Langerhans cell histiocytosis in the occipital condyle: a case study and a brief review of the literature

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SUMMARY

We present a case study of a 5-year-old patient, who presented with left-sided torticollis. Due to persistence of problems, a CT and an MRI were made showing a single osteolytic lesion centred on right occipital condyle. After an open biopsy, histology confirmed it to be Langerhans cell histiocytosis (LCH). Torticollis or restricted range of motion is a presenting feature in 76% of children with LCH with cervical involvement. There remains much debate on the best treatment strategy. The clinical and radiological outcomes of the case study presented on this article support the treatment of LCH with chemotherapy in cases with solitary involvement of the occipital condyle.

BACKGROUND

Langerhans cell histiocytosis (LCH) is a disease of the myeloid dendritic cells with mononuclear phagocyte dysregulation.[1] ''Histiocyte' refers to several types of cells including monocytes/macrophages, dermal / interstitial dendritic cells and Langerhans cells. Histiocytes are hypothesised to arise from a CD34+ progenitor cell within the bone marrow that, depending on the cytokine milieu, will differentiate into either CD14− cells or CD14+ cells. CD14+ cells further differentiate either into tissue macrophages or dermal/interstitial cells, whereas CD14− cells become Langerhans cells.[2]

The diagnosis of LCH includes diseases previously designated as histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian syndrome, Hashimoto–Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, type II histiocytosis and non-lipid reticuloendotheliosis.[3]

LCH affects predominantly males.[4] The estimated incidence is 1–6 per million,[5 6] primarily encountered in paediatric patients; 50%–90% of cases are diagnosed between the ages of 1 year and 15 years.[7 8] When focusing only in children, the estimated incidence of LCH is 2–9 per million[9–12] with a median age at diagnosis of 3 years old.[9]

Presentation of LCH is highly variable. The disease may affect any organ or system, more frequently bones, skin and pituitary gland.[13] The most common site of involvement is the skull (27%), followed by the femur (13%), mandible (11%) and pelvis (10%). Skull lesions tend to manifest more often in the orbits and calvaria than in the base of the skull. Cases involving the skull base region are rare.[14] Next to bone, the skin is the most frequent site of LCH involvement. Characteristic papulosquamous granulomatous lesions are most often found in the scalp, and mucosal lesions of the oral cavity and genitals are common.[15] Lymph nodes, liver, spleen, gut, the central nervous system, pituitary and the haematopoietic system are less frequently affected.[13] Clinical manifestations of LCH vary depending on the organ or system affected, from self-healing disease to chronic recurrences. Of all patients with LCH, 16%–30% may present with pituitary dysfunction that results in various (and often multiple) endocrinopathies. Presentation includes polyuria from secondary diabetes insipidus, but a range of thyroid, growth hormone and gonadotropin disturbances have been reported, as well.[13]

We present a case study of a 5-year-old female patient, with focal bone disease, subjected to biopsy and chemotherapy, with good outcome.

CASE PRESENTATION

A 5-year-old female, previously healthy, presented with a sudden difficulty on neck motion associated with posterior subtle neck pain, related to neck movement.

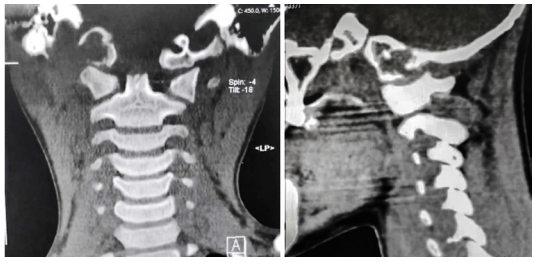

Figure 1 CT coronal (A) and sagittal (B) imaging planes, soft-tissue window, showing a single osteolytic lesion centred on right occipital condyle.

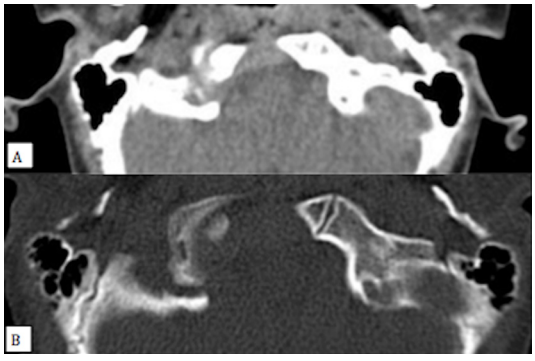

Figure 2 CT axial osseous window (A) and soft-tissue window (B) imaging planes, showing a single osteolytic lesion centred on right occipital condyle.

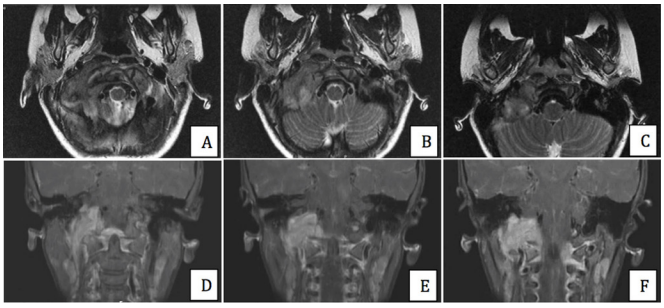

Figure 3 Axial T2-weighted images on MRI (A–C) and coronal T1-weighted images with contrast enhancement (D–F) imaging planes, showing the same lesion in relation with the adjacent structures.

Her physical examination was relevant for a left-sided torticollis with left-side inclination (30°) and rotation (30°). The child presented difficult active range of motion to the right side, tolerating passive range of motion. There was no soft-tissue swelling. A right deviation of the tongue was observed.

There were no vision-related symptoms, neither other sites of muscle ache. No other positive findings as fever or skin rash were present. No symptoms or signs of polyuria, polydipsia or weight loss were recorded. There was not any history of recent trauma or any other illness.

INVESTIGATIONS

Being one of the most common child acquired causes of torticolis, in the absence of infection or trauma, the presumptive diagnosis of atlantoaxial rotatory instability was made. Due to persistence of problems and findings after an initial period of 1-week treatment with pain control medication, soft collar and exercise programme, a CT (figures 1 and 2) and an MRI (figure 3) were made, showing a single osteolytic lesion centred on right occipital condyle, which extended paravertebrally until C2, with a soft-tissue component. The lesion extended into the hypoglossal canal (figures 4 and 5).

She was also submitted to a full bone scintigraphy scan (figure 6), which confirmed a single lesion located on the right occipital condyle.

DIFFERENTIAL DIAGNOSIS

The patient was submitted to an open biopsy 6 weeks after the beginning of problems, through an extracranial lateral suboccipital approach. Intraoperatively was identified a soft, whitish non-haemorrhagic mass in relation with the occipital condyle and the nearby cervical soft tissues.

After surgery, she was instructed to use soft collar. No new neurological findings were detected. Histology confirmed it to be LCH.

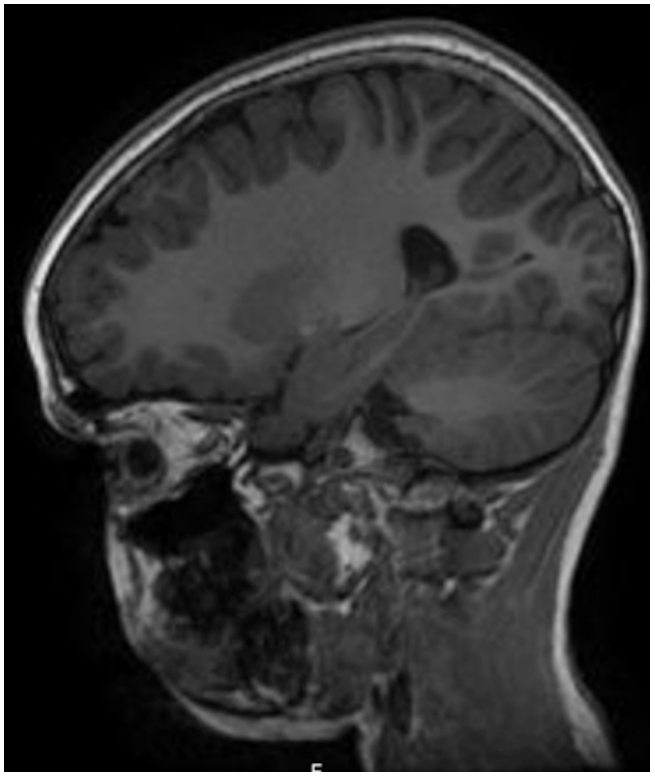

Figure 5 CT sagital T2-weighted image on MRI, showing relationship with the hypoglossal canal.

TREATMENT

In the month after surgery, chemotherapy was started according to LCH4 Group 3 protocol. This protocol consisted of an

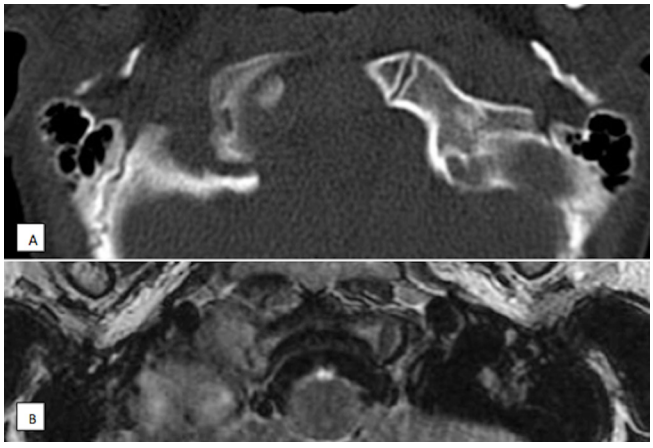

Figure 4 CT axial osseous window (A) and axial T2-weighted image on MRI, showing relationship with the hypoglossal canal.

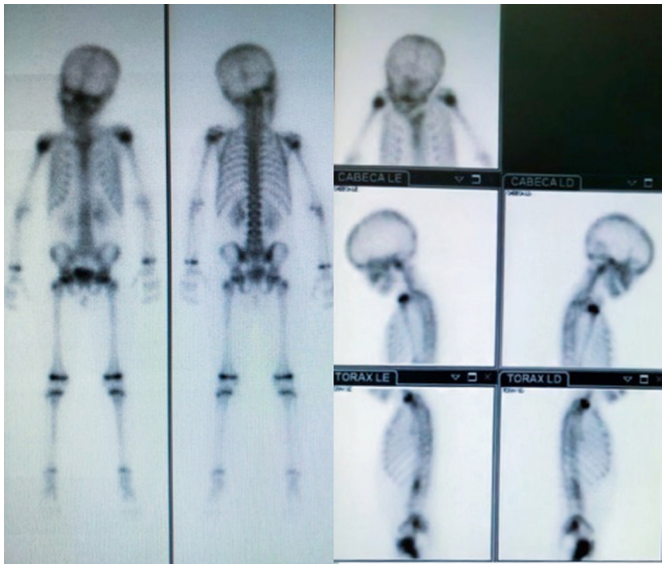

Figure 6 Bone scan with 99mTC-HMDP, showing increased capture in right occipital condyle. Remaining skeleton with no relevant changes.

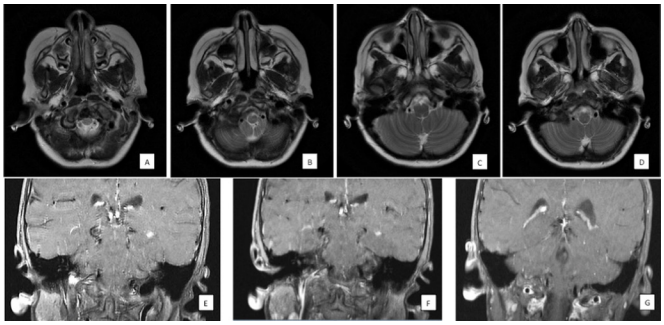

Figure 7 Axial T2-weighted images on MRI (A–D) and coronal T1-weighted images with contrast enhancement (E–G), showing no residual lesion.

induction phase with vinblastine weekly (6 mg/m^2) and prednisolone daily (40 mg/m^2) for 28 days, followed with 2 weeks weaning of prednisolone. Afterwards, 12 weeks of maintenance therapy were completed. Each cycle consisted of a 21 days period of vinblastine (6 mg/m^2) at day 1 and prednisolone at days 1–5 (40 mg/m^2).

OUTCOME AND FOLLOW-UP

At the end of the maintenance therapy, the child presented without any movement restriction and without residual disease. She was allowed to leave the collar, which she tolerated with no difficulty. No right-sided tongue deviation was present.

After 12 months, control MRI and CT (figures 7 and 8) presented without residual lesion and reossification of the osteolytic lesion. At 3 years follow-up, the patient remains without functional limitations and symptom free (figure 9).

DISCUSSION

The incidence of torticollis in children is 1,3%, and 97% of all infantile torticollis resolve with a conservative treatment.[16] The incidence of 1–6 cases/million/year of LCH as previously stated, and the diversity of clinical presentations makes the diagnosis even more difficult. About 64% of patients of paediatric with unifocal bone lesions have solitary skull involvement and 8% have cervical spine involvement.[17]

Swelling, torticollis or restricted range of motion are a presenting feature in the majority of children with LCH with cervical or skull involvement.[17 18] The differential diagnosis of neck stiffness and malposition is difficult, due to the diversity of possible pathology (box 1), and even more difficult when there are no other symptoms associated.

Torticollis might be congenital-muscular in origin but it can also be associated with acquired processes such as trauma, infections or inflammatory diseases, central nervous system neoplasms, drug reactions, and a variety of different syndromes.[19] In our patient, the expansive soft-tissue component of the LCH likely contributed to ligamentous laxity causing torticollis.[20]

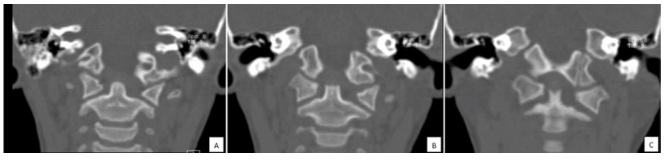

Figure 8 CT coronal (A,B,C) imaging planes, bone window, showing reossification of the osteolytic lesion.

Figure 9 At 3-year follow-up, the patient presents without functional limitations.

As LCH is a very rare cause of torticollis, it is often not considered in the initial differential diagnosis.[21] Radiographic findings suggestive of LCH might include osteolytic lesions that could represent LCH or other pathologies such as chordoma, rabdomyosarcoma, chondrosarcoma, infection and histiocytosis.[22 23] Laboratory workup has frequently uncharacteristic findings.[24] Because of the rarity of the disease, LCH is difficult to diagnose accurately with a non-invasive method, which, generally means to perform a biopsy.

The presence of neurological signs as hemidysaesthesia[25] should prompt the differential diagnosis with a non-benign aetiology as a space occupying lesion. In this case, the relationship with the hypoglossal canal explained the right-sided tongue deviation. Additionally, a torticollis that lasts for 2 months or longer should be evaluated with TC or MRI.[21]

LCH can involve any bone of the body.[6] As far as we know, solitary involvement of the occipital condyle was previously reported in just one case study.[26] For patients with multisystemic or multifocal single-system bone disease, core needle or open biopsy of the most suitable lesion should be performed. Fine needle aspiration is inadequate.[14] The choice of a surgical biopsy becomes important because a sufficient amount of histological tissue must be obtained to confirm the diagnosis, but the bony structures and muscular structures should be preserved so as not to increase craniocervical instability. When the structures

Box 1 Main causes of neck stiffness and malposition

Trauma
- Fracture of the cervical spine
- Subluxation of the cervical spine
- Epidural haematoma of the cervical spine
- Muscular contusions/spasm of the neck

Infectious/inflammatory conditions
- Bacterial meningitis
- Infections of the spine (osteomyelitis, tuberculosis, epidural abscesses, discitis)
- Collagen vascular diseases (juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and other spondyloarthropathies)
- Primary or reactive cervical lymphadenitis
- Muscle strain

Tumours, other space-occupying and vascular lesions of the central nervous system
- Brain and spinal cord tumour
- Other tumours of the head and neck
- Arnold-Chiari malformation

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supporting the skull on the cervical spine such as the occipital condyle are involved, progress of the disease can cause instability in the craniovertebral junction, which may possibly become aggravated after surgical intervention.[23] The progress of an osteolytic lesion in the occipital-cervical level can have highly debilitating consequences, and the early diagnosis and treatment might mitiguise the occurence of irreversible damage or the use of more agressive treatments.[27] Atlantoaxial rotatory subluxation secondary to LCH might be the cause for recurrent torticolis, requiring posterior atlantoaxial fusion with pedicle screw fixation for estabilisation.[21]

The biopsy itself presents risks, namely of reducing the tonus of the nuchal muscles on the ipsilateral side (worsening lateral torticollis) or increasing instability at the craniovertebral junction, which would then require a further invasive procedure of craniocervical fusion.[26] The new technologies might allow the use of minimally invasive biopsy using a navigation system as a routine. In the case of spinal instability, spinal fusion is an option. However, this leads to a limited range of motion in the spine and if possible should be avoided.

The Histiocyte Society has attempted to standardise evaluation, management and follow-up of LCH.[28] The main issues to address when treating a patient with LCH are if the disease is focal, organ related or multisystemic, and whether the lesion is at high risk for central nervous system involvement. CT can be used as the initial modality of diagnosis.[17] CT shows the extent of the bone lesion, and MRI is ideal for detecting an abnormal signal intensity, paravertebral soft-tissue mass or spinal cord compromise.[21] The use of whole-body MRI might have a higher detectability for LCH lesions versus Bone scan, but they apear to have comparable accuracy in the initial risk stratification of LCH.[29]

Still, there remains much debate on the best treatment strategy.[30 31] The choice of treatment is based on the disease severity, whether there is single-system or multisystem involvement, and on the involvement of high-risk organs (bone marrow, liver and spleen).[1] Treatment modalities include performing surgery, administration of combined chemotherapeutic agents, and performing radiotherapy.[6] Even simple observation for unifocal bone lesion is described as having good outcomes, if no important structures are at risk.[17] Surgical resection is limited to unifocal primary or recurrent disease. But the location of the lesion should influence other options.[28] The management might not be clear if the surgical procedure is in a high-risk anatomic region such as the right occipital condyle.

If possible, surgical intervention and radiotherapy in childhood spinal LCH should be reserved for patients with instabilities or serious neurological deficits.[32] Surgery intervention is the mainstay treatment to unifocal skull bone lesion.[33] A combination of cytotoxic chemotherapy and steroids is indicated for polyostotic bone lesions and multisystem disease.[1 5] The use of chemotherapy to treat solitary LCH is still controversial, but it seems safe and effective in some studies.[20] Low-dose radiation may be employed.[34 35] However, radiation has been generally avoided recently owing to concerns regarding damage to endochondral ossification centres and other long-term toxicities including secondary malignancy.[20 32]

As, after her biopsy and diagnosis, she remained clinically stable and without new problems or physical findings, the decision to advance to isolated chemotherapy was done. During this phase, her torticollis gradually disappeared and CT showed remission of the lesion and marked regeneration of the right occipital condyle. Avoidance of surgery allowed preservation of vascular supply and progenitor cells in the periosteum,[20] which allowed bone healing and regression of the osteolytic lesion. The patient has not needed further surgical procedures.

In case of no regression of the osteolytic lesion, the use of Zoledronic acid,[9] alendronate[23] or other bisphosphonates[22] could also be an option, even without the concomitant use of chemotherapy. Nevertheless, prospective trials are needed to confirm the efficacy and safety of bisphosphonates in this condition.[23]

Defining cure in patients with LCH can be difficult because of the paucity of clinical data and variable clinical course. The high recurrence rate and diverse clinical course highlights the importance for long-term multidisciplinary follow-up. It has been shown that prognosis is dependent on the number of organs involved, as well as the presence of organ dysfunction, and to a lesser degree, the age of the patient at the onset of the disease.[36]

Based on the results of several large multicentre therapeutic trials, it has been shown that the single best prognostic indicator is the patient's response to chemotherapy during the 6-week induction phase.[35 37–42]

Patients with involvement of multiple organ systems who respond to chemotherapy have 88%–91% survival rate, but for patients who do not demonstrate an early response the survival rate drops to 17%–34%. Therefore, it has been advocated that these non-responders be identified early so that more aggressive therapy may be employed.[29 43–45]

Learning points

- Most of infantile torticollis resolve with a conservative treatment, but in the presence of a torticollis that lasts for 2 months or longer, the possibility of rare, non-benign causes (as Langerhans cell histiocytosis (LCH)) should be evaluated.
- The clinical and radiological outcomes of the case study presented on this article support the treatment of LCH with chemotherapy alone in cases with solitary involvement of the occipital condyle.
- All patients with LCH require long-term follow-up to identify disease recurrence or late-stage complications.

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