Solitary Cranial Langerhans Cell Histiocytosis: Two case reports

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a proliferation of Langerhans cells intermixed with inflammatory cells, in particular eosinophils, that may manifest as a unisystem (unifocal or multifocal) or multisystem disease. We describe the clinical and histologic spectrum of LCH of the orbit and skull in our two cases. Both cases had unifocal erosive skull lesions with a history of trauma. Typical histologic features included numerous histiocytes with varying degrees of giant cell formation and scattered eosinophilic granulocytes. The presence of Langerhans cells was confirmed by CD1a and S100 immunohistochemistry. LCH has an excellent prognosis when treated with surgical resection, steroids and radiotherapy or chemotherapy. One of our patients is disease free at 7 year follow-up and one patient had regression of lesion on follow-up.

Key words: *Langerhans cell histiocytosis, Skull, Immunostaining, Histology*

Langerhans cell histiocytosis (LCH) is an uncommon proliferative disorder of the Langerhans cells and antigen-presenting cells of the dendritic cell line. The usual clinical presentation reveals pathological masses or granulomatosis with destruction of surrounding tissues[9]. The lesions are dominated by Langerhans cells, which are bone marrow derived cells of the dendritic cell line with antigen presenting and processing properties. They are involved in a variety of immune responses and are found in the normal brain parenchyma and pituitary gland[10,11]. The most common presentation of LCH is that of a solitary skeletal lesion, usually of the calvarium, and it predominantly affects children, adolescents, or young adults. Here we present two cases of solitary cranial LCH, both of which presented with symptoms after trauma. The lesions were examined pathologically and compared with the abnormal findings on MRI.

Case 1

A 4-year-old boy came with a complaint of left temporal region pain and fever for one month. He had history of a fall from a 50-cm height with bruising on the left temple without loss of consciousness approximately one month prior to his complaint. On examination, he had left eye swelling without redness and slight exophthalmos with fever. A CT scan showed bony erosion accompanied by soft tissue involvement in and around the left orbit (Fig. 1A). There was obvious osseous destruction involving parts of the sphenoid wing (Fig. 1B). An MRI study showed a lesion centered in the left retro-orbital space, extending into the middle cranial fossa. The intraorbital extension caused a mass effect upon the external rectus muscles, optic nerve, and globe. There was no intraconal extension. On T1-weighted image, it was slightly hyperintense (Fig. 1C), hypointense on T2-weighted image (Fig. 1D) and enhanced on gadolinium administration (Fig. 1E). A skeletal survey and whole body bone scan confirmed that the lesion was limited to the left orbit, with no other bony involvement. Gallium 67 scan of the head showed increased uptake corresponding to the left orbital bone lesion as seen on the CT (Fig. 1F). The patient underwent surgery for biopsy of the lesion (Fig. 1G). Histopathologically, clefted and lobulated large multineucleated histiocyte-like or Langerhans cells along with infiltration of lymphocytes, neutrophils and eosinophils were observed (Fig. 2A & 2B). Furthermore, the histiocyte-like cells were immunohistochemically positive for CD68 (Fig. 2C), CD1a (Fig. 2D) and S100 (Fig. 2F). Immunostaining was also positive for vemintin (Fig. 2E). MIB-1 index

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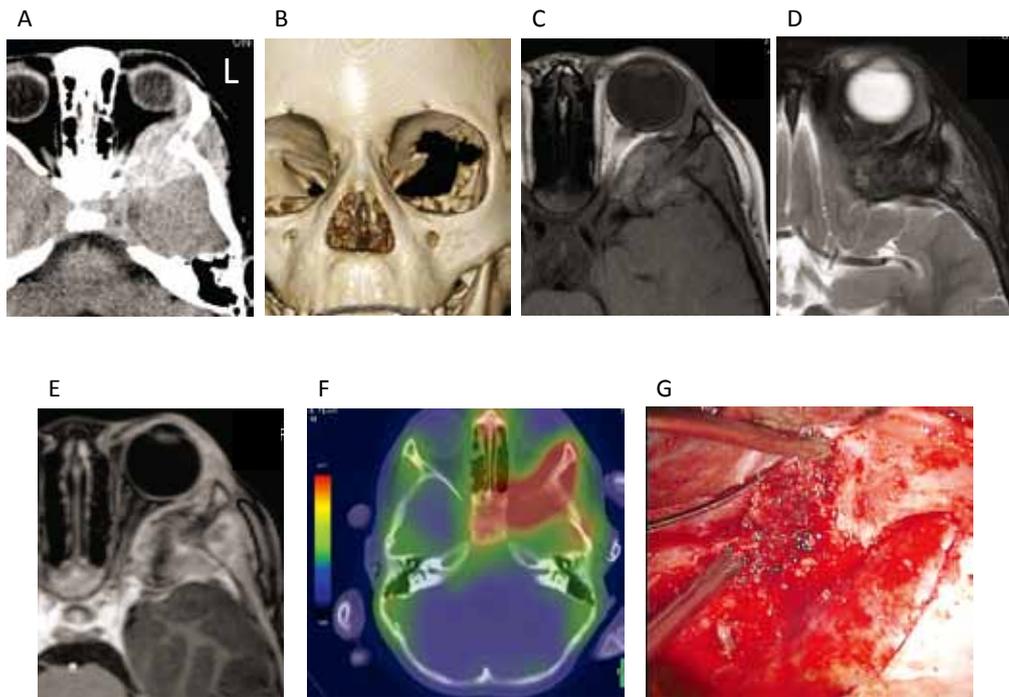
Fig. 1. Neuroimaging of Case 1
A. Axial non-contrast computed tomography (CT) scan showing a hyperdense lesion in left orbit and sphenoid region.
B. A three-dimensional CT scan showing osteolytic lesion on left orbital and sphenoidal bone.
C. Axial T1-weighted magnetic resonance image (MRI) demonstrating a slightly hyperintense mass around left lateral orbital wall and sphenoid bone.
D. Axial T2-weighted MRI reveals an hypointense mass in the left lateral orbit and sphenoid bone.
E. Axial T1-weighted contrast enhanced MRI showing heterogeneously enhancing lesion.
F. Gallium 67 scan of the head showed vague, increased uptake on the left orbital bone.
G. Intraoperative photograph showing site of biopsy of the lesion on supero-lateral wall of left orbit.
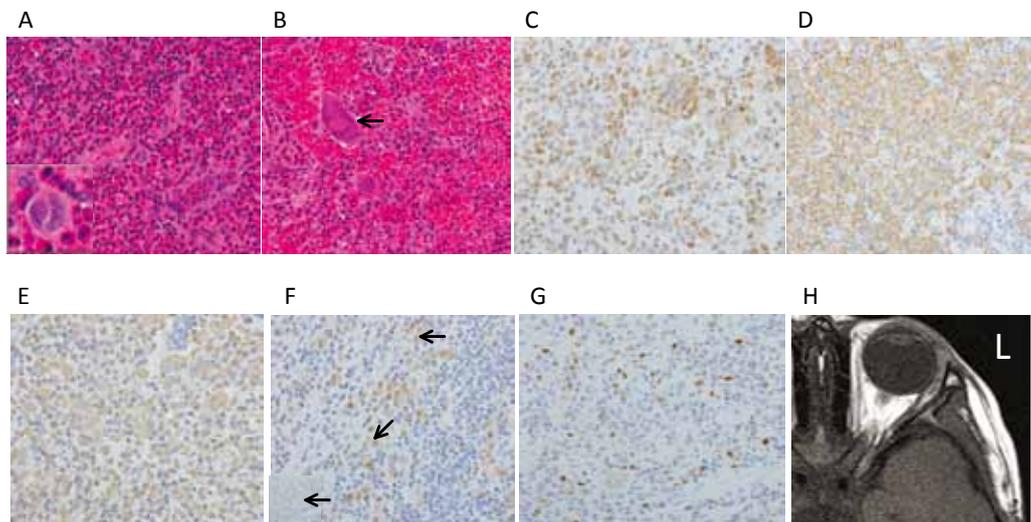
Fig. 2. Pathology of Case 1
A. Hematoxylin and Eosin (H & E) staining (original: × 400) showing large number of eosinophils while lower left panel shows clefted and lobulated Langerhans cells.
B. Hematoxylin and Eosin (H & E) staining (original: × 400) showing giant multinucleated forms of Langerhans cells (arrow).
C. Immunohistochemistry showing positivity for macrophage marker CD 68 (original: × 400).
D. Immunohistochemistry showing positivity for histiocytic marker CD 1a (original: × 400).
E. mmunohistochemistry showing positivity for vimentin (original: × 400).
F. Positive immunohistochemical staining for antibody to S-100 protein is seen as dark brown areas in both the nucleus and cytoplasm of the Langerhans cells. Note 'pac-man' appearance (arrows) of the nucleus as a result of a prominent nuclear groove (original: × 400).
G. MIB-1 staining of specimen (original: × 400).
H. Axial T1-weighted magnetic resonance image (MRI) demonstrating regression of lesion.

was 19%. Bone marrow biopsy showed no invasion of Langerhans cell. Postoperatively prednisolone was administered at 40 mg/m^2 per day for one month which improved his symptoms, thus the dose was reduced to 1.7 mg per kg body weight per oral. The patient was followed up for 5 months after biopsy; MRI showed marked regression of the lesion; after which, he continued with a low dose oral steroid (Fig. 2H).

Case 2

An 8-year-old boy presented with a complaint of a gradually increasing round bump on his right parietal area. He had been hit in the same area 2 months earlier while practicing Judo and was operated to remove a subcutaneous hematoma. On examination, occipital lymph nodes were swollen to about 1 cm in diameter. On skull X-ray, 3.0 × 2.5 cm bony erosion was detected. MRI (Figs. 3A-C) demonstrated a right parietal extra-cranial mass, ovoid in appearance, with an adjacent skull defect involving the inner and outer tables. The lesion was hyperintense on T1-weighted image (Fig. 3A) with heterogeneous intensity on T2-weighted image (Fig. 3B) and enhancement on gadolinium administration (Fig. 3C). Of concern was adjacent meningeal enhancement and there was slight signal change within the adjacent brain parenchyma. The patient underwent surgery and total removal of the mass was achieved with repair of the skull using titanium plate. Post-operative Gallium scintigraphy of whole body showed no other lesion. Histopathologically, Langerhans cell was seen in the form of a giant multineucleated cell (Fig. 3D). Staining was also positive for CD68 (Fig. 3E), CD1a (Fig. 3F), vemintin (Fig. 3G) and S100 (Fig. 3H). MIB-1 index was 14%. Follow-up MRI was performed 5 and 7 years after operation and showed no reoccurrence.
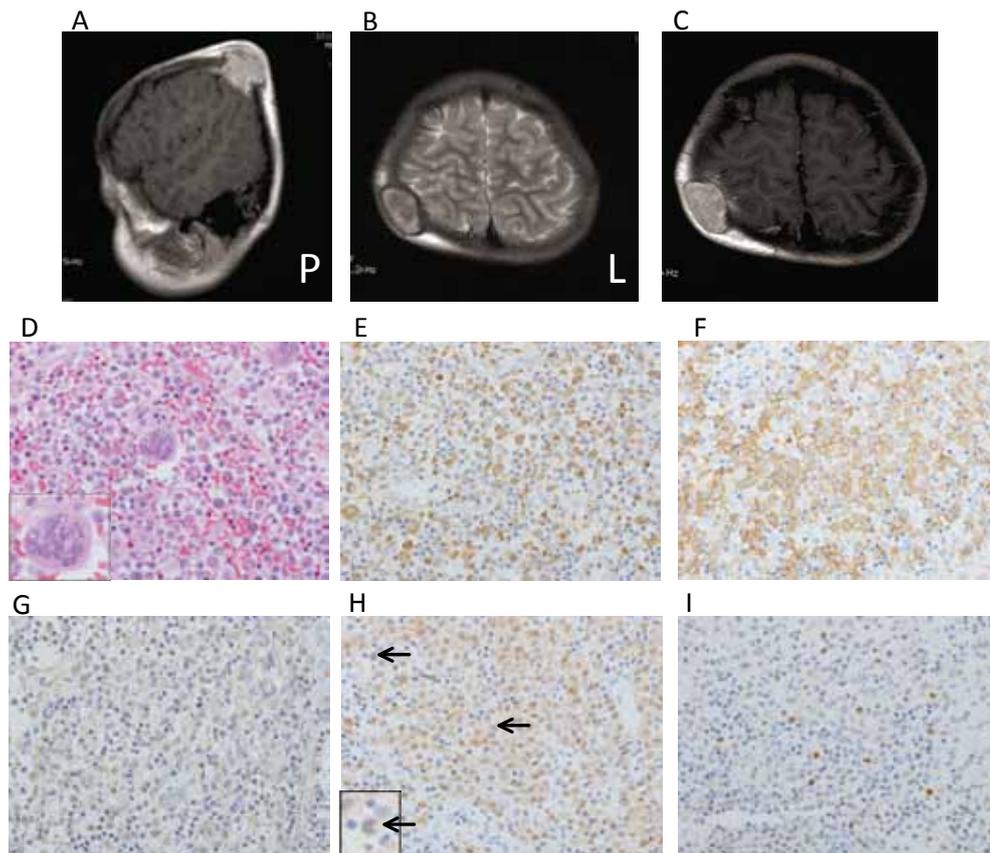
Fig. 3. Neuroimaging and pathology of Case 2
A. Sagittal T1-weighted magnetic resonance image (MRI) demonstrating a hyperintense lesion in right parietal skull bone.
B. Axial T1-weighted MRI demonstrating a slightly hyperintense mass in right parietal region.
C. Axial T1-weighted contrast enhanced MRI showing enhancing lesion with slight brain parenchymal enhancement.
D. Hematoxylin and Eosin (H & E) staining (original: × 400) showing giant multinucleated forms of Langerhans cells.
E. Immunohistochemistry showing positivity for macrophage marker CD 68 (original: × 400).
F. Immunohistochemistry showing positivity for histiocytic marker CD 1a (original: × 400).
G. Immunohistochemistry showing positivity for vimentin (original: × 400).
H. Positive immunohistochemical staining for antibody to S-100 protein similar to first case. Note 'pac-man' appearance (arrows) of the nucleus (original: × 400).
I. MIB-1 staining of specimen (original: × 400).

DISCUSSION

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 at ages 2−4[7]. This disease has a preponderance in males, sometimes as high as 60−70%[17]. The incidence appears to be higher in whites of northern European descent than in blacks[14]. The most common site involved is the skull and accounts for more than 50% of cases. The most common presentation is a painful immobile mass in the calvarium[9]. The frequency of diabetes insipidus, the hallmark of hypothalamic pituitary region (HPR) involvement, is 5−50%[10], whereas the estimated incidence of neurodegenerative LCH is 1−3%[10,25]. CT scanning helps in confirming the presence of the bone lesion and soft-tissue involvement. MR imaging is more useful for precise delineation of the extent of the soft-tissue lesions and their relationship to adjacent structures.

The etiology of LCH remains unknown, and it is still uncertain whether LCH is a neoplastic disorder, suggested by the monoclonality in lesions, or a reactive disorder resulting from a dysregulation of the immune system[19,25]. Both of our cases had preceding trauma, and there is a report in which trauma was the first presentation of LCH in orbit[6]. Acute injury triggered MyD88 dependent inflammatory responses[16]. MyD88 plays an important role with extracellular signal-regulated kinase in brain[22]. Preceding trauma might be coincidental but it is plausible that trauma accelerates immune system activation of undiagnosed LCH.

A single skull lesion may be the only presenting symptom. However, there may be an underlying multifocal disease that can be investigated by nuclear medicine techniques. In our second case, scintigraphy of whole body showed no other lesion. Additional changes of bone may occur for as long as 4 years after initial diagnosis which determines the disease prognosis[1]. The multiplicity of clinical forms of LCH is accompanied by a great variation in outcome. The localized focal form of LCH has a more favorable prognosis than the multifocal disseminated form, which involves organs as well as the skeletal system[20].

Involvement of the orbit by LCH is uncommon and accounts for less than 1% of all orbital tumors[21]. In most cases, LCH in orbit is present as a symptom with multisystem disease and multifocal bone disease[8]. The most frequent presenting signs are proptosis, periocular redness, pain, and upper eyelid edema[15]. When the orbit is involved, it is usually the superolateral aspect[3]. Orbital masses are usually extraconal and are thought to be of bone origin[5]. If clinical signs are present, a lytic lesion of the orbital wall is usually found, as in our case. Proptosis is the most common symptom and dislocation of the globe has also been reported[26]. Despite its rarity, reported to be as low as 0.01% of orbital biopsies in children[23], even if the CT appearance may look aggressive, the possibility of Langerhans cell histiocytosis must be kept in mind when examining a young child with orbital and periorbital lesion. Central nervous system sequela is concerned in orbital LCH, but there is little evidence that orbital unifocal cases increase that risk[8]. The differential diagnoses of the orbital LCH include metastatic neuroblastoma as well as mesenchymal osteogenic sarcoma. All these pathologies can present as a rapidly progressing facial and orbital swelling. The initial differential diagnosis of the first case was a focal infection following trauma and neoplastic lesion. A biopsy was done and yielded the final result of LCH.

Pathologically, LCH presents as typical granulomas or as xanthogranulomas, characteristics of chronic inflammation[18], i.e typical granulomas consist of an accumulation of CD1a-positive (+) Langerhans cells, indeterminate and interdigitating cells, macrophages and T-lymphocytes. Typically, the histiocytic cells have folded nuclei. The Langerhans cell infiltrate is accompanied by a varying amount of osteoclast-like giant cells and eosinophils. The combination of immunopositivity for the neuronal marker S100 and CD1a, which is specific for Langerhans cells (and thymocytes) and is not expressed by macrophages, helps to confirm the diagnosis[13].

Various ways to treat the unifocal LCH have been described in the literature. Some LCH show spontaneous regression; therefore, treatment may not be required[12]. Partial resection or complete excisional biopsy of the lesion helps in definite diagnosis. Biopsy followed by low-dose radiation to the lesion usually with 6−10 Gy has a local control rate of approximately 80%[11]. Unifocal LCH can also be treated with peroral or intralesional corticosteroids[4]. Further options, especially for multifocal or aggressive LCH, include first line chemotherapy with a combination of prednisone/ vinblastine or second line agents with a 24 weeks course consisting of prednisolone, vincristine and cytarabin[2].

In conclusion, we reviewed two cases of LCH limited to one part of the skull coincident with the site of a preceding injury. Although there are various treatment options for unifocal LCH, prednisone alone appears justified and may avoid overtreatment with subsequent complications from radiation or chemotherapy. However, long term follow-up with serial imaging is recommended.

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