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Langerhans Cell Histiocytosis of the Spine in a Child: A Rare Case and a Diagnostic Dilemma

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Abstract

Introduction: Langerhans cell histiocytosis (LCH) comprises a rare spectrum of disorders characterized by abnormal proliferation of histiocytes. Lesions may be limited to a single system, or present as disseminated disease, with subsequent worse prognosis. Radiologic findings for spinal LCH are non-specific however and must be carefully differentiated from Pott's disease (spinal tuberculosis, or [TB]) in endemic countries.

Case Report: An 8-year-old female was brought for consult due to back pain and compression deformity on plain radiographs, unaccompanied by constitutional symptoms. Computed tomography (CT) scan of the thoracic spine was done, which showed osteolysis of the T11 vertebra and paravertebral soft-tissue extension. Findings were deemed suggestive of tuberculous spondylitis, and CT-guided biopsy was performed for confirmation. Acid-fast Bacilli smears as well as Gram stains were negative. While waiting for definitive results, the patient was started on an empiric treatment regimen for TB. Final tissue and fluid cultures were negative for Mycobacterium tuberculosis, as were Gene Xpert and TB polymerase chain reaction studies. Histopathologic analysis showed atypical mononuclear histiocytes surrounded by inflammatory cells, suggestive of LCH. At present, the patient is 2 years post-biopsy, with stable lesions and no evidence of multi-system involvement.

Conclusion: In the setting of a spinal lesion in a child with a benign clinical history and no other pertinent laboratory findings, histopathologic analysis constitutes the gold standard in differentiating non-specific features of LCH from spinal TB. Both conditions necessitate long-term follow-up, due to the risk of progression, deformities, and neurologic sequelae.

Keywords: Langerhans cell histiocytosis, pediatric spine, Pott's disease, tuberculosis, vertebra plana.

Introduction

Langerhans cell histiocytosis (LCH) comprises a rare spectrum of disorders characterized by abnormal proliferation of histiocytes. Among children, its annual incidence ranges from $2.2/10^6$ to $8.9/10^6$ [1, 2, 3]. Granulomatous lesions filled with antigen-presenting dendritic cells called Langerhans cells give LCH its name and can affect any system. The exact cause for clonal proliferation of histiocytes and its occurrence in the setting of chronic inflammation remains unknown [3]. Osseous involvement is noted in up to 80% of LCH cases, with spinal lesions accounting for as much as 25% [2]. Among pediatric patients, the incidence of spinal LCH ranges from 6.5% to 25%, with a majority affecting children <10 years old. Pain is the most common presenting symptom, and the thoracic vertebrae are the most frequently affected [4, 5].

While characteristic, radiologic features of spinal LCH are non-specific and are often misdiagnosed as fractures, malignancies, or sequela of an infectious process such as tuberculosis (TB) [4, 5, 6]. Of special relevance in a highly endemic country such as the Philippines is the high incidence of spinal TB, or Pott's disease. If left undetected, granulomatous infection of the spine caused by Mycobacterium tuberculosis may rapidly progress and cause severe neurologic as well as cardio-pulmonary symptoms, disfiguring deformities, and drug-resistant osteomyelitis [7].

Performing a biopsy of the spinal lesion constitutes the gold standard in differentiating LCH from spinal TB infection. Both conditions necessitate long-term follow-up, due to the risk for progression and possibility of neurologic sequelae. If left undetected or inappropriately treated, Pott's disease, and spinal LCH may both lead to disastrous consequences, particularly for a developing child.

We sought to describe a rare case of LCH of the spine in an 8-year-old female, initially diagnosed with spinal TB, or Pott's disease. Presenting symptoms were back pain and compression deformity on plain radiographs, without constitutional symptoms. This non-specific clinical picture led to our diagnostic dilemma, emphasizing the importance of a multi-disciplinary approach to diagnosis. The ensuing work-up and outcomes will be discussed, as well as the patient's current status and plan for management.

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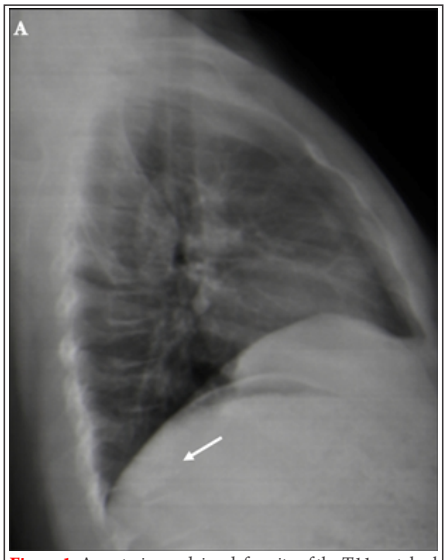

Figure 1: An anterior wedging deformity of the T11 vertebral body is demonstrated on lateral view of the thoracic spine radiograph (arrow).

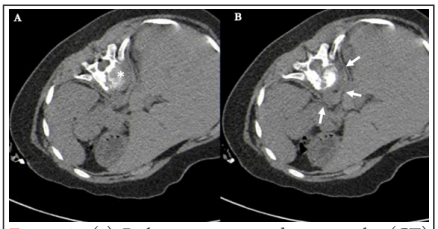

Figure 2: (a) Preliminary computed tomography (CT) scanning of the chest showed a fairly defined paravertebral soft-tissue mass at the level of the T11 vertebral body (*, showing osteolysis without involvement of posterior elements). (b) Under CT guidance, gauge 22 spinal and gauge 18 core biopsy needles were used to access the lesion in the right paraspinal region (arrows along periphery).

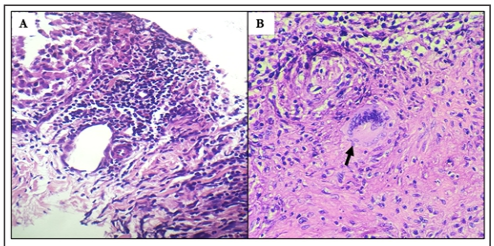

Figure 3: (a) Histopathologic specimen from patient showing histiocytes surrounded by lymphocytes, eosinophils, and fibroblasts, consistent with histologic appearance of Langerhans cell histiocytosis. (b) Photomicrograph of a representative tuberculous lesion showing chronic granulomatous inflammation, caseation necrosis and Langhans' type giant cell (arrow).

Case Report

An 8-year-old female was referred for pediatric orthopedic assessment due to back pain. One month before consult, the patient sustained mild, direct trauma to her posterior mid-thoracic area during Taekwondo practice. No sensory or motor deficits were noted after the incident, and she remained ambulatory. The patient, however, reported persistent pain localized over the same area, unaccompanied by fever, weight loss, or night sweats.

She was brought for consult with her pediatrician, who prescribed oral anti-inflammatory pain medications. A lack of improvement despite compliance and rest prompted referral to a pediatric orthopedic surgeon. Laboratory exams were done on initial consult, which revealed normal inflammatory markers (both erythrocyte sedimentation rate and C-reactive protein) as well as blood parameters.

Following initial assessment, chest and whole spine radiographs were requested, which revealed anterior wedging of the T11 vertebral body (Fig. 1). Evidence of a previous pulmonary infection was absent on chest radiograph. A computed tomography (CT) scan of the thoracic spine with contrast was performed, which revealed osteolytic destruction of the T11 vertebral body, with surrounding paravertebral soft-tissue swelling (Fig. 2a, b). Results were signed out as suggestive of tuberculous spondylitis, prompting a request for CT-guided biopsy. Specimens were then sent for extensive microbiologic and histopathologic analyses. Initial results revealed negative acid-fast Bacilli smears as well as Gram stains, and the patient was sent home a day after the procedure, following an unremarkable course during admission. While waiting for definitive results, the patient was started on an empiric "TB directly observed treatment" (TB DOT) regimen by the pediatric service.

Six weeks after discharge, the patient's tissue and cerebrospinal fluid cultures were found to be negative for M. tuberculosis, and no growth of anaerobic and fungal organisms was reported. Gene Xpert and TB polymerase chain reaction (PCR) studies were likewise negative. Final histopathologic analysis revealed inflammatory cells with fibroblasts and histiocytes, suggestive of LCH (Fig. 3a). Additional analyses have been advised but remain to be completed due to logistic constraints. The ongoing TB DOT regimen was discontinued, and the lesions have remained stable without further medical or surgical intervention. The parents were well-advised regarding regular follow-up to monitor for neurologic symptoms. At present, the patient is 2 years post-diagnosis, with stable lesions and no evidence of multi-system involvement.

Table 1: Characteristic features of spinal tuberculosis and Langerhans cell histiocytosis

	Spinal tuberculosis	Langerhans cell histiocytosis
Pain as chief complaint	May be present with or without constitutional symptoms/deformity	May be present with or without constitutional symptoms
Extent of involvement	Single system presentation possible	Single system disease is sub-type
Radiologic appearance	Osteolytic vertebral body destruction beginning at anterior cortex, causing wedge deformity or collapse	Osteolytic vertebral body destruction typically presenting as vertebra plana in children
Histologic appearance	Multinucleated Langhans' giant cells, caseation necrosis and predominantly lymphocytic infiltrates	Atypical Langerhans cell histiocytes with single, large, and ovoid nucleus surrounded by inflammatory infiltrates

Discussion

LCH comprises a rare spectrum of disorders characterized by abnormal proliferation of histiocytes. While more prevalent in the pediatric population, its overall incidence is rare, ranging from $2.2/10^6$ to $8.9/10^6$ children annually [1, 2, 3]. Osseous involvement develops in approximately 80% of cases, with the spine accounting for 7–25% of cases [2]. Among pediatric patients, the incidence of spinal LCH ranges from 6.5% to 25%, with 80% of these occurring in children <10 years old. The most common symptom related to these lesions is localized pain [5]. This presentation is consistent with the demographics and clinical picture seen in our 8-year-old patient.

Three disease entities comprise the spectrum of LCH, from least to most disseminated: Eosinophilic Granuloma (EG), Hand-Schüller-Christian Syndrome (HSCS), and Letterer-Siwe Disease (LSD). EG typically affects children between 5 and 15 years old, with unifocal or multifocal lesions limited to the skeletal system. It is both the most common and least aggressive among the LCH subtypes, following a benign course with minimal sequelae. HSCS is more often seen among children 1–5 years old, involving the reticuloendothelial system and comprising 20% of all LCH cases [8, 9]. In approximately 15% of patients, the triad of cranial lesions, diabetes insipidus, and exophthalmos may be found, and mortality

may be as high as 15%. LSD represents the disseminated form of LCH, affecting children younger than 2 years and following a more fulminant course. Occurring in 10% of all LCH patients, this rapidly progressive variant is associated with early morbidity and significant mortality [8, 9, 10]. Among these disorders, our patient's clinical presentation appears to be most consistent with that of EG. While paravertebral soft-tissue extension was noted adjacent to the affected thoracic vertebra, the patient's laboratory examinations revealed normal blood parameters, liver enzymes, and kidney function. No dermatologic lesions were observed and the patient was otherwise at par for age in terms of developmental history.

Lesions affecting the skull, pelvis, and ribs account for over 50% of all skeletal LCH. Approximately 30% may be found in the long bones and spine. Spinal lesions most commonly affect the vertebral body at the thoracic level [4, 5, 10], as in the case of our patient. The characteristic radiographic features seen in LCH of the spine are vertebral collapse with flattening of the vertebral body, termed "vertebra plana," and to a lesser extent, anterior wedging deformities [5, 9]. While typical, these features are by no means specific: Among the most common causes of vertebral body collapse in children are hematologic malignancies and spinal TB [9, 10].

According to statistics from the national TB prevalence survey, the prevalence of culture-positive M. tuberculosis cases in the Philippines increased from 4.7/1000 in 2007 to 10.6/1000 in 2016. This is the highest percentage ever reported among the four most recent national surveys (1983, 1997, 2007, and 2016) [11]. While only 10% of patients with extrapulmonary TB have skeletal involvement, close to 50% of these cases affect the spine, more commonly known as Pott's disease [7, 12]. The absence of a previous pulmonary infection in a child's history does not rule out the possibility of developing spinal TB, particularly in an endemic country such as the Philippines [7, 13].

The vascular nature of the intervertebral disc in pediatric patients makes the spine particularly susceptible to infection by an obligate aerobe such as M. tuberculosis. Lesions of Pott's disease typically involve the anterior portion of the vertebral body, causing progressive bone destruction. If left undetected or untreated, this may lead to vertebral collapse or wedge deformities, abscess formation, and eventual complications such as severe kyphotic deformities, neurologic compromise, and spinal cord compression [13]. Prompt and accurate diagnosis is imperative, because the consequences of uncontrolled spinal TB can be catastrophic in a growing child [12].

In countries endemic for TB infection therefore, Pott's disease must be carefully differentiated from osteolysis secondary to LCH. Both conditions are often mistaken for the other: In a series of 18 patients pathologically-confirmed to have spinal LCH by Peng et al. [5] Every case was initially misdiagnosed as either TB or secondary to a neoplasm, before final diagnosis of LCH was confirmed through biopsy. This led to treatment delays, with two patients undergoing TB antibiotic regimens for 2 weeks before correct diagnosis was made. Other authors have likewise reported similar cases of "mistaken identity" before histopathologic confirmation, due to various similarities [2, 5, 6, 7] (Table 1).

A similar progression of events was noted for our patient, with a TB DOTS regimen initiated by the pediatric service while waiting for initial cultures and TB-specific workup. The absence of vertebra plana in our patient's spine radiographs, which is more typical of LCH, together with the high local prevalence of TB, led to the team's initial consideration of Pott's disease.

Distinguishing spinal TB from LCH may be difficult based on clinical and radiologic findings alone. A tissue biopsy, therefore, is key to making a definitive diagnosis, particularly because cultures are not always positive even in cases of active infection (Fig. 3a and b).

The gold standard for diagnosis of both conditions is through histopathologic confirmation, with immunohistochemical staining and/or electron microscopy recommended for LCH [2, 8]. Amplification of DNA using TB-PCR is a useful adjunct to facilitate an accurate diagnosis of Pott's disease [13]. In the case presented, both TB-PCR and Gene Xpert studies were negative, as were all cultures at the end of 6 weeks. Histology revealed histiocytes in the setting of chronic inflammation, and the absence of Langhans giant cells/caseous necrosis that would have been more typical of granulomatous infection secondary to M. tuberculosis (Fig. 3b). Positive CD1a and/or CD207 (also known as Langerin) staining of lesional cells is necessary for definitive diagnosis, but the Histiocyte Society has acknowledged the challenge of confirmation for some specimens where Birbeck granules may not be present, and immunohistochemical stains may still be negative despite adequate sampling due to cellular regression [8]. In addition, local health-care service delivery concerns such as limited finances, the lack of available facilities, and inconsistent follow-up often remain barriers to a full diagnostic workup that complies with international standards. These issues are all present in our patient's case and can in fact be found in every locally-published case report and case series on LCH [6, 14, 15, 16, 17].

Like spinal TB, LCH can present as a single system disease (SS-LCH), limited only to one organ system, or may involve two or more organ systems, and manifest as multi-system disease (MS-LCH). Children with SS disease may present with little to no symptoms and as many as 60% survive without long-term sequelae. In contrast, as few as 30% of patients diagnosed with MS disease were reported to be alive and free of complications at long-term follow-up, with neurologic deficits, secondary malignancies, and respiratory dysfunction among the reported negative outcomes [3, 8]. Our patient was diagnosed with single-system disease affecting the thoracic spine in July of 2018. In accordance with Histiocyte Society recommendations, serial whole-spine radiographs are planned at 6 months post-diagnosis, to be adjusted thereafter depending on clinical findings.

The goals of treatment for Pott's disease and spinal LCH are similar: To control the causative lesion or organism, preserve neurologic function, ensure stability of the spine, and prevent deformity. While a universally-accepted protocol for management is available for spinal TB, the etiology and clinical course of spinal LCH remain uncertain, and no standard treatment regimen exists [2, 3, 11, 12, 13].

Some authors have reported a self-limiting course for SS-LCH and single-level spine involvement, with no further intervention necessary other than close follow-up. Conservative treatment does not invariably

lead to good results, however, due to the unpredictable nature of this condition: As many as 30% of patients eventually develop multisystem disease, while soft-tissue extension of single-level lesions may be seen in as much as 50% [2, 3, 8, 5]. On diagnosis, our 8-year-old patient had evidence of osseous lesions affecting the thoracic spine, with paraspinal soft-tissue extension. Similar to current recommendations for MS-LCH, a more favorable prognosis has been reported following systemic chemotherapy in this subgroup of patients. It must be emphasized, however, that retrospective studies on both spinal LCH with soft-tissue extension and MS disease have observed a higher likelihood of surgical intervention or radiation therapy for both groups [2, 5, 12].

Conclusion

For a patient presenting with a non-specific clinical picture leading to a diagnostic dilemma, a high index of suspicion is imperative to arrive at an accurate assessment and holistic treatment plan. Differentiating spinal TB from LCH depends on a multidisciplinary approach to work-up and definitive histopathologic findings. Characteristic radiographic features of LCH of the spine are vertebral collapse secondary to osteolysis, most commonly presenting as flattening of the vertebral body, or vertebra plana. Up to 50% of cases may be associated with para-spinal soft-tissue extension, as seen in our patient. These imaging findings are similar to typical radiographic presentation of spinal TB, which include vertebral body involvement, well-defined areas of osteolytic bone destruction, and compression deformities. In the setting of vertebral body involvement with a benign clinical history and no other pertinent laboratory findings, performing a tissue biopsy serves as the gold standard to differentiate LCH from Pott's disease.

While a universally accepted treatment protocol exists for Pott's disease, the etiology and clinical course of spinal LCH remain uncertain, and no standard regimen for intervention has been determined. Both conditions necessitate long-term follow-up, due to high propensity for progression, subsequent deformities, and the risk of neurologic sequelae. If undetected or left untreated, both conditions can lead to disastrous consequences for a developing child. Early detection with a multidisciplinary approach to management is key to minimizing morbidity and preventing future complications.

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