# Langerhans cell histiocytosis of bone in children: a clinicopathologic study of 108 cases

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***Background:*** **Langerhans cell histiocytosis (LCH) is a rare disease that is characterized by abnormal proliferation of pathological Langerhans cells (LCs). In this study, a total of 108 pediatric patients with LCH of bone were evaluated retrospectively for illustrating the clinicopathologic features of this disease, with a goal of improving the diagnosis, treatment, and prognosis.**

***Methods:*** **A retrospective study was based on the clinical records and pathological data of 108 patients (13 days to 12 years of age) with LCH of bone from a single hospital. Hematoxylin-eosin stain and immunohistochemical stain were applied. The follow-up was conducted to June 2008.**

***Results:*** **The peak age of the patients ranged between 3 years and 6 years (80.6%, 87/108), and male gender predominated. The most common clinical presentation was local pain, and the imaging findings commonly showed an isolated lytic lesion in the bone. Of the 108 patients, 79 (73.1%) had single bone involvement, 27 (25.0%) had multi-bone involvement (with or without related skin involvement), and 2 (1.8%) had multi-system involvement. Histologically, all the lesions revealed abnormal proliferation of pathological Langerhans cells along with an admixture of eosinophils, lymphocytes, and other inflammatory cells. The LCs have similar shape and are positive for cluster of differentiation 1a (CD1a) (100.0%, 60/60), S100 (90.0%, 54/60), CD68 (41.7%, 25/60), lysozyme (Lys) (40.0%, 24/60), and macrophage antigen compound (MAC) 387 (30.0%, 18/60); cytokeratin (CK) and epithelial membrane antigen (EMA) were negative. The overall survival rate was 98.0% at a median follow-up of 5 years.**

***Conclusions:*** **LCH of bone in children is predominant in males and usually shows as an isolated lytic lesion. Histologically, the lesions reveal abnormal proliferation of pathological Langerhans cells, admixed with various types of inflammatory cells. The patients have a good prognosis, except those with multi-system involvement.**

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***Key words:*** **bone;**
**clinicopathological study;**
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## Introduction

Langerhans cell histiocytosis (LCH), formerly known as eosinophilic granuloma, is a rare disease in children. It is characterized by abnormal proliferation of pathological Langerhans cells (LCs). LC is derived from the bone marrow and normally present in the lymph nodes and other organs. Being a subset of dendritic cell, a kind of antigen-presenting cell, LC can take up and process microbial antigen on infection of related areas.[1] In general, LC is categorized into histiocytes, correspondingly, LCH represents a type of histiocytosis.

LCH affects many organs and bone is most frequently affected in children.[2] In most cases, LCH of bone presents as an isolated lytic lesion in bone; however, LCH can become a disseminated disease. A definitive diagnosis should be established on pathological studies, especially the expression of characteristic immunohistochemical and ultrastructural markers. A few patients with LCH have a fatal outcome, but the majority of the patients have a good prognosis.[3]

Over the last few decades there has been considerable progress in the understanding of LCH and great advances have been made in the diagnosis and treatment. However, due to the low incidence, LCH poses difficulties to the diagnosis and treatment. Besides, the etiology and pathogenesis of LCH is still unclear.[3] This study was conducted to assess the clinicopathologic features of this disease and provide some insight for further investigation.

## Methods

### Patients

Between June 1989 and March 2007, all pediatric patients with LCH of bone who were diagnosed and treated at Xinhua Hospital, Shanghai Jiaotong University School of Medicine, were enrolled in this study. The clinical and pathologic data were obtained from hospital records. All the patients underwent routine peripheral blood laboratory studies, X-ray and computed tomography (CT), and biopsy. All of them were diagnosed with LCH of bone by pathologic studies. The specimens for pathological studies were obtained at the initial presentation of patients. Hematoxylin-eosin stain and immunohistochemistry were used. The patients were classified according to the traditional classification system[4] and followed up until June 2008.

### Morphology and immunohistochemistry

Tissue biopsy was conducted after patient permission was granted. The tissue samples were fixed by 10% neutral formalin, embedded in paraffin, and cut into 5 μm-thick slides. The slides were then routinely stained by hematoxylin-eosin. Immunohistochemistry was performed on 60 formalin-fixed paraffin sections with the EnVision method. A panel of monoclonal antibodies against CD1a, S100, CD68, Lys, macrophage antigen compound (MAC) 387, cytokeratin (CK), and epithelial membrane antigen (EMA) (Dako, Glostrup, Denmark) were used. We replaced the first antibody with phosphate buffered solution (PBS) as a negative contrast and used known positive sections as a positive contrast.

## Results

### Demographic data

There were 108 patients aged 13 days to 12 years (median, 4.21 years) at the time of diagnosis, and their peak age ranged between 3 years and 6 years (80.6%, 87/108). There were 66 males and 42 females (male to female ratio: 1.6).

### Clinical presentation

The clinical presentations included local pain only (63 patients), local pain with fever (20), local pain with edema (20), local pain with claudication (4), and a pathologic fracture (1). The lesion sites were as follows: ilium (27 patients), femur (21), tibia (17), skull (17), clavicle (9), sternum (4), cervical vertebra (3), ulna (3), humerus (2), metacarpal bone (2), hip bone (2), and fibula (1). There were 79 patients with single bone involvement, 26 patients with involvement of 2 bones, 1 patient with involvement of 3 bones, and 2 patients with multiple organ system involvement (bone, liver, spleen, skin, and lymph nodes).

### Laboratory examination

The erythrocyte sedimentation rate (ESR) increased in 54 patients and the eosinophil (EOS) count from peripheral blood was slightly elevated in 25 patients. The remaining laboratory examination results were normal.

### Imaging examination

The most commonly affected site was the ilium. In the patients with long bone involvement, the diaphysis was the most common tumor site, followed by the metaphysis. The X-ray image always appeared as a round or ovoid isolated lytic damage, $1.5 \times 1 \times 1$ cm$^3$ to $3 \times 2 \times 1$ cm$^3$ in size, with clear margins (Fig. 1). In some patients, the bone mineral density surrounding the lesions was increased and the adjacent bone cortices were thinner.

### Pathologic features

All the lesions displayed an abnormal proliferation of pathological LCs. The shape of these LCs was similar; specifically, the LCs were 15-25 μm in diameter, with pale eosinophilic cytoplasm, and an ovoid deep-grooved nucleus with few mitoses. Besides, there were amounts of eosinophils, lymphocytes, plasma cells, and other inflammatory cells (Fig. 2). These inflammatory cells were seen diffusely scattered or in cluster. Eosinophilic abscess was noted in many cases (Fig. 3).

The tumor cells were positive for CD1a (100.0%, 60/60) (Fig. 4), S100 (90.0%, 54/60), CD68 (41.7%, 25/60), Lys (40.0%, 24/60), and MAC387 (30.0%, 18/60), but negative for CK and EMA.

### Treatment and outcomes

All of the patients underwent surgical excision and bone graft. Some of them also received postoperative chemotherapy or radiotherapy.

A total of 96 patients were followed up for 1-10 years. During the follow-up, only 2 patients with multi-system involvement died of LCH after a median follow-up of 25 months. Among the other 94 patients who were alive, 6 patients with single-system involvement relapsed. Thus, the overall survival rate was 98.0% at a median follow-up of 5 years.

## Discussion

LCH refers to a group of conditions with different clinical courses, but all of which are characterized by abnormal proliferation of pathological LCs. Before these pathological LCs were identified, this disease had

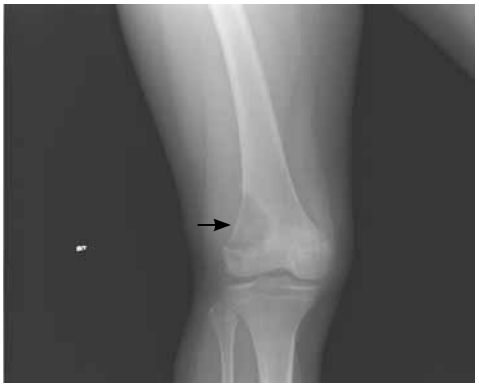

**Fig. 1.** X-ray showing a lytic lesion in a long bone.

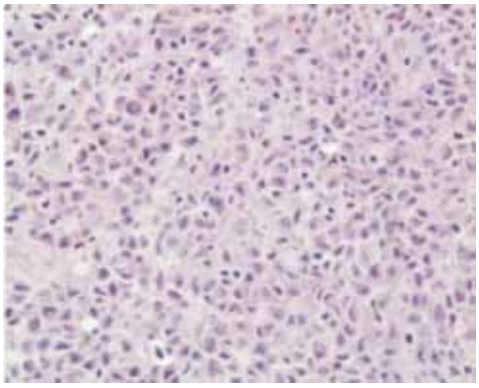

**Fig. 2.** Microscopically, the lesion composed of a large number of Langerhans cells admixed with eosinophils, lymphocytes, and plasma cells (HE, original magnification × 400).

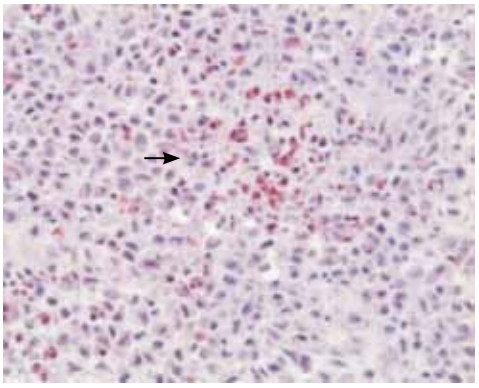

**Fig. 3.** Eosinophilic abscess (HE, original magnification × 400).

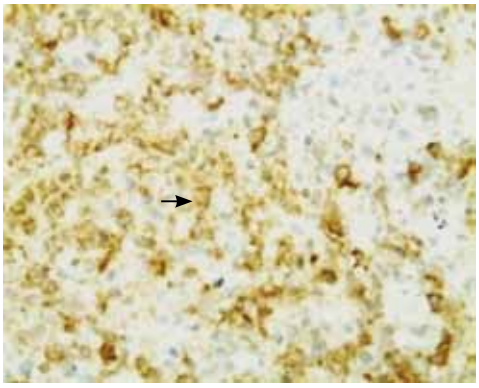

**Fig. 4.** The cells positive for CD1a (EnVision method, original magnification × 400).





been known by several names, including eosinophilic granuloma, Hans-Schüller-Christian disease, Letterer-Siwe disease, and Histiocytosis X. In 1987 it was renamed LCH by the Histiocyte Society.[5] Although the stem cell of LCH has been identified, the pathogenesis is still unclear.[5] Whether the abnormal proliferation is a neoplastic or reactive process has been widely discussed, but with no conclusion.[2,5]

LCH is a rare disease which can occur at any age but is mainly present in children and predominant in males.[6] The incidence of LCH in children is 1 to 5 children per million per year.[7] LCH almost affects any organ in the form of unifocal or multifocal lesions.[3] In children, bone is the most common single organ and the skull is the most affected site.[2] However, the ilium was the most common affected site in the current study (25.0%), which challenges this view. The relative small size of sample or different race and geographic location may have partially contributed to this inconsistence.

LCH of bone is traditionally divided into three categories that are not exclusive and overlap each other:[4] (1) unifocal LCH (eosinophilic granuloma); (2) multifocal unisystem LCH (including Hand-Schüller-Christian disease with or without related skin involvement); and (3) multifocal multisystem LCH (Letterer-Siwe disease). In the current study, unifocal LCH is the most common category (73.1%), followed by multifocal unisystem LCH (25.0%), and multifocal multisystem LCH (1.8%). Thus, it confirms that pediatric patients with LCH of bone mainly present with a unifocal lesion in bone.[2]

Since LCH refers to a group of conditions with different clinical courses, the clinical presentation of this disease is a broad spectrum. The patients with LCH of bone commonly present with bone-lesion-related symptoms such as local pain, local mass and swelling. However, proptosis, diabetes insipidus, or organ dysfunction can be seen in some special cases.[2] In the current study, nearly all patients presented with local pain initially. As the disease progressed, the pain was aggravated. However, in 5 cases of our study, the pain was tolerable and the patients did not require medication until claudication or even a pathologic fracture occurred. The radiographic findings in the current study mainly display a lytic lesion with well-defined margins in bone, similar to the patterns described in other reports.[6]

Histological examination of LCH is characterized

by abnormal proliferation of pathologic LCs. It has been suggested that these pathological LCs may be blocked in the activation or differentiation state of normal LCs,[8] so the shape of LC in LCH lack the thin-finger dendritic processes of normal LCs and display ovoid to round morphology.[9] Gong[10] has divided these pathologic LCs into four types: (1) typical LC, 12-15 μm in diameter with pale eosinophilic cytoplasm and ovoid or round deep-grooved nuclei without a nucleolus; (2) monocyte-like LC, similar to typical LC but with relatively regular nuclei; (3) multinucleated giant LC, with large, abundant cytoplasm and multiple typical-LC-like nuclei; and (4) large-round LC, with large, abundant cytoplasm and large round nuclei with 1-2 small red nucleoli. In our study, the majority of LCs in every lesion were categorized into typical LCs. However, the same shape did not lead to the same outcome; two patients with typical LCs died of LCH. Thus, morphologic features do not predict the outcome of LCH.[3]

In addition, there are various kinds of inflammatory cells in LCH lesion, which produce cytokines to help develop LCH.[9] Among these inflammatory cells, eosinophils are easily seen. They often accumulate in clusters and even form eosinophilic abscess.[10] A great number of lesions in our study displayed eosinophilic abscess. It seems that eosinophils, especially eosinophilic abscess, may be a good indicator for LCH. In some cases of our study, the osteoclastic-like multinucleated giant cells can be seen.[11] Da Costa et al[12] suggested that these multinucleated giant cells were induced by some cytokines such as receptor activator of nuclear factor κB ligand and macrophage colony-stimulating factor secreted by the LCs and T cells; they also suggested that these multinucleated giant cells were responsible for the destruction of the architecture. In our study, multinucleated giant cells always accompany with necrosis.

A precise diagnosis of LCH should be established on pathologic results, especially molecular and immunohistochemical results.[3] Under electron microscope (EM), abnormal LCs reveal the LC characteristic marker-Birbeck granule, which is generally regarded as a "gold standard" for the diagnosis of LCH.[3] However, the insensitivity of the Birbeck granule[3] as well as the rarity of performance of EM greatly reduces the value of Birbeck granules for the diagnosis of LCH. Apart from Birbeck granules, the characteristic immunohistochemical markers such as CD1a and S100 are also used to diagnose LCH. In our study, an immunohistochemical panel including CD1a, S100, CD68, Lys and MAC387 was used. The expression of CD1a and S100 was 100.0% and 90.0%, respectively, whereas CD68 was 41.7%, Lys was 40.0%, and MAC387 was 30.0%. Thus CD1a and S100 were the most characteristic markers of LCH. Currently, langerin (CD207), which reacts to the LC transmembrane protein, is suggested to associate with Birbeck granules with 100% concordance.[2] Compared with CD1a, CD207 is reported to be more sensitive and specific for LC.[13] Therefore, CD207 may be a better immunohistochemical marker for LCH than CD1a and S100. However, CD207 has not been included in the LCH immunohistochemical panel[13] while the detection of CD1a and S100 in LCH has been extensively used as a cost-efficient test. Therefore, CD1a and S100 are still the most key immunohistochemical markers for LCH.

The differential diagnosis of this disease includes a wide array of entities, of which osteomyelitis and bone malignant tumor are commonly considered in pediatric patients.[14] Osteomyelitis shows various types of inflammatory cells, which are similar to the histological patterns of LCH. But typical LC proliferation and eosinophilic abscess are absent in cases of osteomyelitis, which are able to distinguish from LCH. In some cases, however, the differential diagnosis causes problem when the presence of LC is difficult to identify. Clinical presentation, laboratory examination and especially immunohistochemical examination are very helpful in the differential diagnosis. Another differential diagnosis is made for bone malignant tumors such as lymphoma and Ewing's sarcoma. These images of these diseases mimic those of LCH. However, the mixed background of inflammatory cells is absent in them, and in contrast to LCH, the size of tumor cells is relatively identical. Furthermore, none of them express CD1a and S100. Lymphoma expresses LCA, L26 and UCHLA while Ewing sarcoma expresses CD99.

Surgical intervention, radiotherapy, chemotherapy, local injection of corticosteroids or a combination of these therapies has been applied to treat LCH.[2,15] The Histiocyte Society suggests that the treatment protocol for LCH should be determined according to the number of organs involved, their functions, and vital importance.[15] Radiotherapy is usually reserved for specific lesions or emergent situations,[3] and multi-agent chemotherapy is recommended for patients with multi-system involvement.[14] In our hospital, curettage and bone graft are routine treatments. For some clinicians, radiotherapy or chemotherapy is also considered as a routine treatment, which may be excessive for some patients.

Although the outcome of LCH is a broad spectrum, ranging from spontaneous remissions to death, the prognosis is generally good. The overall survival rate in our study was 98.0% at a median 5-year follow-up. Only 2 patients with multi-system involvement died of LCH after a median 25-month follow-up. This finding

confirms that the number of organs involved is a key factor affecting the prognosis of LCH.[2] Apart from it, the age of disease onset, the function of organs, the involvement of organs at risk, and a patient's response to chemotherapy during the 6-week induction phase are also the key factors affecting the prognosis.[15] So the prognosis of LCH is determined by multiple factors. It has been suggested that the Lavin-Osband criteria including the age of disease onset, the number of organs involved, and the function of organs can judge the outcome of LCH.[16]

In conclusion, the present study demonstrates the clinicopathologic features of LCH of bone in children. LCH of bone is prominent in males. In most cases, this disease shows as an isolated lytic lesion in bone. However, although LCH of bone is rare, it could be part of a multi-system disease. The histopathologic feature is characterized by abnormal proliferation of pathological LCs, admixed with various types of inflammatory cells, in which eosinophils are often seen and multinucleated giant cells correlate directly with necrosis. Immunohistochemical markers, especially CD1a and S100, could help to identify LCH and rule out other diseases. Morphological characteristics could not predict the outcome of LCH while the presence of multi-system involvement is a poor prognostic factor. In general, the prognosis for cases of LCH is good.

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