

Fundamental Neurosurgery

Histiocytosis X: Characteristics, behavior, and treatments as illustrated in a case series

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Abstract

Background: Langerhans cell histiocytosis (LCH) is a proliferative disorder predominantly found in children. It often presents with pain in calvarium or spine and may cause neuroendocrine symptoms. The gold standard for diagnosing LCH is the detection of Birbeck Granules by EM. Here, we describe two unique presentations of LCH and we review current treatment guidelines.

Case Description: The first patient was a 23-year-old man who presented with progressive swelling and redness of the left eye. MRI revealed a left retrobulbar lesion extending into the middle cranial fossa with no signal abnormality in the brain parenchyma. The lesion was resected and pathological analysis revealed LCH. Bone scans were negative and the patient was discharged soon after. He later underwent fractionated radiotherapy (cumulative dose 26 Gy). Follow-up MRIs show no disease at 24 months post-op. The second patient was a 56-year-old man with left frontal skull pain for 5 months. Imaging showed a solitary osteolytic lesion extending into both dura and scalp with no signal abnormality of the parenchyma. Excisional biopsy revealed LCH. Surgery was well tolerated and follow-up imaging shows no recurrence at 24 months post-op.

Conclusion: We demonstrate that LCH, though uncommon, must remain on the differential when osteolytic lesions present in the adult. Although LCH often has the clinical and radiographical presentation of an abscess, pathology analysis can successfully diagnose LCH based on markers and morphological characteristics. LCH has an excellent prognosis when treated aggressively with surgical resection and radiotherapy as both of our patients were and are now disease free at 2 year follow-up.

Key Words: Birbeck granules, histiocytosis X, langerhans cell histiocytosis, magnetic resonance imaging, neurosurgery, radiotherapy

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease that

is found mostly in children, with an estimated incidence between 0.2 and 2.0 cases per 100,000 children under 15 years of age and a peak incidence of ages 2–4.^[4] It is

an uncommon proliferative disorder of the Langerhans cells and antigen-presenting cell of the dendritic cell line. The usual clinical presentation reveals pathological masses or granulomatosis with destruction of surrounding tissues.^[12] Lichtenstein (1953) grouped the Eosinophilic Granuloma, the Hand-Schüller-Christian disease, and the Letterer-Siwe disease, three different syndromes with the same histology, under the term “Histiocytosis X”.^[16] This term has been replaced nowadays by LCH.^[19]

This disease has preponderance in males, sometimes as high as 60–70%, and is more common in whites of northern European descent.^[15,19] The most common presentation is unifocal (about 65%) and the bone is the most frequently affected tissue making up 90% of such cases. The most common site involved is the skull and accounts for more than 50% of cases. The location of lesions is similar in unifocal and in multifocal disease (about 35% of presentations), with 60% affecting only bone, 25% affecting bone and soft tissue, and 15% affecting only soft tissue.^[3,4,15] The semiology of the disease depends on the site of the involvement and can vary from an incidentally found lesion on an X-ray, to severe and possibly lethal disease with multiorgan-dysfunction. The most common presentation is a painful immobile mass in the calvarium. In the spine it can present with local pain and stiffness only, but also with progressive deformity such as torticollis or kyphoscoliosis. In cases involving the central nervous system (CNS), LCH generally presents with diabetes insipidus as a consequence of involvement of the pituitary infundibulum.^[17] When soft tissues and the reticuloendothelial system are involved, it can present with fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, or skin lesions.^[19]

The key diagnostic feature in any biopsy for histological study is the pathognomonic evidence of Langerhans cells, which show positive immunostaining for CD1a and S-100 markers. Still, the diagnostic gold standard is the identification of characteristic ultrastructural features designated as *Birbeck granules*, which are 34 nm wide tubular or tennis-racket-shaped intracytoplasmic pentalaminar structures with a zipper-like central core.^[4,12,17,19] The full function of the Birbeck granules is currently unknown. On imaging studies, LCH lesions of the skull are characteristically isointense to gray matter on T1-weighted images with enhancement on CT and MRI after i/v contrast administration, and show destructive infiltration of the osseous structures affected.^[4,8,19] Here, we report two typical but distinct cases: one is of a 23-year-old man with progressive swelling of the eye and proptosis following an MVA. The other is a 56-year-old man with a 5-month history of pain in the left frontal skull.

CLINICAL PRESENTATION

The first patient was a 23-year-old man with no previous

medical history, presenting with “swelling of the left eye”. He had been involved in a motor vehicle accident 3 months prior, in which he suffered a left forehead laceration. Thereafter, he noticed progressive swelling of the left eye, peri-orbital redness, and some sensation of sinus fullness. He did not show any fever, chills, sweats, or weight loss. He was seen by an internist about 1 month after the accident and was prescribed antibiotic ointment. The patient used the ointment and felt that this was helping, so he continued using it for about a month. With time the eye became progressively more swollen, so he was referred to an ophthalmologist, who prescribed oral antibiotics and requested a head and orbit CT. The CT revealed that the exophthalmos was caused by a retrobulbar lesion. This mass clearly demonstrated rim enhancement after i/v contrast administration and also showed a low-density center. The lesion was located retroorbitally, eroded posteriorly the roof of the orbit and extended into the middle cranial fossa. He was thus referred to neurosurgery. On examination he had significant left periorbital swelling, erythema, chemosis, and mild proptosis as well as a discrete limitation in upward gaze on the left eye, but no cranial nerve palsy.

An MRI study was requested which showed a 2.8 cm × 2.7 cm × 2.1 cm lesion centered within the left retroorbital space, extending into the temporal lobe in the middle cranial fossa and laterally into the infratemporal fossa. There was obvious osseous destruction involving parts of the sphenoid wing. The intraorbital extension caused a mass effect upon the rectus muscles, optic nerve, and globe. There was no intracanal extension. The lesion was T1-isointense, and following the administration of intravenous gadolinium contrast, there was heterogeneous enhancement. There was altered signal intensity in the soft tissues adjacent laterally, in the infratemporal fossa, and the preseptal soft tissues. Of concern was adjacent meningeal enhancement, but there was no abnormal signal identified within the brain parenchyma itself [Figure 1].

The lesion was initially thought to be a possibly chronic aggressive infection, hence the patient was started on antibiotic therapy. The next day, the patient was taken to surgery for exploration, decompression, and planned evacuation. The fresh frozen analysis of the lesion confirmed a polymorphonuclear infiltrate consistent with chronic inflammation and the initial thinking was that this represented an abscess. Tissue was sent off for culture analysis. The lesion was nearly completely removed with no microscopic residual. The patient tolerated the procedure well and the case was concluded without complications. Since the area was considered infected, no attempt at a definite orbital roof reconstruction was made. However, final pathology analysis revealed that the lesion represented a LCH. This prompted us to study the patient with an X-ray survey as well as bone scanning, but both studies failed to demonstrate any other lesions.

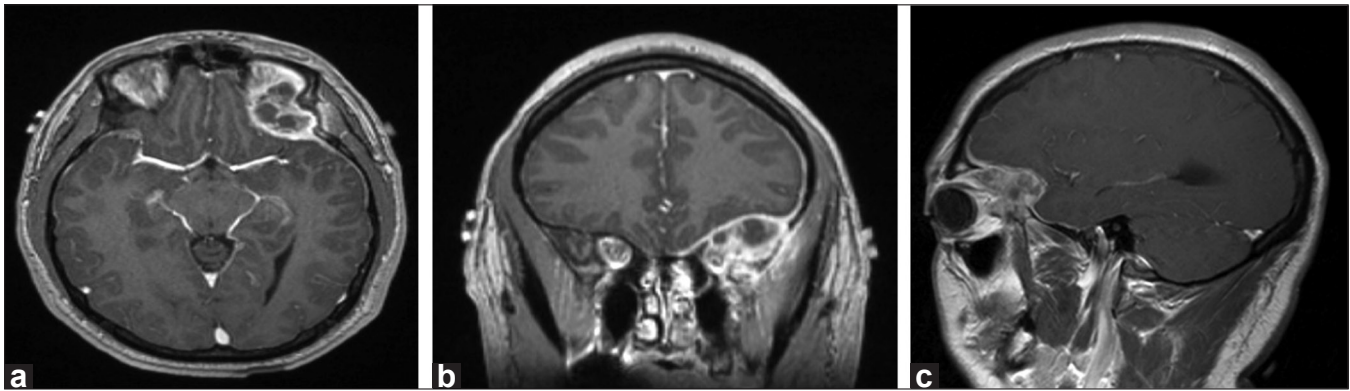


Figure 1: T1-weighted MRI scans with contrasts showing (a) axial, (b) coronal, and (c) sagittal images of the lesion

The patient had a short hospital stay and was discharged to home on postoperative day #4. After the final diagnosis was established, the patient was brought back and discussed at our interdisciplinary tumor board, which recommended referring him to radiation oncology. He subsequently underwent therapeutic radiotherapy of 26 Gy fractionated into 13 intervals. The therapy was well tolerated. The patient's only complaints were occasional mild headaches, lasting as long as 1 year post-op before resolving completely. The patient also had an initial partial left-sided ptosis but was otherwise in excellent health and without symptoms. Sequential follow-up MRIs showed no recurrent disease up to 24 months post-op. Currently, the patient is not in need of any medications or therapy and will continue to undergo annual surveillance MRIs.

The second patient was a 56-year-old man with a medical history of HIV, hepatitis C, and cirrhosis. He presented with persistent left frontal skull pain for about 5 months. He denied vision problems, headache, nausea or vomiting, seizures, urinary incontinence, or imbalance. Physical and neurological examination was unremarkable upon presentation. The HIV viral load was undetectable, and the CD4 count in the 300s, factually ruling out an opportunistic infection. Family history was notable for two siblings who died from cancer (sister—smoke-related lung CA, brother—leukemia). A gadolinium-enhanced MRI study revealed a small frontal lesion that was bone eroding and contrast enhancing. This transosseous calvarial mass was located in the left frontal bone and extended both into dura and scalp. The lesion was isointense to gray matter and hyperintense on T2-weighted images. There was no signal abnormality in the brain parenchyma. The mass was thought to likely be a malignancy due to the low viral count and the patient's overall healthy disposition. A head CT revealed an osteolytic lesion with a faint sclerotic rim in the left frontal skull. A *Tech99* bone scan was obtained and showed focal avid radionuclide uptake, but no other lesions. The patient was then taken to surgery and underwent craniotomy for excisional biopsy of this solitary

mass followed by a cranioplasty for cosmetic closure. The surgery was well tolerated and a postoperative CT confirmed a complete resection and no complications, so the patient was discharged to home the following day. The tumor has not recurred on follow-up imaging since (24 months).

PATHOLOGY

For the first case, the intraoperative cultures were negative and the pathological study demonstrated a lesion with histiocytic and eosinophilic infiltrate, which stained positive for CD1a (+) and S100 (+) [Figure 2]. The morphologic “coffee-bean groove” characteristic of Langerhans cells was clearly visible. Electron microscopy studies were not performed. However, the presence of Langerhans cells, the histopathological staining pattern, and the atypical characteristics of the histiocytes and eosinophils led to the diagnosis of LCH.

In our second case, cultures were also sent for infection and confirmed as negative. The pathology study showed eosinophil aggregates on a background of fibroblastic proliferation. Staining was positive with CD1a (+) and S100 (+). The absence of emperipolesis (an intact cell within the cytoplasm of another cell) and the presence of eosinophils confirmed the diagnosis of LCH. EM studies revealed atypical inclusion bodies consistent with pathognomonic Birbeck granules [Figure 3].

DISCUSSION

The clinical presentation of our first case is comparable to a patient previously described in the literature, who also presented with an orbital LCH causing proptosis and periorbital edema. In this case, the lesion caused inferior globe displacement and erythema.^[4,11] Such ill demarcated and bone eroding soft tissue tumors in the young are rather rare and deserve diligent workup followed by swift intervention, since the differential diagnoses of the orbital LCH include mesenchymal

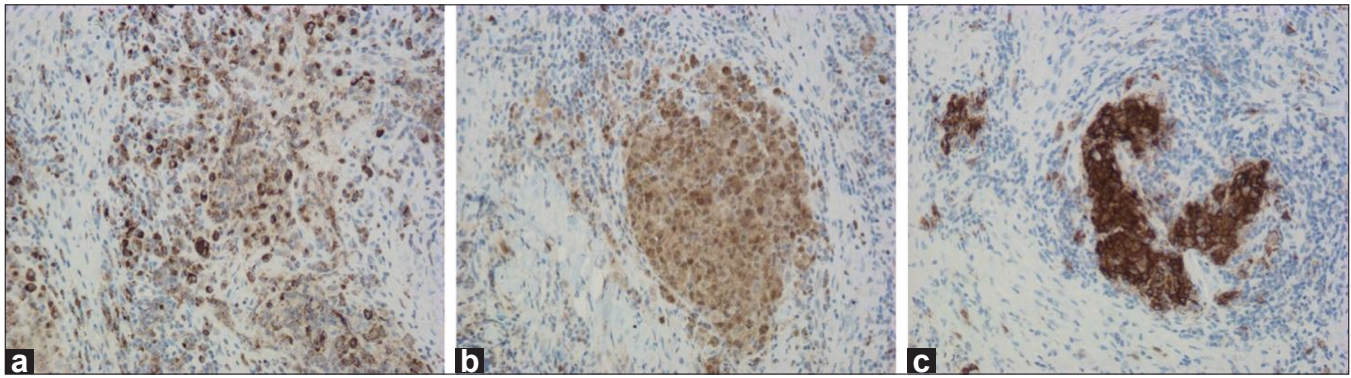


Figure 2: Immunohistochemical stains of the biopsied tissue. (a) CD68, (b) S100+, and (c) CD1a+ stains (original magnification, $\times 100$)

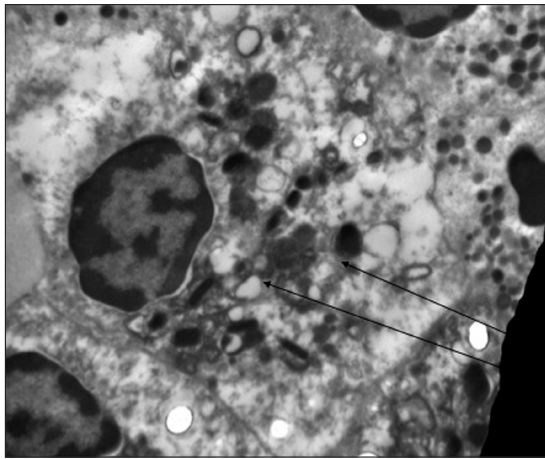


Figure 3: Electron micrograph of the biopsied tissue. Electron micrograph was of compromised quality as the thin sections were recovered from fixed paraffin embedded tissue. Membrane bound electron lucent vesicles suggestive of a component of Birbeck granules are seen within the histiocytes. The typical cross-striated rod domain is not as evident

malignancies such as rhabdomyosarcoma, Ewing sarcoma, osteogenic sarcoma as well as metastatic neuroblastoma. All these pathologies can be located in the orbit and can present as a rapidly progressing facial and orbital swelling.^[14] The pathology in our first case was at first considered to be a chronic abscess, also rooted in the notion that the patient had been involved in a MVA, which may have left him with a retained foreign body. The initial intraoperative analysis of the biopsy specimen focused on the observed polymorphonuclear cell infiltrate and seemingly corroborated the possibility of an underlying abscess, until the final immunopathology revealed the true underlying pathology.

Our second case presented in a rather typical manner with unifocal sharp pain localized to the skull lesion. However, the age of the patient was atypical, since the incidence of new-onset LCH in adults is extremely low. Again, the initially entertained differential diagnosis of this lesion was a malignant tumor or focal infection in

the setting of predisposing disease, but the latter was rather unlikely in the setting of his low HIV viral load. As for malignancies, the tumor could have arisen from the bone, bone marrow, or the dura. A biopsy was warranted and yielded the final result of LCH.

What needs to be known about LCH?—LCH is a disease caused by the monoclonal proliferation of Langerhans cells. The trigger factor that leads to this proliferation is unknown yet. It has been proposed that different environments can cause an immune dysregulation, with different cytokines involved such as GM-CSF and TNF- α , which will cause a monoclonal proliferation of the Langerhans cells.^[20] LCH has a higher incidence in patients with a persistent or transient systemic immunodeficiency, such as viral infections, leukemia, lymphoma, or genetic defect; thus it is possible that this immunodeficiency leads to an immune dysregulation.^[11]

There are three key subtypes of LCH: unifocal, multifocal, and systemic LCH. Unifocal LCH (eosinophilic granuloma) is most common and the bone is the most often affected tissue—usually the skull. Unifocal LCH is found most commonly in older children and adults and presents as a very aggressive tumor, with large areas of tissue destruction and a time course showing quick expansion, but still carries an excellent prognosis due to its confined and self-limiting growth.^[4] Multifocal LCH (Hand-Schüller-Christian disease) involves multiple sites and is most common in young children.^[19] Lastly, diffuse (systemic) LCH (Abt-Letterer-Siwe disease) is typically found in newborn babies and carries a very poor prognosis. On the other hand, one can find systemic LCH in older patients, which also carries a significantly worse outcome and higher rates of mortality, when compared to the limited disease forms. When systemic disease causes organ dysfunction, mortality can be as high as 50%.^[2]

CNS involvement occurs in 20–25% of patients with LCH and can present as three different types of syndromes. The most common syndrome is diabetes insipidus with neuroendocrine deficits, caused by the

involvement of the hypothalamic–pituitary axis. It can also present as an intracranial mass usually involving the choroids plexus or the meninges. And lastly, it can present as a neurodegenerative syndrome. The two major risk factors for developing CNS involvement in LCH are lesions from the facial bones, or lesions from the anterior or medial cranial fossa that expand intracranially.^[9,11] This is paralleled in our first case, which presented as an intraorbital isointense lesion with profound enhancement, reflecting the typical imaging for an orbital LCH. Characteristic MR-imaging showed a lesion isointense to gray matter on the T1, T2, and proton density sequences. The lesion enhanced brightly on CT and MRI after contrast administration and was avid on nuclear medicine studies.^[3,4,14,18]

There are different ways to treat the unifocal LCH and there have been four approaches described in the literature. First option, not to offer any treatment at all, because in some eosinophilic granulomas self-limited growth has been reported, as was spontaneous regression.^[10,11] We consider this management option as rather risky, because we feel that a biopsy is warranted to rule out other differential diagnosis of concern. Second option is to attempt at least a partial resection or to perform a complete excisional biopsy of the lesion. In both of our patients, such a resection was performed and both are doing well with no recurrence at 24 months. Third option is a biopsy, followed by low-dose radiation to the lesion usually with 6–10 Gy with a local control rate of approximately 80%.^[7] Radiotherapy was recommended to complete the treatment in our first patient, since he had extensive eroding skull base disease with nondistinct margins and likely postoperative residual disease with microscopic involvement of adjacent soft tissues. An established radiation protocol of 26 Gy fractionated over 13 sessions was instituted and well tolerated. Fourth option, unifocal eosinophilic granuloma can also be treated with intralesional corticosteroids, usually methylprednisolone 30–125 mg to limit immunoresponse, followed by sequential imaging.^[2,3,11] But for our cases, involving osseous structures this was not a valid option.

Finally, systemic chemotherapy may be indicated when LCH progresses systemically or is recurrent. A popular agent is 2-chlorodeoxyadenosine (2-CdA), an adenosine-analog that is resistant to deamination, which can block cell proliferation in histiocytes and eosinophils. A recent study demonstrated the effectiveness of 2-CdA in children with recurrent LCH.^[13] Recurrences are more common when the disease is multifocal than in patients presenting with disease that is confined to a solitary focal point. However, there have been reports of recurrent unifocal tumors.^[1] The treatment plan for a recurrent unifocal tumor should include consideration of systemic

treatment instead of or in addition to radiation therapy or surgical resection, since such patients must be treated more aggressively. While tumor recurrences typically occur within 2 years of the primary diagnosis, reports have been made of LCH tumors recurring up to 16 years later, which advises us to follow these patients long-term with serial imaging.^[6]

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