

Clinical Quiz

Adult case of Langerhans Cell Histiocytosis with single site vertebral involvement

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Case

A 35-years-old male was referred to our Hospital due to dull and deep nocturnal upper lumbar pain which was related to a lytic lesion of the L1 vertebral body. A recent attempt for needle biopsy of the lesion was inconclusive; however, a malignant disease could not be excluded. The patient denied pain in other sites, had no fever or night sweats, and could not recall any recent injury. His pain had an insidious onset approximately 5 months ago, and was progressively deteriorating. Past medical history was unremarkable for trauma or other bone disease. He was currently smoking (12 packet years) and had a family history of coronary heart disease. Physical examination was unremarkable except for slight right postural scoliosis and localized tenderness over the L1 spinous process. The patient underwent a complete radiological investigation including CT and MRI scan of the lumbar spine (Figures 1, 2). Laboratory investigation was also performed and revealed no abnormal findings. Based on the imaging findings, the differential diagnosis included Langerhans Cell Histiocytosis (LCH), lymphoma and Ewing's sarcoma. The patient consented to an open biopsy and curettage of the lesion. The lesion was located in the posterior part of L1 body between the pedicles and was approached through a left L1-L2 facetectomy (Figure 1C). A brownish-yellow and fragile granular mass was removed and the lesion bed was treated with curettage and alcohol. Postoperative spinal instability was treated with posterolateral T12-L2 fusion with autologous bone graft and

transpedicular instrumentation. The patient had an uneventful recovery and histological examination confirmed the diagnosis of LCH. In face of LCH diagnosis, further diagnostic evaluation included a complete skeletal survey, pulmonary function testing and CT of the lungs, pituitary hormonal evaluation and pituitary MRI, and abdominal ultrasound evaluation. No other LCH infiltration was found, and the patient was handled as suffering from single-system and single-site disease requiring no further treatment. Solid fusion was evident radiologically at 3 months postoperatively, and the patient returned free of symptoms to his every day activities at 6 months. At 2 years follow-up, the patient remains disease and symptoms-free.

Commentary

LCH is a rare disease of unknown etiology with a rather unpredictable course since it can spontaneously resolve or progress to a disseminated form, compromising vital functions with occasionally fatal consequences¹. It is characterized by the clonal accumulation and/or proliferation of specific dendritic cells that resemble the normal epidermal Langerhans Cell (LC) and can virtually infiltrate any organ¹. Since the cell of origin in this disease is now clearly defined, the term LCH should substitute all the previously used terms, such as histiocytosis X, eosinophilic granuloma, Hand-Schuller-Christian disease and Letterer-Siwe disease. Among children it occurs at a peak age range of 1-3 years, with an annual incidence of 3-5 cases per million and a male to female ratio of 2:1. In adults the disease is rare, with an estimated prevalence of 1-2 cases per million/year; the mean age at diagnosis is 33 years, and it is regarded as an "orphan disease" due to its rarity and paucity of dedicated physicians dealing with different disease manifestations^{2,3}. Although it is a clonal disorder, LCH also exhibits inflammatory features such as altered expression of cytokines and cellular adhesion molecules important for the migration and homing of LCs¹.

A biopsy from a lesion is mandatory in establishing the presence of the disease and the recently developed histopathological diagnostic criteria require the expression of CD1a antigen on

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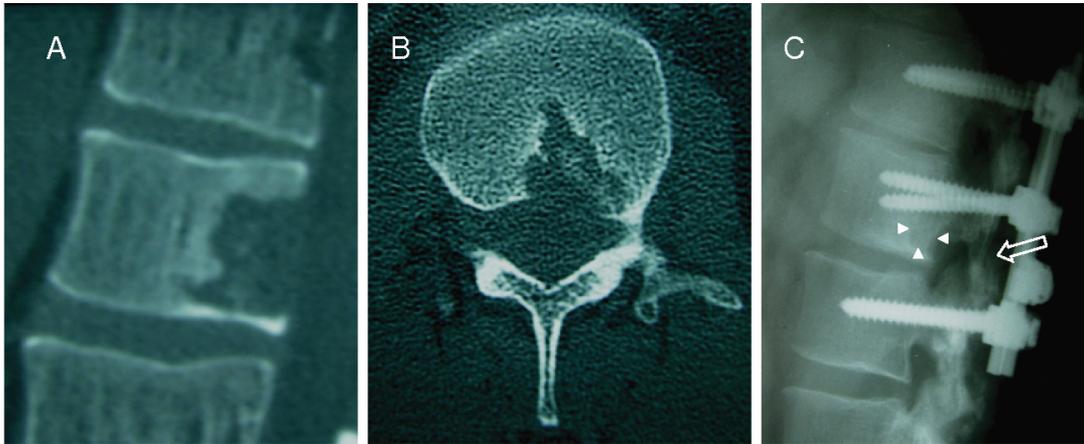


Figure 1. Sagittal (A) and axial (B) CT images showing a lytic lesion with a narrow transition zone and minimal sclerotic changes. (C): Postop X-ray showing the lesion area (arrowheads) and the missing facet joint (arrow) that was managed by spinal fusion.



Figure 2. Sagittal T1 (A), T1 Gd (B) and STIR (C) MRI pictures depicting an enhancing lesion poorly accompanied by extensive bone marrow edema at the posterior half of L1 vertebral body.

the lesional cell surface for “definitive diagnosis”². The natural course of the disease appears to differ among children and adults; involvement of bone, lung, skin and diabetes insipidus (DI) usually predominates in adults, whereas lymph nodes, liver, spleen, bone and bone marrow involvement are among the most common manifestations in children⁴. LCH should be stratified according to system involvement as being either a single-system or multisystem disease². Single-system disease can be further subdivided into single-site (e.g. single bone lesion, isolated skin disease, solitary lymph node) and multiple-site disease (multiple bone lesions, multiple lymph node involvement). This is very crucial for the management of the disease, since single-system disease may require no treatment and is usually associated with a good prognosis, while multisystem

disease includes multiple organ involvement, with or without dysfunction, and always requires several treatment modalities. Multisystem LCH is associated with a 20% mortality rate, while 50% of survivors develop at least one permanent sequela⁴. LCH is a chronic disease with long term follow-up which requires the evaluation of the disease’s state at regular intervals. Permanent sequelae (DI, endocrine deficiencies from anterior pituitary involvement) and/or radiological abnormalities may be evident for decades even in “burned out” disease⁴. Therefore, the disease’s state should be considered as “active”, and probably requiring further treatment modalities, only among patients with progression of disease-related signs or symptoms with or without the appearance of new lesions⁴.

One of the most frequent presenting features in adults, like

our patient, is skeletal involvement, with the classic appearance being that of a lytic lesion, although osteoblastic lesions can occasionally develop^{1,5}. The majority of the lesions are asymptomatic but can also present as a painful swelling⁵. Adjacent soft tissue swelling and ulceration of the overlying skin or mucosa can also be found, mimicking inflammation processes such as osteomyelitis^{1,5}. Pathological fractures may occur in weight-bearing long bones or compressed and infiltrated vertebrae^{1,5}. “Vertebra plana” appearance of collapsed vertebral body is one of the characteristic radiographic findings. Involvement of posterior vertebral elements is rare and the disk space is usually preserved. A paraspinal soft tissue mass may be present. Most frequently involved is the thoracic spine, followed by the lumbar and cervical regions. Especially in vertebral lesions, like the one of our patient, the differential diagnosis must include Ewing sarcoma, osteomyelitis, leukaemia, lymphoma, aneurysmatic cyst, juvenile xanthogranuloma, multiple myeloma, and osteoporotic fractures. Multiple bone lesions and/or multiorgan involvement carry a seven- to twelve-fold risk of LCH reactivation in bone following the initial treatment, in comparison with patients with single bone lesions. Radionuclide bone scan with ^{99m} technetium might not be as sensitive as skeletal plain radiology (x-rays) in most patients^{1,3,5} while T2 MR images show high signal lesions. Complete evaluation of the skeleton requires a whole body skeletal survey with plain x-rays. LCH lesions usually appear as well-defined osteolytic areas with or without periosteal reaction that may frequently resemble malignancy. The presence of a surrounding sclerotic ‘halo’ is indicative for the initiation of the healing process¹.

Up-to-date there is no specific treatment for the disease but administration of glucocorticoids and various chemotherapeutic compounds have been used and are currently incorporated in several therapeutic schemes proposed by the Histiocyte Society (www.histiocytesociety.org). Among adults, the standard therapeutic approach is yet to be defined². In single system/site, non-CNS related

disease, bone lesion’s curettage of the infiltrated site or an intraleisional steroid injection might prove as an adequate therapy¹. This was the case in our patient who remains disease-free two years later. However, most of adult cases with multisystem disease are initially treated with vinblastine and steroids². Recent reports have shown that treatment with 2-chlorodeoxyadenosine with or without cytarabine (Ara-C) can be effective in adults with recurrent and/or disseminated disease involving bones, skin, lymph nodes, lungs and CNS. Intravenously administered bisphosphonates (zoledronate, pamidronate) have been also used successfully in several cases with osteolytic bone lesions, either as principal or adjuvant therapy.

In conclusion, LCH should be included in the differential diagnosis of osteolytic and osteoblastic vertebral lesions. Although some radiological characteristics may suggest the disease, histopathological confirmation is mandatory in order to establish the diagnosis while patient’s management requires a complete evaluation to define the state and extent of the disease.

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Questions

1. Diagnosis of LCH in adults can be made by:

- A. The characteristic radiological findings.
- B. The expression of CD1a antigen on the lesional cells following a relevant biopsy.
- C. The co-existence of a characteristic involvement (bone, lungs, etc) and Diabetes Insipidus (DI).

Critique

LCH can not be safely diagnosed solely from the radiological findings. Although the presence of DI in addition with a typical LCH lesion may strongly suggest the diagnosis, this should be always confirmed with a biopsy from the lesion

The correct answer is B.

2. In adult patients previously treated with chemotherapy for LCH, the decision for an additional therapeutic modality requires:

- A. The presence of radiological abnormalities without any change through long term follow-up.
- B. Persistence of disease’s sequelae (e.g. DI, endocrine abnormalities).
- C. Active disease.

Critique

LCH should be only treated in active disease. Permanent sequelae almost never subside even in quiescent or “burned out” disease. This is also the case in several radiological abnormalities which usually present sclerotic in inactive cases especially among adult patients.

The correct answer is C.