Case Report

Disseminated tuberculosis presenting as lytic bone lesions: A diagnostic challenge in pediatric oncology

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ABSTRACT

Lytic bone lesions in children often raise concern for malignancy, with differentials including Langerhans cell histiocytosis, Ewing's sarcoma, lymphoma, and metastatic neuroblastoma. In tuberculosis (TB) endemic regions, however, infectious causes must also be considered to avoid misdiagnosis and unnecessary oncologic interventions. We report a case series of two immunocompetent children who presented to a pediatric oncology unit with multiple lytic skull lesions. Both had a family history of TB. Initial suspicion was for malignant disease, but histopathological examination confirmed TB. One child had disseminated craniofacial and vertebral involvement, while the other showed multifocal osseous disease, including the mandible, sternum, and scapula. Both children were managed successfully with anti-tubercular therapy in accordance with National TB Elimination Program (NTEP) guidelines. Although osseous TB accounts for only 5–6% of extrapulmonary TB, and multifocal skeletal involvement is rare, TB remains an important differential diagnosis for pediatric lytic lesions in endemic regions. Pediatric oncologists should remain vigilant for TB when evaluating children with multifocal lytic lesions, as early recognition can prevent unnecessary invasive procedures and inappropriate oncologic treatments.

Key words: Extrapulmonary tuberculosis, Lytic bone lesions, Pediatric, Skeletal tuberculosis, Tuberculosis

Pediatric skull lesions can pose significant diagnostic challenges due to their varied etiology and often non-specific presentation. These lesions may be congenital or acquired and may present with or without symptoms. Differential diagnoses include Langerhans cell histiocytosis (LCH), tuberculosis (TB), osteomyelitis, Ewing's sarcoma, lymphoma, and metastatic neuroblastoma. A 25-year study on pediatric skull lesions identified epidermoid cysts and LCH as the most frequent diagnoses, with no cases of TB in the United States of America [1]. Similarly, a Chinese retrospective review of 228 pediatric scalp and skull lesions found dermoid cysts, meningoceles, and LCH to be the most prevalent [2]. Osteoarticular TB accounts for 5–6% of extrapulmonary TB cases, while primary calvarial TB is extremely rare, comprising less than 1% of skeletal TB cases [3,4]. Lytic lesions in children are frequently presumed to be malignant, prompting extensive and costly diagnostic evaluations. This not only increases the healthcare burden but also contributes to considerable psychological distress for the child and family.

Herein, we present a case series of two cases of immunocompetent children with multiple lytic skull lesions secondary to disseminated extrapulmonary TB, underscoring the need to consider TB in the differential diagnosis of pediatric calvarial lesions.

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CASE SERIES

Case 1

A 7-year-old immunized female presented with a painless swelling over the ventral aspect of the right arm for 6 months, followed by swelling at the outer corner of the right eye for 3 months, and a left infraorbital swelling for 1 month. The left orbital lesion was insidious in onset, gradually enlarging into a non-healing ulcer with serous discharge. The earlier two swellings had resolved spontaneously, leaving scars (Fig. 1). There was no history of fever, weight loss, trauma, or other systemic symptoms. Family history was notable for parental TB,

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Figure 1: Clinical photographs of the child. (a) Scar below the right eye, post-incision and drainage. (b) swelling below the left eye, site of the biopsy. (c) Healed scar on the right arm. (d) Mantoux test: Induration and erythema at 48 h

father treated 7 years ago, and mother 5 years ago. The child had no prior hospitalizations, was born at term with an uneventful postnatal history, and her Bacillus Calmette–Guérin immunization was up to date.

Clinical examination revealed pallor, with no evidence of lymphadenopathy or organomegaly. Local examination revealed an ulcerated lesion under the left orbit and healed scars on the right arm and near the outer canthus of the right eye. Initial management with oral antibiotics and incision and drainage was ineffective. A skull X-ray revealed multiple lytic lesions, prompting further imaging with computed tomography and magnetic resonance imaging (MRI) of the brain and spine. Additional craniofacial and upper cervical vertebral lesions with associated soft tissue involvement were discovered on imaging, consistent with disseminated disease (Fig. 2). A biopsy of the skin lesion revealed granulomatous inflammation with epithelioid macrophages, Langhans giant cells, lymphocytes, and central caseation, suggestive of TB (Fig. 3). Mycobacterium TB was confirmed via cartridge-based nucleic acid amplification test on gastric aspirate and biopsy specimens. The child was diagnosed with disseminated extrapulmonary TB and initiated on anti-tubercular therapy (ATT) in accordance with NTEP guidelines. She was administered four drug therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for 2 months, followed by rifampin (HR) for 9 months. She tolerated ATT well and did not require any interruptions of therapy.

Case 2

A 2-year-old immunized male presented with a swelling over the left mandible and bilateral ear discharge for 2 months. The child also experienced intermittent fever for the past 2 months. There was no history of pain, bleeding, or discharge from the swelling. He was the firstborn of a non-consanguineous marriage and was delivered by caesarean section due to fetal malposition. Antenatal

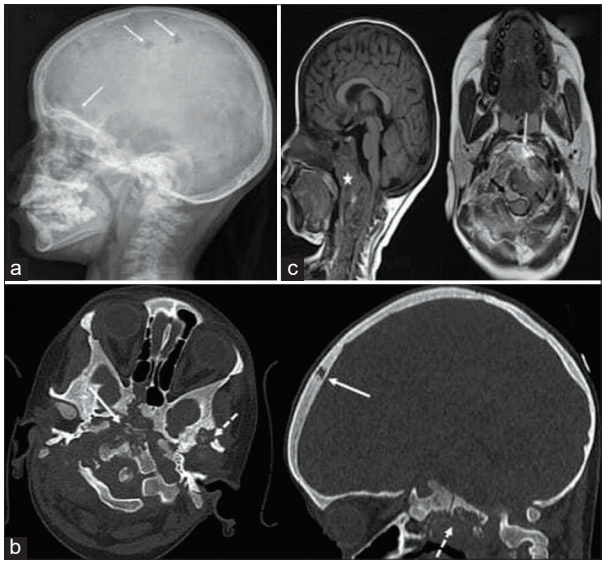

Figure 2: Radiological findings in Case 1. (a) X-ray of the skull shows multiple lytic lesions on skull bones; (b) computed tomography Skull showing the presence of lytic lesions of occipital condyles; (c) magnetic resonance imaging brain showing lytic lesions of occipital condyles and upper cervical vertebrae with pre and paravertebral soft tissue

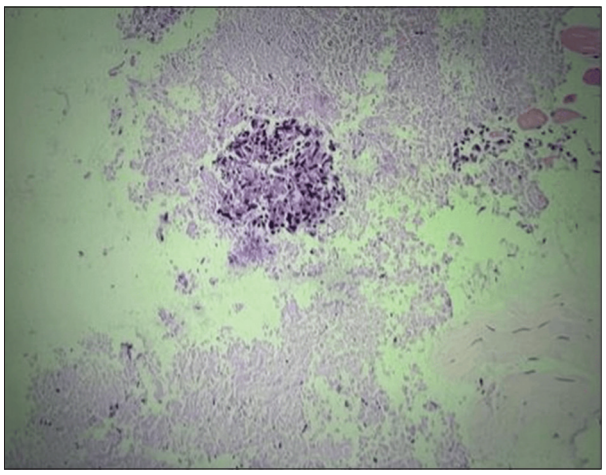

Figure 3: Histopathology of Case 1. Presence of granulomatous inflammation with granulomas containing epithelioid macrophages, Langhans giant cells, and lymphocytes; a characteristic caseation in the center.

and postnatal periods were uneventful. A maternal uncle was undergoing treatment for pulmonary TB, diagnosed 3 months prior.

On examination, the child had mild pallor and bilateral cervical lymphadenopathy, with the largest node measuring 1 × 2 cm. A 3 × 3 cm firm, well-defined swelling was noted in the left mandibular region, involving the inferior border and angle of the mandible. The overlying skin appeared normal. Additional diffuse swellings were observed over the sternum and first metatarsal of the left foot (Fig. 4). MRI revealed multifocal lytic lesions involving the mandible, skull, sternum, left scapula, and D2 vertebra, with periosteal reaction and soft tissue inflammation. A biopsy was taken from the sternal lesion, and histopathological examination revealed granulomatous inflammation with epithelioid cells, Langhans giant

cells, lymphocytes, and focal necrosis. Ziehl–Neelsen staining was negative for acid–fast bacilli (Fig. 4). A diagnosis of extrapulmonary TB was made, and the child was initiated on ATT per NTEP guidelines. He received 4 drug intensive therapy (HRZE) for 2 months, followed by continuation phase 2 drug (HR) therapy. He has completed 4 months of continuation therapy with a reduction in the size of the swellings. The investigations done on both patients have been summarized in Table 1.

DISCUSSION

Children presenting with multifocal lytic bone lesions often raise immediate concern for malignancy, particularly LCH, Ewing's sarcoma, lymphoma, or metastatic neuroblastoma [1]. In oncology practice, this predisposition to suspect a malignant etiology frequently leads to extensive investigations and invasive procedures. However, in TB-endemic countries such as India, TB remains an important yet often overlooked differential

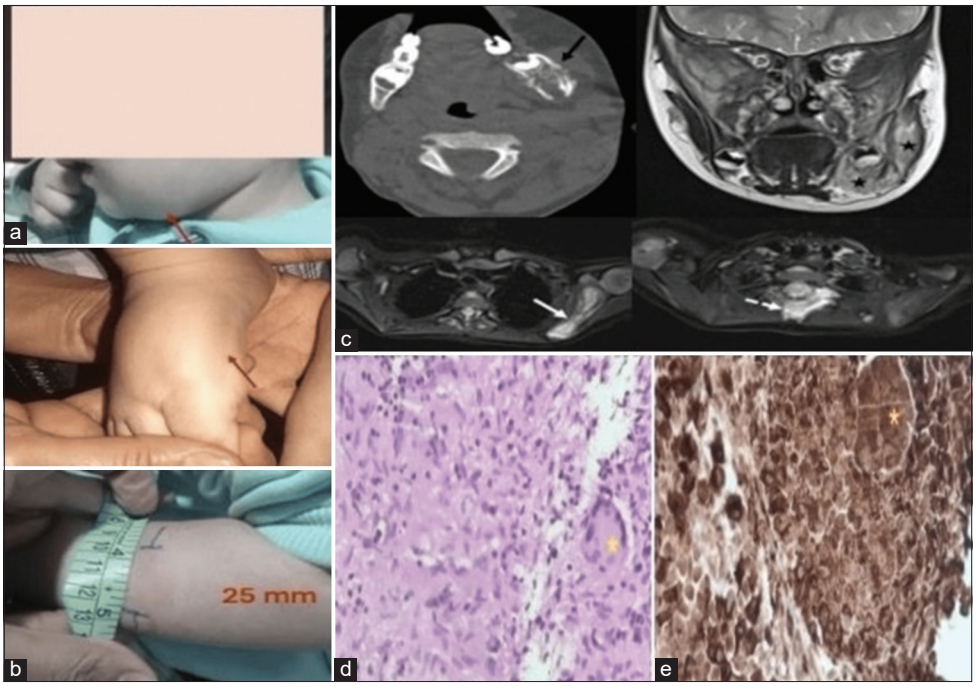

Figure 4: Clinical, radiological, and histopathological details of Case 2; (a) Clinical photograph of the child showing mandibular swelling and swelling over the metatarsal; (b) Positive Mantoux test; (c) magnetic resonance imaging showed multifocal lytic lesions in the mandible, skull, sternum, scapula, and spine; (d) Histopathology showing granulomas comprised of epithelioid cells, lymphocytes, and occasional Langhan's giant cells, Hematoxylin, and eosin, ×400. (e) Immunohistochemistry for CD68 showing positivity in the epithelioid macrophages, DAB chromogen, ×400 S100

Table 1: Results of laboratory investigation of both the children

Age/sex	7 years/female	2 years/male
Presenting symptom	Swelling over right arm, right and left eyes	Swelling over mandible and left foot
History of contact	Present	Present
TLC	6.9×103/uL (4.5–14.5×103/uL)	22.9×103/uL (5–17×103/uL)
Monocytes	0.5 (0.2–1.0×103/uL)	1.0 (0.2–1.0×103/uL)
Eosinophils	0.1 (<1.01×103/uL)	0.7 (<0.81×103/uL)
Basophils	0.01 (<0.21×103/uL)	0.2 (<0.21×103/uL)
Platelet count	663×103/uL (150–400×103/uL)	813×103/uL (150–400×103/uL)
ESR	Not available	93
X-ray skull AP and lateral	Multiple lytic lesions involving the skull bones	Not available
Mantoux test	Positive	Positive
MRI	Lytic lesions of occipital condyles and upper cervical vertebrae with pre and paravertebral soft tissue	Multifocal expansile lytic lesions in the mandible, skull, sternum, left scapula, and vertebrae with associated periosteal reaction.
CT head	Lesions at the base of the skull.	Not available
Histopathology	Presence of granulomatous inflammation with granulomas containing epithelioid macrophages, Langhans giant cells, and lymphocytes; a characteristic caseation in the center	Presence of several granulomas comprising epithelioid cells with admixed small lymphocytes, occasional plasma cells, and Langhans' giant cells. Tiny foci of necrosis are also seen. No acid–fast bacilli identified on Ziehl–Neelsen stain.

TLC: Total leukocyte count, ESR: Erythrocyte sedimentation rate, AP: Anteroposterior, MRI: Magnetic resonance imaging, CT: Computed tomography

diagnosis. In both of the cases described, the initial clinical and radiological findings strongly suggested LCH, a common mimic of disseminated TB in children.

India contributes approximately 28% of the global pediatric TB burden, with nearly 333,000 children (0–14 years) affected annually [5]. Children are particularly vulnerable due to their developing immune systems, and the disease often presents atypically, mimicking other childhood disorders. Moreover, difficulty in obtaining appropriate pulmonary samples further complicates diagnosis [6].

Jungling disease, or osteitis tuberculosa multiplex cystoides, first described in 1920 in adults, represents a rare form of skeletal TB characterized by multiple cystic lytic bone lesions, predominantly affecting the hands and feet [7]. Such lesions may arise from diverse etiologies, congenital, traumatic, inflammatory, or neoplastic and can be distinguished based on age, systemic symptoms, and immune status.

LCH typically manifests as punched-out lytic skull lesions, sometimes involving the vertebrae, leading to collapse. Among 263 patients with LCH, 38% of osseous lesions involved the skull [8]. TB lesions, however, more often exhibit irregular sclerotic margins, abscess formation, bone sclerosis, and button sequestrum, radiologic features that aid differentiation. Several case reports highlight TB's ability to mimic neoplastic or inflammatory conditions. Singh *et al*. described a 3-year-old child with scalp swelling, discharging sinus, and lytic lesions of the skull, iliac bone, and femur neck; TB was confirmed on cervical lymph node biopsy despite a negative gastric aspirate GeneXpert [9]. Similarly, Mandai and Singh reported a child with intraorbital swelling and TB confirmed on pus aspirate, without any known TB contact [10]. Babu *et al*. described six ocular TB cases, including a 15-year-old girl with orbital swelling and previous drainage scars, where histopathology confirmed TB [11]. Scapular TB is particularly rare; Haghighatkhah *et al*. reported a 12-year-old girl with frontal scalp swelling and multifocal skeletal involvement on scintigraphy, where TB was confirmed by scalp lesion histology [12].

These reports collectively underscore that TB, though uncommon, should remain a crucial differential diagnosis in children with multifocal lytic bone lesions, particularly in endemic regions. In our cases, TB was not initially considered, reflecting an inherent bias toward malignant etiologies within pediatric oncology units.

CONCLUSION

Despite its rarity in high-income countries, TB must be actively considered as a differential diagnosis for multifocal lytic bone lesions in children, especially in TB-endemic, resource-limited regions, irrespective of immune status.

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