Multifocal Osseous Tuberculosis Mimicking Langerhans’ Cell Histiocytosis: A Case Series

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Abstract

Langerhans cell histiocytosis (LCH) is a common cause of multifocal lytic skeletal lesions in children. However, multifocal osseous tuberculosis can affect children and mimics LCH on imaging, especially in endemic regions. We report cases with atypical manifestations of multifocal osseous tuberculosis which were presumptively diagnosed as LCH. The findings of our series of cases suggest that on computed tomography (CT) irregular sclerotic margins, abscess formation, sclerosis of involved bone, and button sequestrum point toward a diagnosis of multifocal osseous tuberculosis, especially in endemic regions.

Introduction

Several etiologies present with aggressive multiple lytic skeletal lesions in children with overlapping clinical features such as fever and pain in extremities. These include tumors such as Langerhans’ cell histiocytosis (LCH), lymphoma/leukemia, metastatic neuroblastoma, Ewing’s sarcoma family of tumors, enchondromatosis, as well as infectious processes such as tubercular osteomyelitis. Among the gamut causes of multifocal skeletal lytic lesions, common diseases which present with multiorgan system involvement are LCH, lymphoma/leukemia, and disseminated tubercular infection. Tuberculosis is endemic in developing countries with varied manifestations. Disseminated disease and skeletal involvement is less common overall but is often seen in immunocompromised patients or young children and accounts for approximately 4 to 5% of extrapulmonary tuberculosis.¹ Multifocal bone involvement occurs in approximately 10% patients with skeletal tuberculosis.² Such multifocal forms of tuberculosis in young children are commonly misdiagnosed as LCH because of similar clinical and radiological manifestations. Pathological confirmation is often required for diagnosis. In this case series, we intend to report the radiological findings which may help in resolving the diagnostic dilemma between tuberculosis and LCH.

Case Reports

Case 1

An 8-year-old girl presented with on and off skin rash for 11 months, lower back, and neck pain for 8 months. On physical examination, there was tenderness in the lower back.
Patient reported to our hospital pediatric oncologic clinic. Initial laboratory investigations revealed mildly elevated erythrocyte sedimentation rate (ESR) and normal leukocyte counts. Mantoux test was negative. Chest radiography was normal. Skeletal survey showed multiple lytic lesions involving the right parietal bone (Fig. 1A), multiple vertebral bodies with collapsed third cervical (C3) vertebra; possibilities of LCH, tuberculosis, and metastasis were considered. Contrast-enhanced computed tomography (CT) of chest and abdomen revealed vertebra plana with sclerosis of C3 vertebra, wedge collapse of sixth dorsal (D6) vertebra, small lytic lesions with surrounding sclerosis involving second, fifth lumbar (L2, L5; Figure 1B), and first sacral (S1) vertebrae.

Pathological evaluation of L2 vertebral body biopsy did not show any atypical cells. Immunohistochemistry for CDla was negative. A clinicoradiological diagnosis of tuberculosis was considered and patient was started on antitubercular drugs. Patient had symptomatic improvement on follow-up.

Case 2
A 7-month-old boy presented with complaints of fever and abdominal distension for 1 month. Physical examination revealed hepatosplenomegaly and few tender scalp swellings. Anemia, leucocytosis with predominant lymphocytes, and elevated ESR was noted. Gene expert from the gastric aspirate was negative. A clinicoradiological diagnosis of tuberculosis was considered and patient was started on antitubercular drugs. Patient had symptomatic improvement on follow-up.

Case 3
A 3-year-old boy presented with discharging sinus involving the right upper eyelid, scalp swellings, fever, and pus discharge from the right ear for the duration of 10 months. Local examination revealed tender scalp swellings and few enlarged cervical lymph nodes. Laboratory examinations suggested mild anemia (hemoglobin: 8.4 g/L). Gene expert from the gastric aspirate was negative. Lactate dehydrogenase (LDH) was within normal limits.

Skeletal survey was performed initially which showed multiple lytic lesions with sclerotic margins in the frontal, parietal, and temporal bones (Fig. 2A). Following this, contrast-enhanced CT of chest and abdomen was performed on which lytic lesions involving dorsal vertebral bodies (Fig. 2B) and manubrium sterni were noted. Multiple necrotic mediastinal lymph nodes were also seen (Fig. 2C). In addition, there was consolidation with nodules in bilateral lungs and hepatosplenomegaly with multiple hypodense parenchymal lesions. Pathological evaluation with ultrasound-guided fine-needle aspiration and cytology (FNAC) from scalp swelling showed necrotizing epithelioid cell granulomas and acid fast bacilli (Fig. 2D and E). Diagnosis of disseminated tuberculosis with multifocal skeletal and extraskeletal involvement was made in this case.

Patient was started on category-I antitubercular drugs. Clinical and radiological improvement was seen during follow-up.
adjacent soft tissue component. CT chest and abdomen showed enlarged mediastinal and periportal lymph nodes in addition to multifocal lytic skeletal lesions (►Fig. 3D). Consolidation in bilateral lungs and hepatosplenomegaly was also noted. Based on the clinical and imaging findings, LCH or disseminated tuberculosis was considered.

Cervical lymph node biopsy evaluation showed multiple necrotizing epithelioid cell granulomas compatible with tuberculosis (►Fig. 3E). Patient was started on category-I antitubercular drugs. During follow-up, symptomatic improvement was seen, as well as healing of bone lesions was also noted (►Fig. 3F).

Clinical details and laboratory and radiological findings are summarized in ►Tables 1–3.

Discussion
Among the varied causes of multifocal osteolytic lesions in young children, LCH is the commonest. However, especially in endemic regions, the presentation may overlap with disseminated forms of tuberculosis. All children in our series had lytic lesions in skull and variable involvement of other extraskeletal sites. Primary calvarial tubercular lesions are very rare and has been described in 0.2 to 1.3% cases of skeletal tuberculosis.3 Three types of calvarial tubercular lesions are described depending on pattern of destruction as follows: (1) circumscribed lytic, (2) circumscribed sclerotic, and (3) diffuse forms.4 Frontal and parietal bones are often affected in tuberculosis and show involvement of both inner and outer table with sclerosis and/or abscess formation. Button sequestrum (as seen in case 3), though a nonspecific finding, has classically been described in osteomyelitis.

Tubercular spondylitis is the most common manifestation of musculoskeletal tuberculosis. Lower dorsal and lumbar vertebrae are commonly involved. Patterns of involvement can be paradoxic, central, anterior marginal, posterior, skipped lesions, and synovial.5 In central lesions, disc is not involved and vertebral collapse can lead to vertebra plana (seen in case 1). Noncontiguous, multifocal, and posterior element involvement, as well as vertebra plana are atypical manifestations of spinal tuberculosis (seen in cases 1 and 2) in children. These imaging features often leads to consideration of other diagnosis such as LCH.

Apart from skull and vertebrae, scapula, and ilium are rarely involved in tubercular osteomyelitis (seen in case 3).6 Rib Singh, et al: Multifocal osseous tuberculosis mimicking Langerhans cell histiocytosis a case series and sternal involvement is also rare and accounts for 1 to 2% cases of musculoskeletal tuberculosis (seen in cases 2 and 3).7

Regarding the pattern of bone involvement, tuberculosis manifests as a well-defined lytic lesion with sclerosis and may show central SEQUEST. Soft-tissue abscesses may also be formed.

Imaging findings of extramusculoskeletal sites of involvement in tuberculosis and LCH may work as problem-solving tools to resolve the diagnostic dilemma. Thoracic involvement is the most common manifestation of tuberculosis. It manifests as mediastinal lymphadenopathy, parenchymal consolidations/nodules, and pleural effusion (seen in our cases 2 and 3). Abdominal lymphadenopathy is also common in tuberculosis. Hepatic and splenic tubercular involvement can be micronodular or macronodular; micronodular form being common.
### Table 1  Clinical details and laboratory findings

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| Age    | 8 years| 7 months | 3 years |
| Gender | Female | Male | Male |
| Presenting complaints | Skin rash | Fever | Right upper eyelid discharging |
|                     | Lower back, neck pain | Abdominal distension | sinus |
|                     |                   |              | Fever |
|                     |                   |              | Right ear discharging pus |
|                     |                   |              | Scalp swelling |
| Physical examination | Lower back tenderness | Few tender scalp swellings | Tender scalp swellings |
|                     |                   |              | Hepatosplenomegaly |
|                     |                   |              | Cervical lymphadenopathy |
| Laboratory tests | Mildly elevated ESR | Mild anemia | Mild anemia |
|                   |                   | Leukocytosis | Gene expert: negative |
|                   |                   | Elevating ESR | LDH: normal |

Abbreviations: ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

### Table 2  Osseous radiological findings

| Site of involvement | Case 1 | Case 2 | Case 3 |
|---------------------|--------|--------|--------|
| Radiological        | Skeletal survey, CECT chest, and abdomen | Skeletal survey, CECT chest, and abdomen | Skeletal survey, CECT head, chest, and abdomen |
| Investigations      |        |        |        |
| Skull lesions       |        |        |        |
| Location            | Parietal bone | Frontal, parietal, temporal, bones | Zygomatic process, temporal, clivus, pterygoid plate, parietal bone |
| Number              | Multiple | Multiple | Multiple |
| Shape               | Irregular | Rounded | Rounded |
| Margin              | Irregular | Circumscribed | Irregular |
| Sclerosis           | Absent | Present | Present |
| Button sequestrum   | Absent | Absent | Present |
| Vertebral lesions   |        |        |        |
| Location            | C3, D6, L2, L5, S1 vertebral bodies | D6, D8 vertebral bodies | D8, D9, D10, L3 vertebral bodies, D7 transverse process right lamina, and pedicle, D4 spinous process |
| Pattern             | Lytic | Lytic | Lytic |
| Margin              | Irregular, sclerotic | Sclerotic | Irregular, nonsclerotic |
| Vertebral collapse  | Present, C3 (vertebral plana), and D6 | Absent | Absent |
| Abscess formation   | Absent | Absent | Present |
| Pelvic lesions      | Absent | Absent | Present |
| Location            |        | Left ilium |        |
| Pattern             |        | Lytic |        |
| Margin              |        | Irregular, sclerotic |        |
| Extremities lesions | Absent | Absent | Present |
| Site                |        |        | Right femur and right tibia |
| Pattern             |        |        | Lytic |
| Margin              |        |        | Sclerotic, irregular |

Abbreviation: CECT, contrast-enhanced computed tomography.
LCH radiographically presents as punched-out lytic lesions often involving skull bones and show beveled margins and associated soft-tissue component. Lesions tend to be more aggressive and destructive nature. Dorsal vertebrae are commonly involved with early lytic lesions leading to vertebral body collapse. Rib, scapula, and long-bone involvement is common in LCH. In rib and scapula, lytic lesions associated with soft-tissue components are usually seen. Pulmonary involvement is common in multisystem LCH and can be seen in 23 to 50% of cases. On chest radiograph, bilateral symmetrical reticulonodular pattern can be seen initially which later gives honeycomb appearance due to superimposition of air filled cysts. Small nodules with cavitation or cysts can be seen on CT. Mediastinal lymphadenopathy is rare in LCH, due to nonspecific clinical and laboratory findings. However, subtle findings on CT. Mediastinal lymphadenopathy as seen in our cases should be done for early diagnosis.

Disseminated tuberculosis is common in developing countries especially in young children. Diagnosis is often delayed due to nonspecific clinical and laboratory findings. However, the above-mentioned imaging findings would help to suggest the diagnosis. Finally, histopathological confirmation should be obtained for definitive diagnosis.

**Conclusion**

In children presenting with multifocal osseous lesions and clinical suspicion of LCH, presence of irregular sclerotic margins, abscess formation, sclerosis of involved bone, and button sequestrum should suggest possibility of osseous tuberculosis over LCH.

**Declaration of Patient Consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed.

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**Conflicts of Interest**

There are no conflicts of interest.

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