

# A Case Of Langerhans' Cell Histiocytosis Of The Temporal Bone Masquerading As Acute Mastoiditis.

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## Citation

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## Abstract

Langerhans' Cell Histiocytosis is a rare disease ranging from a benign to a rapidly fatal condition affecting predominantly young children. We report the case of a 20-month old infant presenting with acute mastoiditis which failed to resolve with appropriate treatment. An urgent mastoid exploration revealed a large mass of organised tissue. The diagnosis of Langerhans' Cell Histiocytosis was confirmed by histopathological examination. This report describes an unusual mode of presentation masking and thereby delaying diagnosis. The distinctive histopathological and radiological features, coupled with awareness of the condition, were crucial in establishing a definitive diagnosis, and instituting appropriate management.

## INTRODUCTION

Since 1987, Langerhans' Cell Histiocytosis has become the accepted name to describe the collection of conditions previously individually known as eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease [1]. These conditions were initially linked together by the American pathologist Louis Lichtenstein in 1953, who from the results of studies performed in the 1940's, observed an identical accumulation of abnormal histiocytes within tissues of patients affected by all three of these diseases [2]. He described these histiocytes as containing abnormal cytoplasmic bodies and gave them the collective name of Histiocytosis X, the 'X' implying unknown aetiology [2,3,4]. More recently, subtle differences observed in the shape of the nucleus of the abnormal histiocytes have been described and these have been identified as 'Langerhans' cells' [1,4]. The primary pathogenesis is, therefore, now thought to be an abnormal accumulation and proliferation of monoclonal Langerhans' cells [4,5] and, in 1987, the more accepted name Langerhans' Cell Histiocytosis (LCH) was coined by the Writing Group of the Histiolytic Society [1].

The three conditions collectively known as LCH span a spectrum of clinical severity of the same basic disorder [6]. Eosinophilic granuloma is a benign form of the disease, characterised by single or multiple benign osteolytic lesions [3]. Hand-Schüller-Christian disease is a chronic and multifocal diffuse disease consisting of multiple osteolytic and soft tissue lesions, such as of the skin and mucous

membranes [3]. In 10% of cases, a classic 'Christian triad' of symptoms has been described of diabetes insipidus, cranial bony lesions and exophthalmous [2,3]. Letterer-Siwe disease is an acute, fulminant and rapidly fatal condition [7], characterised by extensive skin eruptions, erosive osteolytic lesions, pulmonary infiltrations and hepatosplenomegaly [3]. These conditions were shown histopathologically to represent benign, acute and chronic forms of the same systemic disease process [2].

There has been very little progress since 1953 in identifying an underlying aetiological factor leading to the proliferation of Langerhans' cells [8,9]. Many potential factors have been described in the literature, such as an inflammatory, viral, neoplastic, immunological or a genetic cause, but little evidence has been provided to substantiate these [10,11]. Weintraub et al in 1998 described finding 'p53' in every biopsy specimen of LCH and postulated that inactivation of p53 may lead to uncontrolled proliferation of Langerhans' Cells, but again the cause of this inactivation remains unclear [12].

The incidence of LCH in the literature ranges from 1 to 9 cases per million, per year [4,7,11,13,14]. A survey by Alston et al (2007) looked at 101 cases of LCH in northern England between 1954 and 1998 and found an incidence of 2.6 per million, per year [13]. The National USA Cancer Unit quotes an incidence of 5 per million per year in the USA [14] and the highest incidence has been reported in Sweden, with 8.9 cases per million, per year [15]. The

majority of cases occur before the age of 20 yrs (75%) [7], with the median age of presentation being 30 months [16]. There appears to be a male predominance with a ratio of 2:1 [7].

As eluded to previously, LCH can present as unifocal or multifocal disease, with lesions affecting the bones, skin, soft tissue or viscera [10]. The clinical presentation can, therefore, vary enormously. One of the reported presentations of the disease is with osteolytic lesions in the temporal bone. Temporal bone involvement represents 20% to 30% of all cases of LCH [10]. Initial identification of LCH in the temporal bone can be difficult due to presenting symptoms being non-specific. Commonly described presenting symptoms and signs include otorrhoea, otalgia, dizziness and conductive hearing loss [10], middle ear polyps and granulations [17]. Very rarely, facial nerve and vestibulocochlear nerve palsies may be present [18], as well as sensorineural hearing loss [7]. These symptoms may mask the underlying disease and delay diagnosis until failure of symptomatic treatment regimes [10]. This report concerns a patient with temporal bone LCH who initially presented with symptoms and signs suggestive of acute mastoiditis.

## **CASE REPORT**

A 20 month old child presented to our department with a four week history of right-sided otalgia which had progressed despite oral antibiotics from his General Practitioner. The pain was constant, but particularly severe at night and not helped by basic analgesia. There was no associated discharge or trauma to the right ear and he had been systemically well. Apart from persistent conjunctivitis there was no other concurrent or past medical history of note. He was born through a normal vaginal delivery and was up to date with immunisations.

On examination, the child was febrile at 38°C. There was a palpable, tender, erythematous mass posterior to the pinna, with associated protrusion of the ear compared with the contralateral side. The tympanic membrane on the right was obscured with wax, but normal on the left. Facial nerve function appeared normal and there was no associated lymphadenopathy within the neck.

The white count was within normal limits at  $9.7 \times 10^9/L$ , C-reactive protein was 7 mg/L and erythrocyte sedimentation rate was 26 mm. Haemoglobin was 10.1 g/L and all other blood tests were normal. The patient was treated for acute mastoiditis and admitted for intravenous antibiotics and analgesia. After significant clinical improvement, the child

was discharged three days later. An urgent computed tomography (CT) scan of the petrous temporal bones was requested on review in the outpatients a week after discharge, as there was some suspicion of an ongoing low-grade mastoiditis.

The CT scan (Fig. 1) showed extensive destruction of the right mastoid bone with loss of the bony integrity exposing the middle and posterior cranial fossae. There was invasion of the sigmoid plate, the middle ear and the posterior part of the facial nerve canal, but no evidence of intracranial involvement. A skeleton survey x-ray showed no other bony disease, chest x-ray was normal and ultrasound of the abdomen showed no abnormalities.

## **Figure 1**

Figure 1 – Computed tomographic scan showing extensive destruction of the right mastoid with loss of bony integrity both anteriorly and posteriorly, exposing the middle and posterior cranial fossae.

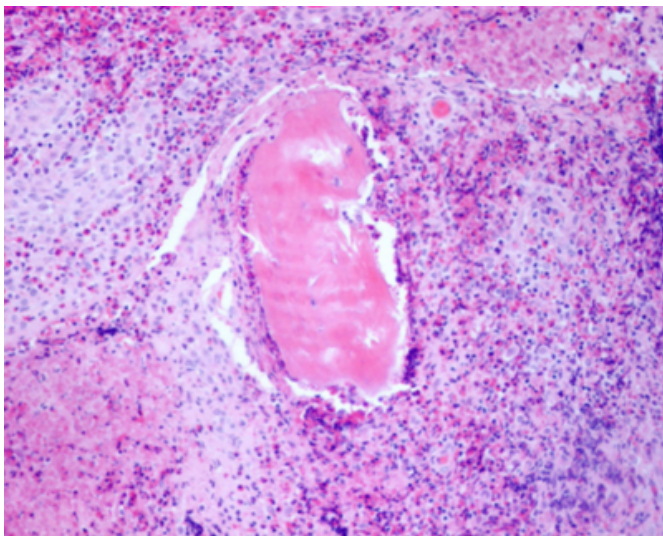


The patient underwent an urgent right mastoid exploration, revealing a large mass of organised tissue obliterating the mastoid. This was surgically debulked and sent for histopathological examination revealing fragments of bone with attached hypocellular fibrous tissue, eosinophil cell infiltrates and histiocyte cells with reniform type nuclei, suggestive of LCH (Fig 2). Immunohistochemistry showed positive staining of the cells with CD1a (Fig. 3), S100 and Langerin, confirming the diagnosis of LCH. The patient was referred to the paediatric oncology team where he is

currently being treated with a 12 month course of vinblastine chemotherapy with prednisolone. On his most recent review 6 months following the initial diagnosis, the patient was tolerating chemotherapy well and showing a good response with further reduction in the size of the residual soft tissue mass on repeat MRI.

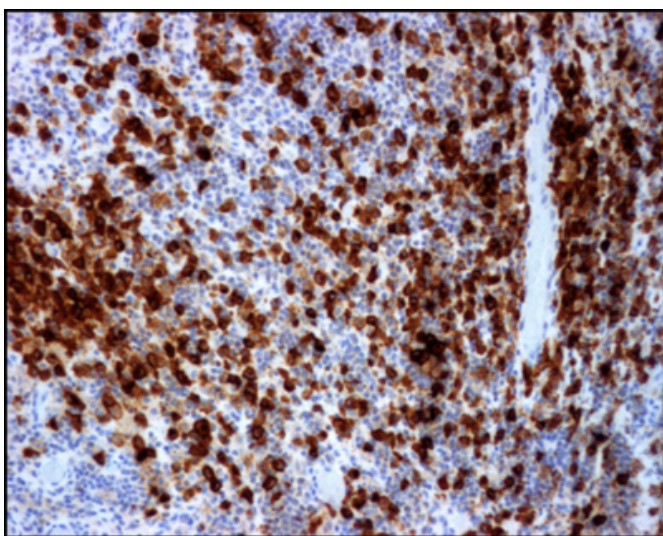
**Figure 2**

Figure 2 - Haematoxylin and eosin stained, x 20 objective, medium-power – showing a fragment of bone infiltrated at the edge and surrounded by a diffuse infiltrate of eosinophils and histiocytes.



**Figure 3**

Figure 3 - Immunohistochemical staining, x 20 objective – showing diffuse CD1a positive Langerhans cells in LCH. These cells also stained positive for Langerin.



**DISCUSSION**

Histiocytes are mononuclear phagocytes found within the

epidermis and are also scattered in other organs of the body, where they function normally as tissue macrophages as part of a healthy reticuloendothelial system. The diagnosis of LCH lies mainly in the histopathological identification of the unique histiocyte, the Langerhans' cell, within the diseased tissue [1,4,7].

Radiological assessment of LCH of the temporal bone is crucial for identifying the extent of the bony lesion, the margins of any accompanying soft tissue mass, assessment of any adjacent erosions, such as the ossicular chain or bony labyrinth, and identifying intracranial extensions of the disease [17]. Bony LCH can be seen on plain x-ray as round, punched-out lesions [19]. However, the preferred imaging modality for LCH is CT [17]. Characteristic findings of LCH on CT are described as a soft tissue mass with lytic lesions and a central density [19]. Magnetic Resonance Imaging (MRI) is recommended if there is an associated soft tissue mass [17]. On T1-weighted images the characteristic signal intensity is hypointense and on T2-weighted is hyperintense [17,19]. Using Gadolinium helps to enhance the lesion with zones of central hypointensity [10,17]. For multifocal disease, a skeletal survey or bone scintigraphy is useful in identifying further lesions. Marioni et al (2001) showed skeletal radiology to be more sensitive and specific than bone scintigraphy [17]. However, whilst imaging is a useful modality in supporting the diagnosis, it is no substitute to histopathological examination which is pathognomonic [10].

The Langerhans' cells themselves are described as being either elongated or rounded and containing pink or clear cytoplasm [4,10]. Most notably, the nucleus, crucially, is indented by a central sulcus or groove, giving it the appearance of a 'coffee-bean' shape [4,10,20]. This specifically differentiates the Langerhans' cell from the normal histiocyte [4]. Under electron microscopy thin cytoplasmic organelles with zippered membranes, dilated at one end giving a 'tennis-racket' appearance, may be identified attached to the cytoplasmic membrane [7,8]. These are known as Birbeck granules [4,7,8]. As well as light and electron microscopic appearances of Langerhans' cells, immunohistochemical detection of the specific proteins CD1a and S-100 on the cell membrane will give a definitive diagnosis [7,11,21]. Birbeck granules have recently been shown to exclusively express a glycoprotein known as Langerin (CD207). Langerin is now widely able to be stained immunohistologically in combination with the proteins CD1a and S-100 [22] on routine formalin-fixed,

paraffin-embedded sections. CD1a and Langerin immunohistochemical stains predominantly highlight immature dendritic cells [23]. These three specific markers stained positively in the diseased mastoid tissue in this case report, confirming LCH as the underlying diagnosis.

Due to the relative paucity of patients with LCH, there is no current standard treatment regime and management is usually individualised [7,10]. Currently, paediatric oncologists refer to the treatment guidelines on the Childrens Cancer and Leukaemia Group (CCLG) website ([www.cclg.org.uk](http://www.cclg.org.uk)). Treatment options include surgery, chemotherapy and radiotherapy, either individually or in combination, according to the system evoked, extent and severity of disease [7,10]. Surgery is usually required to obtain a tissue diagnosis and often involves debulking of disease followed by low dose radiotherapy, intralesional steroid injections or chemotherapy [7]. Chemotherapy agents include vinblastine, methotrexate, etoposide and sulfamethoxazole which are used in combination with prednisolone [10,19]. In this case, the patient had subtotal disease resection surgically through a mastoidectomy, followed by a 12 month course of vinblastine and prednisolone.

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