Article published online: 2021-07-27

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

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Indian J Radiol Imaging 2021;31:378–382.

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.

Keywords
- button sequestrum
- Langerhans' cell histiocytosis
- multifocal osseous tuberculosis
- skull
- tuberculosis
- vertebra plana

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.

published online
July 27, 2021

DOI https://doi.org/10.1055/s-0041-1734347
ISSN 0971-3026

Thieme Medical and Scientific Publishers Private Ltd. A-12, Second Floor, Sector -2, NOIDA -201301, India

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 IB**), 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. Skeletal survey showed multiple small lytic skull lesions with sclerotic margins (►**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.

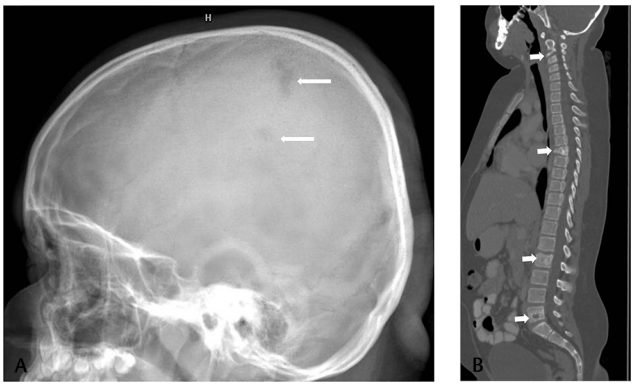

Fig. 1 Multifocal osseous lytic lesions in tuberculosis. (**A**) Multiple irregular lytic lesion with nonsclerotic margin in the parietal bone (arrows) and no beveling. (**B**) C3 vertebra plana, anterior wedge collapse of D6 and lytic lesions with some showing surrounding sclerosis in L2 and L5 vertebrae (arrows).

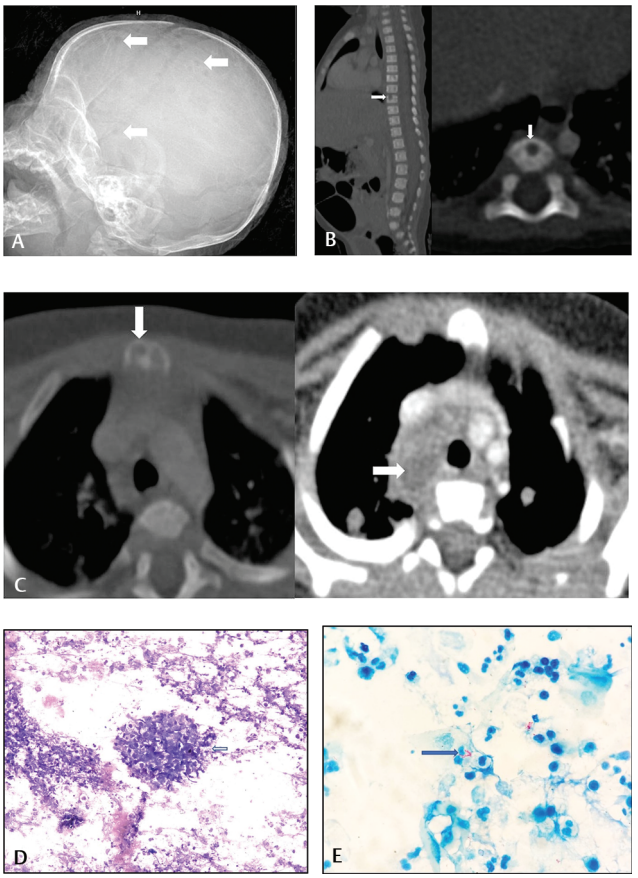

Fig. 2 Multifocal osseous lytic lesions with mediastinal lymphadenopathy. (**A**) Multiple tiny rounded lytic lesions with sclerotic margins in the frontal, parietal, and temporal bones (arrows). (**B**) Lytic sclerotic lesion involving the D8 vertebra (arrows). (**C**) Necrotic conglomerated mediastinal lymph nodes (arrows) and lytic lesion in the manubrium with nonsclerotic (arrow). (**D**) May Grunwald Geimsa (MGG) stained smear highlights an epithelioid cell granuloma (arrow) in a background of necrosis (×200). (**E**) Acid fast stained smear shows bright red colored bacilli with beaded ends of mycobacteria (arrow; oil emersion, ×1,000)

Patient was started on category-I antitubercular drugs. Clinical and radiological improvement was seen during 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 left frontal, parietal, mastoid bones, left iliac bone, and right femur neck (►**Figs. 3A** and **B**). Contrast-enhanced CT of head and orbit was done which showed multiple calvarial and skull base lytic lesions with sclerotic central bone density giving an appearance of button sequestrum (►**Fig. 3C**) with some

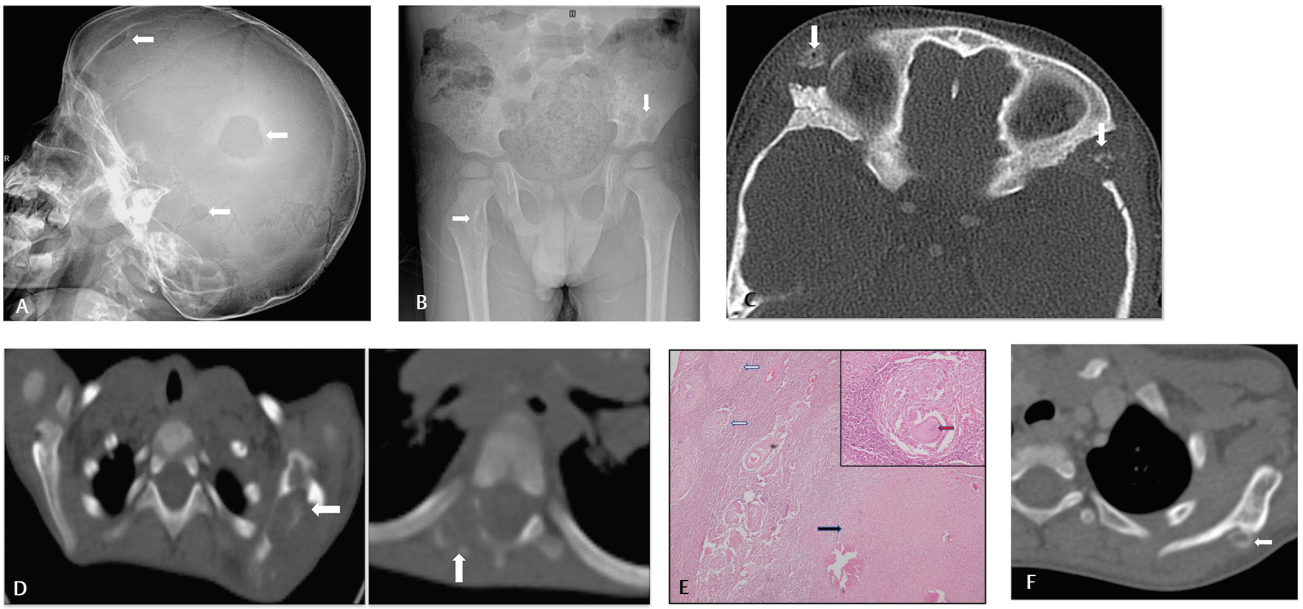

Fig. 3 Multifocal osseous lytic lesions with button sequestrum and healing of lesions post antituberculosis treatment. (**A**) Multiple rounded lesions with sclerotic margins in the frontal, parietal and temporal bones (arrows). (**B**) Lytic irregular sclerotic lesion in the left ilium and right femoral neck (arrows). (**C**) Lytic lesions with central bone density (arrows) giving an appearance of button sequestrum in zygomatic process. (**D**) Irregular lytic lesion involving the scapula with central bone density (arrow), transverse process, right pedicle, and lamina of D7 vertebra (arrow). (**E**) Hematoxyline and eosin stained section from a formalin fixed paraffin embedded tissue shows many epithelioid cell granuloma (white arrow) and large central area of coagulative necrosis (black arrow), (×40). Inset shows an epithelioid cell granuloma with Langhans' type of giant cell (red arrow), (×400). (**F**) Healed sclerotic scapular lesion with new bone formation (arrow).

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 paradiscal, 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
		Elevated 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.

Table 3 Ancillary radiological findings

	Case 1	Case 2	Case 3
Thorax			
Mediastinal lymphadenopathy	Absent	Present	Present
		Necrotic right paratracheal and hilar lymph nodes	Necrotic mediastinal lymph nodes
Pulmonary parenchymal findings	Absent	Bilateral lung nodules	Bilateral lung consolidations
Abdomen			
Liver	No focal lesion	Enlarged with multiple hypodense lesions	Enlarged
Spleen	No focal lesion	Enlarged with multiple hypodense lesions	Enlarged
Lymph nodes	Absent	Absent	Periportal lymph nodes present

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 with associated soft-tissue components are usually seen.[8] Pulmonary involvement is common in multisystem LCH and can be seen in 23 to 50% of cases.[9] 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, especially necrotic lymph nodes. Hepatobiliary involvement occurs in 50 to 60% of cases of multisystem LCH.[10] It typically presents as portal triaditis manifesting on imaging as periportal nodular or band like hypodensity on CT and hypoechogenicity on ultrasound. Nodular intraparenchymal lesions have not been described as a feature of LCH in literature.

Diagnostic dilemma in our cases had resulted from the atypical skeletal involvement. However, subtle findings on CT. such as irregular sclerotic margins, abscess formation, sclerosis of involved bone, and button sequestrum. should favor tuberculosis over LCH. Detailed imaging evaluation for multisystem involvement such pulmonary, hepatosplenic and 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.

Financial Support and Sponsorship

None.

Conflicts of Interest

There are no conflicts of interest.

References

1 Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. Int J Tuberc Lung Dis 2006;10(7):732–738
2 Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. J Infect Dis 2012;205(suppl 2): S199–S208
3 Ravikanth R, Mathew S, Selvam R. Calvarial tuberculosis presenting as multiple osteolytic soft tissue lesions. CHRISMED J Health Res 2017;4:278–279
4 Raut AA, Nagar AM, Muzumdar D, et al. Imaging features of calvarial tuberculosis: a study of 42 cases. AJNR Am J Neuroradiol 2004;25(3):409–414
5 Garg RK, Somvanshi DS. Spinal tuberculosis: a review. J Spinal Cord Med 2011;34(5):440–454
6 Haghighatkhah H, Jafroodi Y, Sanei Taheri M, Pourghorban R, Sadeghian Dehkordy A. Multifocal skeletal tuberculosis mimicking Langerhans cell histiocytosis in a child: a case report with a long-term follow-up. Iran Red Crescent Med J 2015;17(12):e19942
7 Grover SB, Jain M, Dumeer S, Sirari N, Bansal M, Badgujar D. Chest wall tuberculosis - a clinical and imaging experience. Indian J Radiol Imaging 2011;21(1):28–33
8 Khung S, Budzik JF, Amzallag-Bellenger E, et al. Skeletal involvement in Langerhans cell histiocytosis. Insights Imaging 2013;4(5):569–579
9 Smets A, Mortelé K, de Praeter G, François O, Benoit Y, Kunnen M. Pulmonary and mediastinal lesions in children with Langerhans cell histiocytosis. Pediatr Radiol 1997;27(11):873–876
10 Schmidt S, Eich G, Geoffray A, et al. Extraosseous Langerhans cell histiocytosis in children. Radiographics 2008;28(3):707–726, quiz 910–911

