone scintigraphy and CT scan showed marked reduction of bone lesions and complete remission after 5 months of treatment. No recurrence has been recorded after 5-year follow-up.

Case II

An 8-year-old boy previously well, presented with persistent otorrhea of left ear and swelling involving the gums in the superior right side of oral cavity with mobility of teeth, 2 months before diagnosis. Other systems review was unremarkable. Initial lab works were all within acceptable range.

CT scan showed bone lesion localized in left petrous bone and mastoid, involving left internal auditory canal. Bone scintigraphy showed active bone lesions in left temporal bone and right superior maxilla. Abdominal and chest CT scan and bone marrow aspirate, showed no evidence of other involvements.

Histopathologic examination of the lesion revealed a diffuse infiltration of histiocytic cells and isolated plasma cells and eosinophils; immunohistochemical analysis showed positivity for CD1a, CD31, and S-100. Diagnosis of LCH was made.

Treatment was made with chemotherapy according to the protocol LCH-III of the Histiocyte Society for patients with multifocal bone disease and special site involvements, with same regimen of chemotherapy (as previous case) including prednisolone and vinblastine.

After initial treatment, bone scintigraphy and CT scan showed complete remission after 3 months of treatment. No recurrence has been found after 5-year follow up.

Discussion

The oral cavity may be the first or the only site of presentation in LCH. It can present with ulceration of the oral mucosa, bleeding, periodontal defects and dental hypermobility, like these two patients. Maxilla, mandible and other skull bones, are the most frequently affected bone sites.

Tissue examination is essential to make a definitive diagnosis of LCH. Morphologic examination can show the characteristic features

of LCH cells, while immunophenotypic examination and positive staining of lesion tissue with CD1a and/or Langerin (CD207) is required for definitive diagnosis.^{6,7}

Both of our patients have been successfully diagnosed morphologically and immunophenotypically through an incisional biopsy of the lesioned tissues.

The treatment of LCH depends mainly on the site and extent of the disease, and whether it is a single system or multisystem affection.⁸ Multisystem affection with or without risk organ involvement will eventually need chemotherapy of 12month duration. Vinblastine and prednisone have shown to be effective in this setting with less toxicity, nevertheless, multisystem disease with risk organ involvement still show a less favorable outcome especially with progressive disease.^{9,10} Single system LCH has different approach ranging from only observation to systemic chemotherapy. Indications for systemic therapy in single system LCH includes: CNS-risk lesions, multifocal bone lesions and special site lesions.¹¹

Apart from these lesions described above, solitary lesions can be approached differently. For instant, isolated skin involvement can be observed only, unless there is symptomatic disease in the form of bleeding, ulceration and extensive pain. When therapy is indicated, topical steroids, oral methotrexate and oral hydroxyurea can be utilized.¹²

On the other hand, curettage with or without intra-lesional methylprednisolone are regarded as the standard approach for solitary bony lesions. In addition, low dose radiation therapy can be used effectively for lesions that may threaten organ function.¹³

Special-sites LCH -even if single- harbors a big challenge to physicians, either in diagnostic or therapeutic approach. Special sites include: craniofacial bone involvement; such as lesions in the orbit, paranasal sinuses or in temporal, mastoid, sphenoidal, zygomatic, or ethmoidal bones, eye involvement; lesions in the orbit, zygomatic or sphenoidal bone, ear involvement; and it presents with otitis externa, otitis media, otorrhea or lesions in the temporal bone, mastoid, or petrous bone, oral involvement; lesions in the mucosa, gums, palate and mandible.¹⁴

Our first case presented with facial swelling due to affection of the maxillary bone with direct involvement of the oral cavity. Both the swelling and the intraoral ulcerative lesion raised our suspicious toward a malignant behavior following which a biopsy was carried out to confirm the diagnosis. In the second case, the child presented with otorrhea that did not respond to antibiotic treatment and this was associated with oral involvement, which led the clinician to initiate the investigations to rule out LCH. Few reports recommended highest degree of awareness to the oral manifestations of LCH as it will help the physicians greatly to reduce the morbidity and mortality associated with this condition.^{15,16}

Systemic treatment is recommended for this subgroup of patients aiming to reduce the considerable risk of disabilities that may adversely affect their quality of life. Results from DAL-HX 83 and DAL-HX 90 trials indicates that year of systemic treatment with vinblastine and prednisone reduces the risk of relapse and disabilities compared to historical controls.¹⁴ This therapy is essential for disease control in patients with CNS risk lesions (as these two cases), due to increased risk for DI and neurodegenerative CNS-LCH. Treatment with vinblastine/prednisone showed a reduction in DI incidence (12%

vs 40% with single agent therapy or surgery).^{5,17} Both patients were successfully treated according to these recommendations and none of them developed DI or CNS alterations. Follow up is recommended to monitor response, sequelae and late effects of treatment. Image evaluation of initial involved sites and long term comprehensive clinical evaluations are also indicated.¹⁷

Conclusion

Langerhans Cell Histiocytosis can present with unusual manifestations, so we recommended thorough investigations for children who present with eye, ear, oral or cranio-facial bone lesions if there is a high level of clinical suspicion towards LCH, as early diagnosis and prompt management will certainly improve quality of life and prevent adverse consequences.

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Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Competing interests

The author(s) declared no potential conflicts of interest.

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