Langerhans cell histiocytosis of bone in children: a long-term retrospective study

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Langerhans cell histiocytosis is rare and frequently involves the bone. We retrospectively reviewed the orthopaedic aspects (symptoms, localizations, treatments) and the long-term outcome [disease status, overall survival (OS), event-free survival (EFS)] of 121 patients (June 1968–December 2009). The main symptom was local pain. The orthopaedic treatment was mainly conservative. The most frequent localization was osseous monofocal (62% of monosystemic diseases). Monosystemic and osseous monofocal localizations, treatment after 1991 (OS, $P=0.007$; EFS, $P=0.03$) and age older than 2 years (OS, $P=0.003$; EFS, $P=0.001$) were prognostic factors that were positively associated with survival. Oncologic treatment has improved over time, translating into better survival. A biopsy is often mandatory. *J Pediatr Orthop B* **21:457–462 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Langerhans cell histiocytosis (LCH) is a rare group of disorders with a wide range of clinical presentations [1]. Its aetiology is unknown as it was called histiocytosis X in 1953 by Linchenstein, grouping three different entities: Letterer–Siwe disease, Hand–Schüller–Christian disease and eosinophilic granuloma [1,2].

The annual incidence of LCH is about 5–6 per million children per year. More than 50% of cases are diagnosed between 1 and 15 years, with a peak between 1 and 4 years [1,3].

The aetiology is still unclear. Common hypotheses include irregular and uncontrolled proliferation of lymphocytes and histiocytes after an infection or gene mutation, although some sporadic manifestations are not believed to be of a reactive pattern but actually represent real neoplasms [4,5]. Many studies provided an improved understanding of the pathobiology of LCH and, over the years, different classifications on the basis of organ involvement and dysfunction have been established [4–8].

The actual classification proposed by the Histiocyte Society in 1987 divides LCH into three classes: class I and class II include reactive forms on the basis of the proliferation of dendritic cells or phagocytic cells, respectively; class III includes the rare neoplastic forms [6,9,10].

Class I is the most common and represents the old entity of histiocytosis X. The disease may involve bone, skin, lymph nodes or parenchymal organs such as the liver, spleen, lungs and bone marrow and may cause endocrinological disorders or neurological deficits [11].

Bone is often involved; 60% of patients affected present with at least one bone localization, commonly the flat and short bones of the trunk, followed by the long bones of the upper and lower limbs [11].

The involvement can be monosystemic, typically involving bones, or multisystemic. The prognosis varies and, consequently, so does the treatment. In monostotic-monosystemic disease, the prognosis is usually good, with spontaneous regression as the norm. In contrast, in multisystemic disease, the prognosis is poor and the treatment includes chemotherapy and steroids [11].

The aim of this study was to retrospectively review the orthopaedic aspects of LCH and to assess the long-term outcomes of patients treated in our institution over a 40-year period.

Materials and methods

From June 1968 to December 2009, 121 patients affected by LCH were treated at our institution. The average age at the time of diagnosis was 4.1 years (range 12 days–15 years); 79 patients were boys and 42 were girls. The average follow-up was 44 months (range 1–322 months).

An incisional biopsy was performed in all patients with bone involvement as the first manifestation. During the procedure, a Swap test and a bone marrow sample were obtained to exclude, respectively, the diagnosis of infection and lymphoma. In 11 patients with vertebral involvement, the diagnosis was made on the basis of

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clinical and radiological findings due to the potential dangerous sequelae of performing an incisional biopsy.

The symptoms at presentation, bone localization and the orthopaedic treatment provided were noted and analysed.

We used the classification proposed by the Histiocyte Society in 1987, on the basis of histopathological characteristics, that distinguishes two forms of disease: monosystemic and multisystemic [12].

Monosystemic forms may involve the skin, lymph nodes or bone (monostotic or polyostotic); multisystemic forms may involve at 'risk' organs (bone marrow, spleen, liver and/or lung) or 'low-risk' organs (skin, lymph nodes and/or bone). Patients diagnosed and treated before 1987 were classified retrospectively.

Before 1991, patients were treated without a standardized protocol (observation, curettage with or without telecobaltotherapy, or chemotherapy). From 1991 onwards, treatment followed LCH-I, LCH-II and LCH-III protocols [13].

The LCH-I protocol compared the efficacy (response, failure and morbidity) of a 'single agent' therapy with vinblastine (arm A) or etoposide (arm B) without showing a significant difference between the two arms, either in the initial response and the probability of relapse or in the mortality. The LCH-II protocol compared two different treatments: prednisone and vinblastine versus prednisone, vinblastine and etoposide. In the LCH-III protocol, the patients are stratified into three groups: group 1 (multisystemic 'risk' patients), group 2 (multisystemic 'low-risk' patients) and group 3 (monosystemic multifocal bone disease and localized 'special site' involvement, central nervous system lesions with intracranial soft tissue extension or vertebral lesions with intraspinal invasion). Monofocal monosystemic LCH and monosystemic skin or lymph nodes LCH do not receive any oncologic treatment but the evolution is constantly monitored.

The disease status was determined using the following criteria: 'nonactive disease' was defined as a complete radiographic disappearance of the lesions and return to a pain-free state; 'active disease' (AD) was defined and further classified as a reduction in the lesion size (better AD), stable disease (stable AD), development of new lesions associated with remission and/or persistence of others (mixed AD) or progression of the signs and symptoms of the disease (worse AD).

We included patients who relapsed during follow-up and the state of disease was determined at the latest clinical and radiological evaluation in our centre.

The patients were also evaluated once a year by endocrinological and neuropsychiatric specialists to report any dysfunction related to LCH during the follow-up.

Overall survival (OS) was defined as the time (in months) from the diagnosis to the day of the latest follow-up or of the death of the patient due to any cause. Event-free survival (EFS) is defined as the time from diagnosis to the appearance of any event (progression, relapse, death for any cause) or, in the absence of it, to the day of the latest follow-up.

OS and EFS were calculated using the Kaplan–Meier method, with statistical significance determined using the Wilcoxon test. All statistical analyses were performed using SPSS software version 12.0 (SPSS Inc., Chicago, Illinois, USA).

Results

All patients with bone disease at presentation were referred with local pain as the presenting symptom. None of our patients presented with a pathological fracture at diagnosis. Lesions in the long bones were located in the diaphyseal or the metaphyseal region (Figs 1 and 2). Skeletal localizations for osseous monofocal lesions are listed in Table 1.

Bone lesions were studied with plain radiographs and Tc-99 Bone Scan; computed tomography (CT) and magnetic resonance (MR) were seldom performed and were only carried out when the diagnosis was in doubt and mostly in recent cases.

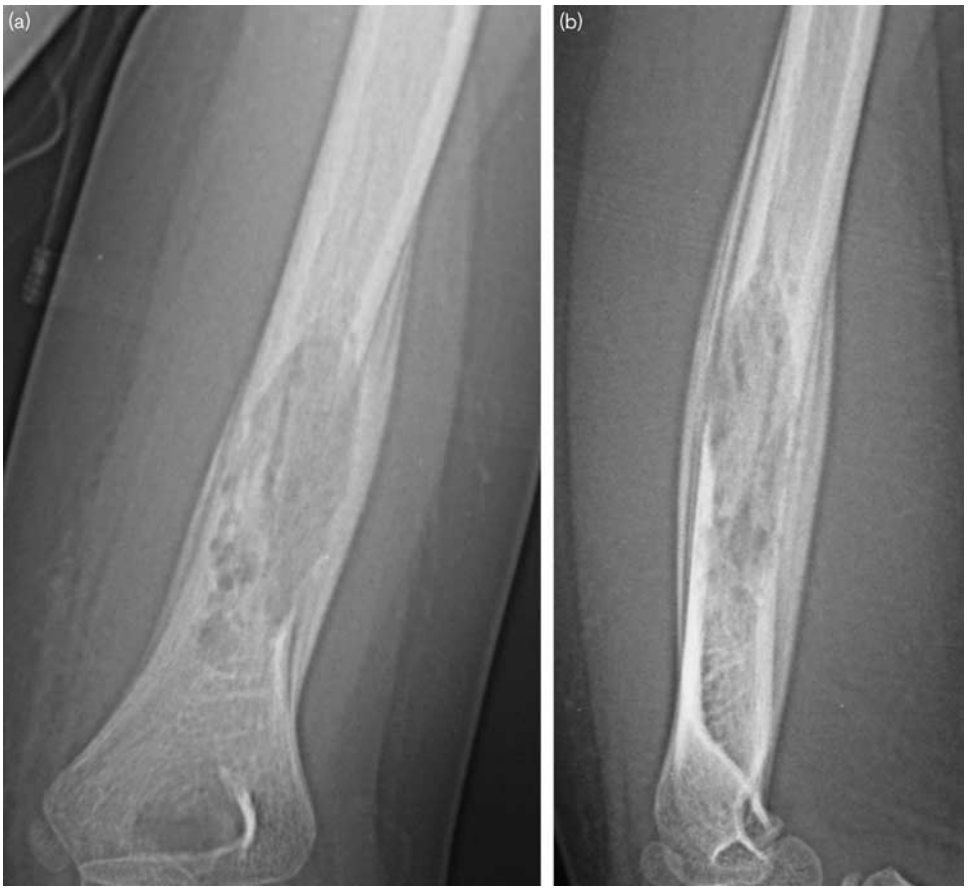
Before 1991, 16 bone lesions (30%) underwent an incisional biopsy and, at the same time, a partial curettage. This was followed by telecobaltotherapy in 11 of these cases. No bone grafting or steroids' injection was performed.

After 1991, an incisional biopsy with a simultaneous partial curettage was performed in 18 patients (26%). In our institution, a biopsy with an intraoperative frozen section is not feasible; therefore, no other treatment was combined with the biopsy. With the final pathology report confirming LCH, no further treatment (detailed curettage, injection, etc.) was provided and the positive evolution was constantly clinically and radiologically monitored (as in the case presented in Figs 1 and 2). In the case of relapse or delayed healing, an accurate curettage would be performed, even if in our experience a simple incisional biopsy revealed itself curative for solitary lesions. In the other cases (vertebral localization), patients were treated conservatively with a 'wait and see' approach and without a biopsy. The overall risk of fracture was very low and the only exception was a cervical lesion at risk of fracturing. In this case, the treatment was an anterior and posterior vertebral stabilization from C3 to C5.

The subgroups of patients divided according to the localization of the disease are presented in Table 2.

Thirty-three patients were younger than 2 years of age and 88 patients were older. In the first group, 9% of

Fig. 1



(a, b) Eosinophilic granuloma of the distal humerus. The lesion appears lytic with a major periosteal reaction. No treatment was provided after the incisional biopsy.

the patients were affected by an osseous monofocal disease and 18% by an osseous multifocal disease. In the second group, 60% of the diseases presented with monofocal bone lesions and 12.5% with multifocal bone lesions.

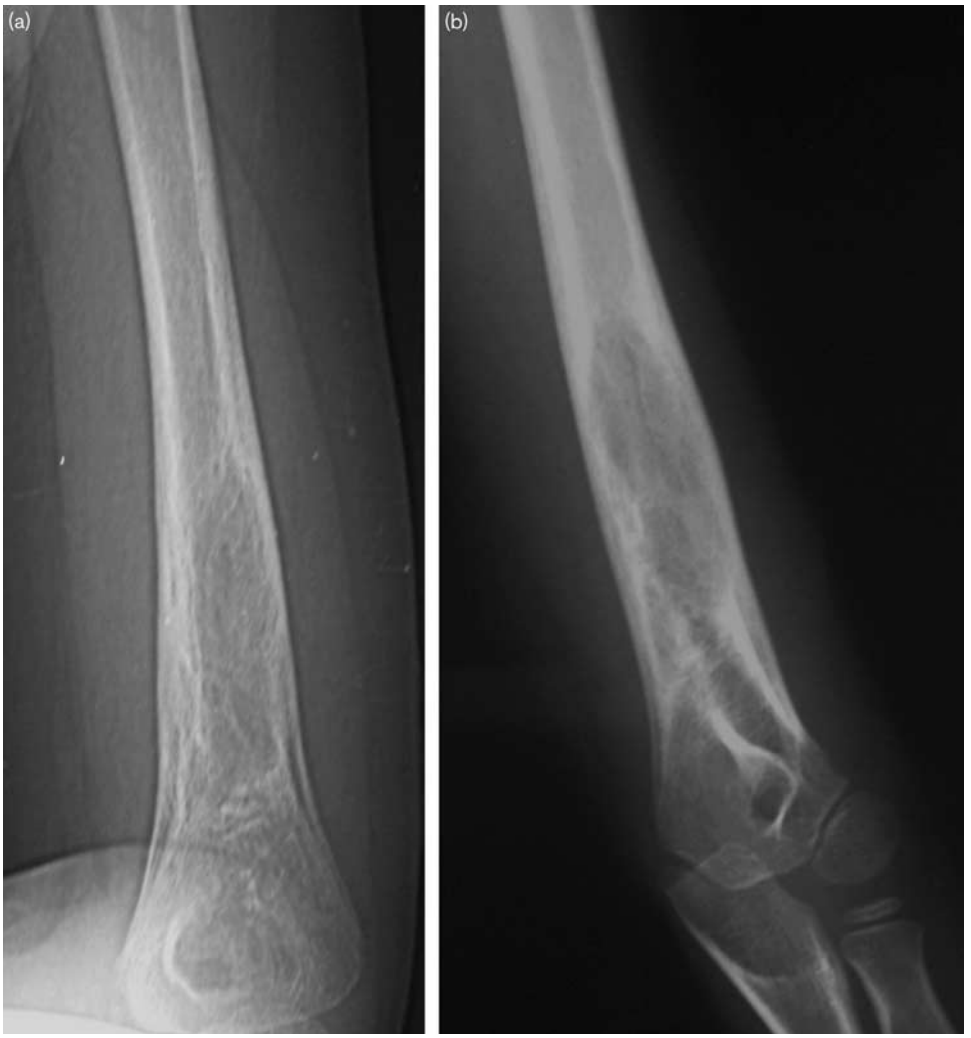
The patients were analysed in two different groups according to the year of diagnosis: before and after 1991. In 53 out of 121 (44%) patients, the diagnosis had been made before 1991. Twenty of these 53 patients diagnosed before 1991 were affected by monofocal osseous disease, 11 had multifocal bone disease, seven had cutaneous or lymph node lesions, five had 'low-risk' localization and 10 presented with multisystemic 'risk' disease. Four (7.5%) patients received no treatment. Curettage alone was performed in five patients (9.5%). Eleven (21%) patients underwent curettage and subsequent telecobaltotherapy and 33 (62%) were treated with chemotherapy at variable doses and durations.

Sixty-eight out of 121 (56%) patients were diagnosed after 1991. Thirty-six had osseous monofocal disease, six had osseous multifocal, 10 had cutaneous or lymph node disease, 10 patients presented involvement of 'low-risk organs' and six 'risk systems'. Seventeen (25%) patients were treated with the LCH-I protocol (1991–1996), 17 patients (25%) with the LCH-II protocol (1996–2001) and 34 (50%) were treated according to the LCH-III (since April 2001).

Under the LCH-III protocol, 10 out of 34 (29%) patients were followed with a 'wait and see' approach (patients with spinal localization without a risk of fracture did not receive any biopsy), 18 patients (53%) affected by monofocal disease were treated with an incisional biopsy and a simultaneous partial curettage, one (3%) child was treated according to group 1 treatment of the LCH-III protocol (multisystem risk patients), two (6%) were included in group 2 (multisystem low-risk patients) and three (9%) in group 3 (multifocal bone disease).

The OS and EFS of all 121 patients was 90 and 69% at 10 years from the diagnosis. The complete remission (CR) rates of monosystemic diseases are presented in Table 3.

Fig. 2



(a, b) The healing of the lesion is almost complete after 1 year. No local pain was reported by the patient.

Table 1 Details of skeletal localizations for osseous monofocal lesions

Skeletal localization	Number of patients (%)
Skull	26 (46)
Spine	10 (18)
Femur	6 (10)
Humerus	4 (7)
Tibia	3 (5)
Scapula	2 (4)
Radius	2 (4)
Ulna	2 (4)
Iliac bone	1 (2)
Total	56 (100)

Table 2 Localization of the disease in monosystemic and multisystemic subgroups

Localization	Number of patients (%)
Monosystemic disease	
Osseous monofocal	56 (62)
Osseous multifocal	17 (19)
Skin	14 (15.5)
Lymph node	3 (3.5)
Total	90 (100)
Multisystemic disease	
'Risk' system	16 (52)
'Low-risk' system	15 (48)
Total	31 (100)

All the patients with monosystemic disease were alive at the time of the latest evaluation in our centre.

Eight out of 15 (53%) 'low-risk' patients are in first CR, three (20%) in the second CR, two (13%) in the third CR, one child (7%) is being treated with indomethacin and one (7%) child is dead. Six out of 16 (38%) of 'risk' patients are in the first CR, two (12%) are in the third CR and eight (50%) patients died.

Table 3 Complete remission rates of monosystemic diseases

Type of disease	First CR	Second CR	Third CR	Fourth CR	Fifth CR	Total
Osseous monofocal	54 (96%)	1 (2%)	–	1 (2%)	–	56 (100%)
Osseous multifocal	11 (65%)	4 (23%)	–	1 (6%)	1 (6%)	17 (100%)
Cutaneous or lymph node	14 (82%)	1 (6%)	1 (6%)	1 (6%)	–	17 (100%)

CR, complete remission.

Overall survival at 10 years from diagnosis was 81 and 94% for patients younger and older than 2 years at diagnosis, respectively. EFS was 47 and 78%. A comparative analysis of the two groups showed statistically significant differences (OS, $P = 0.003$ and EFS, $P = 0.001$).

Overall survival at 10 years from diagnosis for patients diagnosed before and after 1991 was 83 and 98% respectively, whereas EFS was 61 and 78%, respectively. A comparative analysis of the two groups showed statistically significant differences in OS ($P = 0.007$) and EFS ($P = 0.03$).

Overall survival for patients with monosystemic disease and multisystemic disease was 100 and 70% respectively, whereas EFS was 81 and 40% (OS and EFS, $P < 0.001$). In multisystemic disease, OS was 94% in 'low-risk' patients and 47% in 'high-risk' patients ($P > 0.05$); EFS was 47 and 34%, respectively ($P > 0.05$). In all patients with multisystemic disease, the causes of death were determined by the consequences of histiocytosis-related multiorgan dysfunction.

Discussion

This study includes patients with LCH treated at our institution over a 40-year period and substantially confirms the data reported by the literature on the clinical course and the orthopaedic aspects of the disease.

The most common symptom at onset is local pain and this was found in 50–90% of patients with bone lesions [1]. In our patients, pain was almost always the symptom at presentation. Other clinical manifestations described are swelling, pathologic fractures, vertebral collapse and neurological symptoms when spinal involvement is present [1,14,15].

Excluding craniofacial lesions, the spine is the osseous site most frequently involved, followed by the chest and the appendicular skeleton, mostly in diaphyseal segments [1,16].

The radiologic findings of LCH are well defined with plain radiographs, CT, MR and Tc-99 Bone Scan. CT and MR are especially useful in showing an associated soft tissue mass and to define the extent of skull lesions [1,16]. Bone scans have low sensitivity but they have historical importance and play a paramount role in the diagnosis of multifocal osseous disease [15,16].

PET and PET-CT have recently been studied in LCH and found to be useful in detecting disease, especially extraskeletal forms, and in evaluating the response to therapy [17,18]. It seems to be more reliable than conventional radiology and bone scans but further studies are needed before wider clinical use can be recommended [17,18].

Many treatment modalities have been described in the literature and indications are still controversial: the 'wait and see' approach, intralesional injection of steroids, complete curettage, bone grafting, stem cell transplantation, radiation therapy and chemotherapy [1,19–23]. In our experience before 1991, 11 lesions were treated with telecobaltotherapy after curettage but it was abandoned due to the local damages to musculoskeletal structures and the high risk of developing radiation-induced sarcoma. Our recent treatment strategy comprises an incisional biopsy and a 'wait and see' approach because most lesions healed spontaneously or with oncological treatment, and without surgical intervention. In selected painful cases, a brace or orthosis for back pain was useful.

Good prognostic factors reported in the literature are osseous localization of the disease and a recent diagnosis [3]. In particular, with the advent of new protocols of treatment in 1991 (LCH-I, LCH-II and LCH-III), an increase in the OS was observed [1,3]. These data were confirmed in our case series: the OS was 83% at 10 years before 1991 and 98% after 1991.

We cannot draw any conclusions about the differences in OS among the three protocols as our study only compared and analysed OS between patients diagnosed with LCH before and after 1991.

In the literature, solitary bone lesions are studied separately with the old term of 'eosinophilic granuloma'. Different authors [3,23–25] published data on histocytic bone lesions; different treatments (observation, biopsy, curettage, surgical resection) are all associated with 100% OS, with rare cases of local recurrences [26]. Vertebral diseases are treated conservatively, except for lesions with neurologic peripheral symptoms or a high risk of spinal instability [15,27–29]. In our series, only one patient with cervical spine lesions underwent a surgical vertebral stabilization because of the risk of collapse. All the other patients with spine lesions were braced with an orthosis for back pain until sufficient reconstitution to restore stability was observed on the radiographs as recommended previously [14,15].

Monofocal and multifocal osseous diseases were usually benign and can be managed by orthopaedic surgeons with various techniques with very few residual functional deficits [1,20,30]. Multifocal osseous disease is characterized by a higher recurrence rate, 35% in our study, but recurrence rates up to 76% are reported [31].

If the disease is multisystemic, the prognosis is unfavourable and the course is malignant and progressive and treatment should be managed by an oncologist or a haematologist [20]. A further classification of 'low risk' versus 'risk' organ involvement yielded an OS of 94 and 47%, respectively ($P = 0.007$), in our series. Classically, an age younger than 2–3 years indicates a poor prognosis and this was confirmed in our study [32], but on accurate analysis, the age could be misinterpreted because a younger age is associated with a higher stage of disease at presentation.

Conclusion

The most favourable prognostic factors observed in our study are monosystemic (in particular, osseous monofocal) localization and an age older than 2 years at the diagnosis of LCH. Although this is an observational study and it does not represent a controlled study of the treatment of LCH, the number of patients included is comparable with other large institutions. New protocols of chemotherapy have been developed. The treatment of LCH has improved over the past few years, thus leading to improved survival. A bone biopsy is often mandatory to obtain a definitive diagnosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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