

# Langerhans Cell Histiocytosis (LCH) of the Sacrum: Report of Two Cases

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## ABSTRACT

Eosinophilic granuloma of bone (EG) also called Langerhans cell Histiocytosis (LCH) is a benign tumor-like condition, is a relatively rare disorder of unknown etiology, characterized by clonal proliferation of Langerhans-type Histiocytosis in the bone or lung [1]. EG most commonly affects children 5 to 10 years of age, 90% occurs under the age of 15 b [2]. LCH can involve any of the body tissues. The occurrence of LCH in the sacrum is extremely rare, LCH location and the number of lesions determine its mortality and morbidity potentials. The current study reports two cases of LHD involving the sacrum, both less than the age of 5, one of them presented with a significant neurological deficit and both were managed conservatively.

**Keywords:** Langerhans Cell Histiocytosis, eosinophilic granuloma, Bone, Hand-Schüller-Christian disease, autistic disorder

## INTRODUCTION

Langerhans cell histiocytosis (LCH) or eosinophilic granuloma of bone was first described in 1940 by Lichtenstein, et al. [1,3]. LCH of the bone is a relatively rare disorder of unknown etiology, with an incidence of two cases per million children per year [2,4]. Patients may present with a solitary lesion or multiple sites of involvement [3,5]. LCH is most common in children 5 to 10 years of age and prevalence is greater in males, Male:Female ratio of 2:1.1, [4,6]. In 1953, eosinophilic granuloma of bone was classified along with Hand-Schüller-Christian disease and Letterer-Siwe disease as Histiocytosis X and subsequently, the Langerhans cell of the skin was proposed as the underlying shared pathologic feature among these three disorders [5-8]. However, gene expression array analysis of CD207+ (langerin), and histiocytes from bone lesions compared with the Langerhans cells of skin proves that these are two distinctly different cell types [9] [7]. The pathologic cells in LCH are more likely derived from circulating myeloid dendritic cells. Under the direction of the Writing Group of the Histiocyte Society, LCH has been adopted as the appropriate clinicopathologic designation that encompasses and essentially replaces the previous historical terms used to classify this category of abnormal

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histiocyte proliferation [8,10]. The incidence of spinal involvement varies from 6.5% [9,11] to 25% [10,12] of cases with LCH of the skeleton, with an 11.1 % in the largest series (n=314); most commonly affects the thoracic, cervical, and lumbar spine. The occurrence of LCH in the sacrum is extremely rare and accounts for 0.6% [3,5]. We report our experience in 2 children with isolated LCH lesions of the sacrum one of them presented with significant paraparesis; an appraised literature review was done.

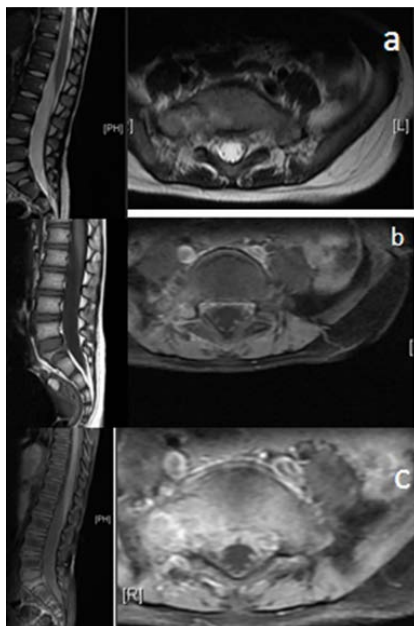
## CASE REPORT

### Case One

RA a 4 years old girl who is known for autistic disorder, presented with low back pain for one month with walking difficulty, and was admitted through the emergency room.

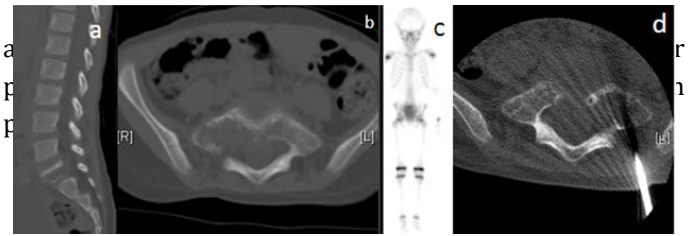
On physical examination she had stable vital signs; the neurological exam was grossly normal apart from unsteady gait.

X-ray showed the decreased vertebral height of the sacral first vertebra, MRI of LSS showed normal segmentation, preserved intervertebral discs seen throughout the vertebral column, compression of S1 body, with flattening, there was heterogeneous high signal intensity on both T1 and T2-weighted sequences with intense contrast enhancement. A small epidural component is also seen projecting into the spinal canal with no major compression (Figure 1).



**Figure 1. MRI of RA:** a) T2 images sagittal and axial, b) T1 sagittal and axial, C) T1 with contrast

CT scan showed destruction of the body of S1 with the decreased height of figure (2 a & b), Bone scan showed increased uptake in the S1 vertebra, with no other organ involvement figure (2c), CT guided biopsy was done by



**Figure 2. RA images:** a) Sagittal CT scan, b) Axial CT, c) Bone scan, d) CT guided biopsy

Diagnosis of single organ involvement was made, and shortly patient was started on LCH single organ protocol, she responded well and discharge home a few days later with a follow-up appointment, no spine intervention was recommended other than bracing as the patient was neurologically stable.

She was followed up by hematology-oncology and received frequent cycles of chemotherapy.

At the last follow up she was neurologically stable with no recurrence, and stable imaging studies.

### Case Two

EA a 3 years old male child was complying with low back pain without trauma, pain increased at night, and was treated by analgesic with no use, and referred to our spine clinic, according to the family there was no disturbance in walking or fever, past medical history was unremarkable, on physical examination he was neurologically intact, waking normally, mild tenderness at the lower back.

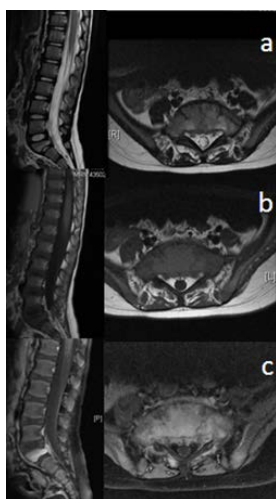
Lab tests were within normal, normal WBC count, and normal ESR.

Lumbosacral x-ray showed a destructive lesion of the sacrum with loss of vertebral height and sclerosis, figure (3 a), skeletal survey didn't demonstrate any other lesion in the skeleton.

The patient was admitted to the hospital for further investigation and management, MRI with contrast showed a lesion occupying S1 bright on T2 weighed images and dark on T1 weighed images and mixed stained with contrast no neurological compromise was seen, figure (4 a, b, and c), CT scan showed destruction of the body of the first sacral vertebra, posterior elements looks intact, Figure (3b and c), bone scan showed increase uptake in the body of S1 no other lesions.



**Figure 3. AA images:** a) lateral X-ray, b) CT scan sagittal images, c) CT scan Axial images



**Figure 4. AA MRI images:** a) T2 images sagittal and axial, b) T1 images sagittal and axial, c) T1 with contrast

Percutaneous biopsy was recommended and done 2 days later; the patient had an uneventful postoperative course, the brace was recommended, and the patient was discharged a few days later.

The pathology report showed large cell proliferation with eosinophilic cytoplasm, consistent with Histiocytosis.

The patient was evaluated by a pediatric hematologist, and reviewed by the tumor board; the recommendation was to treat him as single-site histiocytosis.

The patient followed up as an outpatient for two years and showed a stable lesion with no recurrence.

## DISCUSSION

The location and number of LCH lesions determine its clinical classification as well as morbidity and mortality potentials. Four distinct clinical forms are evident; isolated osseous, multiple osseous, isolated nonosseous and systemic forms, involvement of more than one system, spine involvement can happen in any of the three osseous forms.

In a cohort study consisted of 314 LCH patients diagnosed between 1946 and 1996, at Myoclinic, skull was the most frequent site of bone involvement ( $n = 94$ ), then proximal femur ( $n = 39$ ), spine ( $n = 38$ ) and ribs ( $n = 35$ ) (REF).

Other organ involvement also was found in 40% of patients,

skin was the commonest (26%), then pituitary gland (16%), and lung (14%).

The patient's age was less than 20 years in 42% (131), 114 had isolated osseous LCH, 96 had multisystem LCH and the remaining 104 had nonosseous single system LCH [3,5].

The distribution of lesions revealed a statistically significant difference among the cervical, thoracic, and lumbar spine regions. 5555 in one study, 96 vertebral lesions throughout the spinal column, were found in 76 patients. 49 lesions were found in the cervical spine, 32 in the thoracic spine, 13 in the lumbar spine, and 2 in the sacral spine (a 6 years old male with cervical and sacral lesions and a 7 years old female with thoracic and sacral lesions). The morbidity of the cervical spine was obviously higher than that of thoracic and lumbar spine [11]. LCH may be more aggressive, the lesions may look like a malignancy, which appear as bubbly and lytic lesions, and expand over the neural elements with a soft tissue mass as in our first case. The incidence of LCH of the spine in children with obvious soft tissue extension was up to 50% (9 of 18) patients. Chemotherapy is safe and effective, and surgical decompression was probably not necessary for most patients [12]. Furthermore, osseous lesions with adjacent soft tissue infiltration showed a relapse rate in excess of 80% ( $n = 20$ ) independent of the treatment applied. [13]. Spinal lesions typically involve the vertebral body; pedicular and posterior element involvement are less common. LCH in the spine may present as a lytic lesion or, alternatively, may present with abnormal flattening of the vertebral body. Extensive flattening of an entire vertebral body may assume a "coin on edge" appearance, known as vertebra plana. The intervertebral disc is normal or slightly widened [14]. LCH is typically "hot" on radionuclide bone scans, but can be normal. The extent of destructive lesions can be best defined by computed tomography (CT) scanning. Magnetic resonance imaging (MRI) scans of bone lesions show the lytic lesion with high T2 and low T1-weighted imaging that may break through the bone cortex. Bone marrow edema may extend beyond the boundary of the lytic lesion. The use of gadolinium contrast will demonstrate enhancement of the lesion and often soft tissue components. Sometimes extraosseous soft tissues next to the bone lesion will also have enhancement. The "activity" of lesions may be judged subjectively by MRI or positron emission tomography (PET) scanning [15]. PET scans were the most accurate method of detecting LCH lesions and showing response to therapy in tissues other than the spine where MRI scans were more helpful. Well-localized bone pain was the presenting symptom in 90% of osseous cases. This often was associated with a tender soft tissue swelling overlying the painful bone, and patients frequently were symptomatic both during daily activity and at rest [3]. Histologic diagnosis

is usually straightforward with the presence of Langerhans cells with eosinophilic cytoplasm, indistinct cell borders, and indented grooved (coffee bean shaped) nucleus admixed with inflammatory cells including large numbers of eosinophils. Langerhans cells stain for S-100, CD1a and langerin. Staining for CD1a and/or anti-langerin (CD207) is needed in order to confirm the diagnosis. Recently Badalian-Very et al [16] reported the presence of a canonical  $V600E$ -BRAF mutation in 57% of paraffin-embedded biopsies from LCH granuloma and very recently Satoh et al confirmed these findings and reported the identification of two more B-RAF mutations [17]. Electron microscopy to identify Birbeck granules is performed less frequently. Once the diagnosis is suspected, imaging is necessary to classify the bone involvement into the single or multifocal category. Additional imaging, such as computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI), may be useful depending on the site of the disease. The radionuclide bone scan is a complementary test to the skeletal survey because it can detect some lesions poorly visualized by radiography, and it has been proposed as a method of determining active disease [14]. Suspicion for the presence of extraskelatal sites of LCH requires further imaging. Treatment principles for vertebral LCH have been variable. Without neurologic deficit, authors trend to conservative treatment methods including simple observation, bracing immobilization, steroid, or radiation [a18] [8]. Some have advocated that immobilization and radiation are also appropriate in children with mild neurologic deficit [19]. Intralesional injection of glucocorticoids at the time of biopsy has been proposed as an effective and minimally invasive treatment of solitary lesions in the axial and appendicular skeleton, with the additional benefits of immediate pain control and improved range of motion [4,20]. The LCH lesions of the spine do not involve the endochondral ossification centers. Therefore, reconstitution of some degree of vertebral body height is possible. In patients with neurologic symptoms or unstable lesions, surgical fixation may be necessary [21]. However, there are a minority of patients who suffer this kind of disease with more severe neurologic deficits because of the spinal cord or cauda equina compression and there is no clear evidence to prove that neurologic status will stop deteriorating or improve with conservative treatment. Few studies focus on the surgical treatment of LCH. Lu et al studied the outcome of 12 pediatric patients with vertebral LCH complicated with neurologic deficit. The mean follow-up duration was 43.3 months. Neurologic function completely recovered in all 12 patients from 2 to 12 weeks after surgery [22]. In one study, one pediatric case was treated with posterior fusion because the patient was unlikely to comply

with activity restrictions and immobilization [21]. Systemic therapy with vinblastine and prednisone, not just local therapy or single-drug administration was proposed for patients with multifocal bone disease and those patients with disease at the base of the skull. Patients with CNS-risk lesions and those with the multifocal bone disease should be treated with six months of vinblastine and prednisone on the LCH-III protocol (Group 3). Radiation therapy is generally reserved only for lesions affecting vital structures and for lesions progressing following more conservative treatment [23]. The typical dose range is 6 to 12 Gy delivered at 2 Gy per fraction. However, radiation can damage remaining endochondral ossification centers and inhibit vertebral reconstruction, along with other secondary effects [20]. Douglas et al reported a high overall relapse rate (67%) after initial treatment, there were 211 relapses of 314 patients with significantly greater numbers of adults relapsed compared with children due to the predominance of adult patients with pulmonary LCH. The overall survival rate was 91.4%. After treatment, disease-free survival was ultimately achieved in 111 of the 114 patients (97%) with isolated osseous LCH and 169 patients (90%) with multiple osseous LCH. Nine of the 80 patients with isolated solitary bone lesions had osseous recurrence (local recurrence in four patients and an additional site in five patients), requiring further treatment before achieving disease-free survival. Eight of these patients originally were treated with surgical excision, and, after relapse, seven of them had additional treatment with radiation therapy, and one underwent additional surgery. The remaining patient was treated originally with radiation therapy and, after relapse, had additional radiation therapy. Although relapse occurred in 9 of 26 patients >20 years of age with solitary lesions, all were salvaged, and disease and/or relapse-free survival ultimately was achieved in all 80 patients with solitary bone lesions. Significantly fewer deaths occurred in patients with isolated osseous LCH compared with patients with osseous LCH that also involved other systems (1 of 114 patients vs. 5 of 74 patients;  $P = 0.018$ ; 95% CI, 0.12 and 0). Similarly, deaths in patients with isolated osseous LCH were significantly less frequent compared with patients with the multisystemic disease (1 of 114 patients vs. 11 of 96 patients;  $P < 0.003$ ; 95% CI, 0.17 and 0.04) [3].

## CONCLUSIONS

LCH of the spine is rare. The sacrum is an unusual site of these lesions, only a few cases were reported in the literature. Patients with isolated osseous LCH lesions have an excellent prognosis relative to those with multiple or systemic involvements. The perineural inflammatory process, characterizing this tumor, can cause neurological manifestations that may be managed conservatively



by chemotherapy unless there are substantial neural compression or stability issues where surgical intervention may be required. LCH location and number of lesions determine its mortality/morbidity potentials.

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