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Musculoskeletal Tuberculosis in Children

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Abstract

Paediatric musculoskeletal tuberculosis is very important to understand as it shares similar clinical, radiological and hematological findings with other infectious and non-infectitious conditions. It has become a major health hazard because of its association with immunocompromised states like HIV, Diabetes mellitus and chronic renal and liver diseases. Diagnosis is delayed in paediatric musculoskeletal tuberculosis because of lack of awareness of disease, non-specific clinical and laboratory findings. TB culture is considered as the gold standard in diagnosing tuberculosis and also, detecting drug sensitivity. Because of its potential for multi-drug resistance, there is a dilemma regarding drug of choice and duration of treatment. Surgery is reserved for obtaining samples to establish diagnosis, debridement and sequestrectomy in recalcitrant infections and correction of deformities to restore joint function. This review article briefs about classical clinical presentation, atypical and multifocal musculoskeletal tuberculosis, radiological and laboratory investigations and management of paediatric musculoskeletal tuberculosis.

Musculoskeletal tuberculosis should be kept as a differential diagnosis when managing a case of musculoskeletal infection in children because of its non- specific presentation. Imaging such as MRI and advanced microbiological analysis aids in arriving correct diagnosis. Multidrug chemotherapy is mainstay of treatment. Radical curettage and, antituberculous chemotherapy followed by a period of immobilisation and rehabilitation will give excellent results

Keywords: Paediatric musculoskeletal tuberculosis, Multifocal tuberculosis, Tubercular osteomyelitis

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Introduction

The reported incidence of musculoskeletal tuberculosis was found to be 5-6% of all the extrapulmonary cases in paediatric age group [1]. TB is termed as a great imitator as extrapulmonary TB mimics many other disease entities, and many diseases mimic tuberculosis [2]. Hence, though tuberculosis is endemic in Indian subcontinent, several cases are detected late because of lack of awareness of the condition as well as due to the fact that MSK TB presents with non-specific symptoms and without any characteristic imaging findings [1]. It is essential to diagnose TB in children because it has the potential to damage joints and, sequalae may lead to extensive destruction and loss of function of the joints [1]. Immunocompromised states like HIV, Chronic kidney disease and Diabetes mellitus further complicate the disease [2].

In endemic areas, priority is to improve protocol-based treatment, and in non-endemic regions, perceptions of TB are to be improved [3]. Although principles of diagnosis and treatment are similar in adults and children, specific host characteristics and differences in types of disease will bring up some challenging variations. The present updated guidelines capture the use of newer diagnostics and, therapy modifications for managing musculoskeletal TB in children to achieve the goal of early diagnosis, prompt and effective therapy guided by the sensitivity pattern to key drugs.

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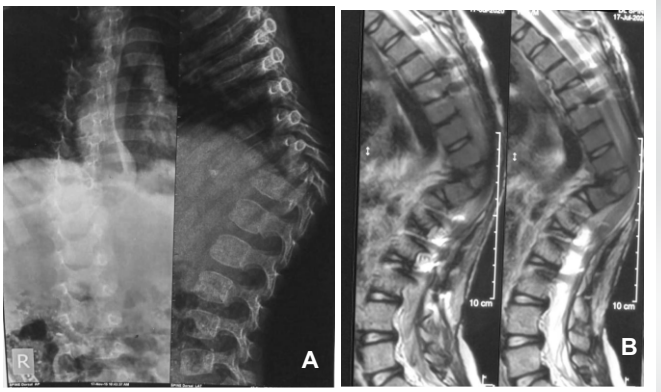

Figure 1: (A): Plain radiograph of a 4 year old male child with mid-dorsal Tuberculosis of spine (D7-D9) with severe collapse of D8 vertebra with gibbus formation (B): MRI of the same child confirming collapse and gibbus formation with large epidural abscess formation

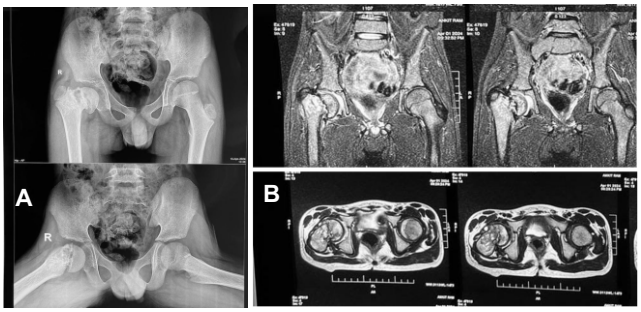

Figure 2: (A): Plain radiograph of the pelvis with both hips of a 8 year old male with right hip Tuberculosis with pathological fracture of the neck of femur (B): MRI of the same child showing confirmation of pathological fracture with effusion and synovial hypertrophy

Etiopathogenesis

There are two different mechanisms through which TB infects children and causes MSK TB. The First mechanism occurs by haematogenous spread from primary focus like lung and lymph node. In very young children, like other bacterial infections, lesions in bones and joints form primary complexes, as there is no previous exposure to TB in infants. These are often exudative and will produce multiple lesions which are potentially infective. Another mechanism is hypersensitivity reaction following primary pulmonary lesion at other sites. The bacilli lie dormant at different sites of the body after an initial haematogenous spread. If host immunity decreases, these dormant bacilli get activated and this leads to single/multiple musculoskeletal lesions. In this mechanism musculoskeletal TB is occurring from reactivation of lesions in bones and joints, which wereimplanted at the time of initial exposure [1]. Nearly half of the musculoskeletal TB affects thoracic spine, and the rest affects appendicular skeleton, either directly through sub-synovial vessels or indirectly by eroding the epiphyseal growth plate [3].

Risk factors

Risk factors in children are immunocompromised states like HIV, Chronic liver and kidney disease, Diabetes mellitus or, long-term immunosuppressive drugs like Corticosteroids [1].

Classical presentation

Tuberculosis can affect any age group and there is no gender predilection but it is most common in the first two decades of life [5]. Clinical features vary depending on the site of involvement and it can be monofocal or multifocal presentation. Most common site in musculoskeletal system is the thoracic spine [3]. TB usually has monoarthritic distribution with high frequency of involvement of hip and knee in the appendicular skeleton [6]. Patients usually present with back pain, swelling of the part involved, discharging sinuses in case of tubercular osteomyelitis and sometimes tubercular ulcers [3]. Classical constitutional symptoms associated with tuberculosis like evening rise of temperature, anorexia and loss of weight are seen only in one third of the patients and an active pulmonary lesion is seen only in a small percentage of cases.

Spine: The most common site in the musculoskeletal system is the thoracic spine [3] (Fig. 1). Spinal tuberculosis is more common in children and young adults [7]. It is the destructive form of tuberculosis, in which there is destruction of Intervertebral disc, vertebral bodies, end plates, collapse of spinal elements, anterior wedging leading to kyphosis and gibbus formation. Classical clinical features include back pain, stiffness of back, cold abscess, paraplegia and spinal deformities [7]. Deformity will be more severe in younger children than older children [1]. Vertebral bodies in children are cartilaginous unlike adults and there is rapid loss of cartilage and consecutive occurrence of spinal deformities in a short period of time. Most sensitive diagnostic test for spinal tuberculosis is MRI which will demonstrate the involvement of vertebral bodies, cold abscess formation, and myelomalacia [8]. Spine tuberculosis is essentially a medical disease while surgery is reserved for its complications and sequalae. (Fig. 1)

Hip: Hip joint is the second most common site of involvement of tuberculosis in children. Clinical features depend on the stage of the disease as it progresses through synovitis, early arthritis and advanced arthritis. In early stages, a child may present with limp and limb will be in flexion, abduction and external rotation to accommodate effusion [9]. It should be

Table 1: Types of TB Hip	
TYPE 1	Normal
TYPE 2	Travelling acetabulum
TYPE 3	Dislocating
TYPE 4	Perthes type
TYPE 5	Protrusio acetabuli
TYPE 6	Atrophic type
TYPE 7	Motor and pestle type

differentiated from septic arthritis and transient synovitis. In advanced stages, there will be marked restriction of movements with shortening of the limb and stiff hip. Radiological presentation of tuberculosis in children has been described depending on the site of affection in hip. Accordingly, 7 different types have been described as per Shanmugasundaram classification [1]. The 7 types of TB hip as described by Shanmugasundaram are described in table 1. Other than the typical 7 types, TB hip can also present with pathological fractures (Fig. 2).

Knee joint: Tuberculosis can affect synovium, epiphyseal region and metaphysis. Common presentations are boggy swelling, joint effusion, painful limp and flexion deformity of the knee joint. In late stages, a child may develop triple deformity at the knee joint (valgus, external rotation, flexion deformity of knee with posterior subluxation of tibia). Epiphyseal lesions are also common as epiphyseal plate offers little resistance to spread of the tubercular focus, and thus MSK TB can affect the distal femur, proximal tibia and rarely the proximal fibular epiphysis also [1, 10].

Shoulder and Elbow joint: Shoulder joint is less commonly affected in children. There are two types of tubercular infection in shoulder i.e caries sicca and caries exudata. Caries exudata presents as swelling, effusion and cold abscess. Sicca is uncommon in children and presents with marked wasting and painful movements. Plain radiographs may reveal regional osteopenia and lytic lesions in the joint.

On the other hand, the elbow is quite commonly affected in children (Fig. 3). The usual presentation is exudative with abscess formation [1]. Most commonly, lesions are seen in ulna than proximal radius and distal humerus. Classical radiological presentation seen with proximal ulna is 'icecream scoop' appearance [1].

Wrist and hand: Disease is more common in age less than 5 years. Usually, wrist tuberculosis in children presents with swelling, restricted movements and chronic pain. Sometimes it may present with abscess formation and discharging sinuses. Tenderness will be localized to one or more of the carpal bones or the distal radius. In some cases, especially in distal radial affections, the radiological picture may mimic a simple bony cyst and the child may present with features of lytic lesions. It may affect growing distal radius epiphysis, causing destructive lesions and presenting as deformities and growth restriction. Rheumatoid-like involvement with reduction in joint space is seen when there are carpal bones involved [11]. There are multiple bony lesions that may present as discharging sinus or skin ulceration.

Usual clinical presentation in Hand and fingers is swelling of insidious onset. Tuberculous dactylitis is common in children [12]. It is described as 'spina ventosa' when short tubular bones are involved and sometimes, multiple digits can be involved as a part of multifocal TB. Spina ventosa refers to spindle shaped expansion of phalanges due to layering of periosteal new bone formation over involved lamellae or sequestrum [1, 13]. Other presentations are diffuse infiltration, honey combing and cystic lesions.

Foot and ankle: TB commonly presents as swelling over the dorsum of foot, around malleoli and sometimes posteriorly

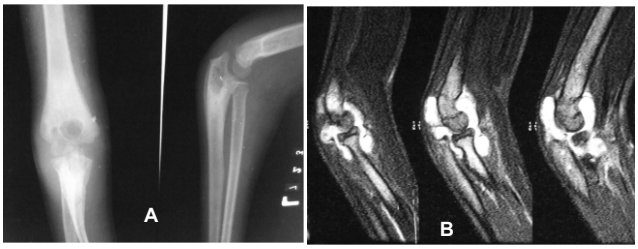

Figure 3: (A): Plain radiograph of the elbow of a 10 year old female with Kochs elbow showing joint space enlargement, and the typical "ice-cream scoop" lytic lesion of the olecranon and proximal ulna (B): MRI of the same child showing large elbow effusion and involvement of the proximal ulna

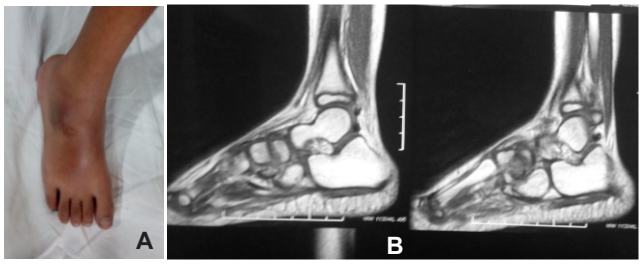

Figure 4: (A): Clinical photograph of the right foot of a 6-year-old boy with severe boggy, tender swelling over the dorsum of the foot. (B): MRI of the same child showing osseous lesion in the medial and middle cuneiforms and collection extending to the dorsum of the foot

near the Achilles tendon (Fig. 4). Painful limp and swelling are early and common symptoms. Ankle joint affection with TB has varied radiological presentations like kissing lesions [14, 15]. Coalescence of multiple small bones may present as 'rheumatoid mass'. Tarsal bones, metatarsals and phalanges may be involved, calcaneum involvement usually presents as 'heel raise sign 'and antalgic gait in a child. Sometimes 'Coke like sequestrum' appearance is seen [1].

Tubercular osteomyelitis: It is one of the less common manifestations of tuberculosis. It occurs through haematogenous route of dissemination. Tubercular osteomyelitis occurs multifocally as a part of primary infection in infants while in older children, it presents as solitary focus of infection as a part of reactivated TB [13]. Typical osteoarticular lesions of tuberculosis in paediatric age group are usually situated in metaphyseal region, but rarely the lesion crosses epiphyseal growth plate and presents in epiphysis. This is usually seen in younger children where vascular channels are open. Child usually presents with localised swelling of insidious onset and mild pain which is sometimes associated with constitutional symptoms like low grade fever, weight loss, and malaise. Sequestra are rarely seen in tubercular osteomyelitis and can be described as 'feathery' due to subperiosteal new bone formation [12]. It should be differentiated from subacute osteomyelitis, chronic osteomyelitis, cartilaginous tumors, bony cysts, and certain malignant bone tumors.

Cystic tuberculosis: Average age at presentation is 4 years. Solitary cystic TB is seen usually in proximal tibia and distal femur. It should be differentiated from tumors [16].

Other forms of musculoskeletal tuberculosis infection are tubercular tenosynovitis affecting flexor tendon sheaths of hand. Ultrasound is the initial investigation of choice to diagnose and to know the extent of disease. Tubercular bursitis is a rare manifestation of musculoskeletal tuberculosis. It usually involves the hips and presents as trochanteric bursitis. Imaging in form of MRI is suggestive of soft tissue swelling. Tubercular myositis is extremely rare as muscles are resistant to mycobacterial infection. Chest wall involvement is common, with direct spread from adjacent pleuritis and lymphnodes. Ponset's arthritis is a rare form of aseptic reactive arthritis in Tuberculosis. Patients present with polyarthralgia in contrast to monoarticular involvement in TB. Symptoms usually subside in few weeks of antitubercular chemotherapy [13].

Multifocal tuberculosis: Multifocal tuberculosis constitutes about 7-11% of the musculoskeletal tuberculosis [17]. It is extremely rare in immunocompetent patients and with normal pulmonary findings. Lesions will demonstrate different stages of healing of tubercular lesions in different organs of body [18]. All the lesions may not be symptomatic, usually 4-6 bones or joints are affected but, as many as 19 different locations have been reported [17]. Since these patients present with vague symptoms, a high level of suspicion of tuberculosis should be there to diagnose the condition and to differentiate it from metastatic tumors. Multifocal TB should be suspected, when we see multiple destructive lesions of bone. Bone scan helps to detect multiple lesions at the earliest stage. CT and MRI will demonstrate the extent of lesion and soft tissue involvement while the diagnosis is confirmed by biopsy [19]. Differential diagnosis in multifocal tuberculosis can include syphilis, dissemenated pyogenic osteomyelitis, coccydiomycosis and neoplasms like LCH and small round cell tumors [6].

Imaging in osteoarticular TB

Plain radiograph is the mainstay of initial investigation in musculoskeletal tuberculosis.

X-ray: Phemister's triad of Juxta-articular osteoporosis, peripheral osseous lesions and gradual joint space narrowing is typical of tuberculous arthritis which is seen in appendicular skeleton. Layered periosteal reaction is seen in paediatric patients unlike adult tubercular arthritis [13]. Joint destruction, pathological subluxation or dislocation and fibrous ankylosis are seen in end stage tubercular arthritis, unlike pyogenic arthritis where bony ankylosis is seen. It sometimes occurs as tuberculous osteomyelitis of long bones in children. Medullary expansion seen in short tubular bones of hands and foot is described as 'spina ventosa'. Loss of height of vertebral bodies, end plate erosions, angular kyphosis and paravertebral abscess are seen in spinal TB but changes on plain radiographs are late to appear [3].

Ultrasound may be used to detect effusion and to guide joint aspiration for microbiologic diagnosis. It is also helpful for diagnosing TB tenosynovitis.

CT scan: CT scan is superior in diagnosing early arthritis and to confirm the extent of bone destruction and sequestration. It is particularly useful for lesions like craniovertebral spine, cervicodorsal spine, rib, sternum, sacroiliac joint, and posterior elements of vertebrae as these locations are not clearly seen on Xray [13]. CT guided biopsy can be done in inaccessible regions like ribs for histopathological examination. CT scans are used when X rays are normal, and MRI is not available.

MRI: MRI is the preferred imaging modality, especially for detecting early stages of disease. MRI is a more sensitive diagnostic tool in this scenario and can also be used for follow-up [8]. It shows early findings such as synovial thickening and joint effusion as these findings are not seen in plain radiographs. It shows hyperintense signal on T2W images and contrast

enhancement involving intervertebral disc and end plates of vertebrae [8]. Paraspinal abscess is seen as a rim enhancing lesion in CE – MRI. Other changes seen are myelomalacia and cord compression in Spinal TB. Healed tuberculosis is seen as altered vertebral marrow signal in the form of hyperintense on both T1W and T2W sequences. MRI is useful for differentiating tubercular and pyogenic spondylodiscitis [6].

However, it is to be noted that these imaging findings of USG, X-ray, CT, MRI, PET scan and other imaging modalities are non-specific in paediatric musculoskeletal TB, and any investigative modality has to be coupled with clinical acumen for efficient diagnosis and management.

Diagnosis Blood investigations: Haematologic tests for musculoskeletal tuberculosis in children are nonspecific. Estimation of Haemogram, ESR, CRP, LFT, RFT are used to monitor disease activity and for general health of children who are on ATT.

Obtaining samples for laboratory studies:

When osteoarticular TB is suspected, an appropriate tissue sample must be obtained. Tissue swabs from discharging sinuses should be avoided, as they may be contaminated by skin contaminants. Tissue samples obtained by biopsy will yield the best results. Adequate and precise tissue can be obtained by image guidance/arthroscopy/open surgical debridement. When spinal TB is suspected, percutaneous transpedicular biopsy is obtained by spine surgeons. Arthroscopy has the advantage of visualization of lesion, obtaining adequate sample and at the same time debridement can also be done. Samples for microbiological examination i.e for smears and culture should be collected in sterile leak proof container and transferred to laboratory at the earliest. Sample for Histopathological examination should be collected in formalin containers [3].

Smear: Smear by Ziehl–Neelsen (ZN) stain is a rapid method to detect AFB. Sensitivity can be increased by using Auramine stain. However, Staining cannot differentiate mycobacterial tuberculosis from non -mycobacterial tuberculosis.

HPE: Histopathological picture will demonstrate TB bacilli, caseous granuloma from specimens using ZN staining and, fluorescent Auramine stain. It will produce two types of lesions as described in literature [3]. One is caseating exudative type with predominant caseation and, cold abscess formation with destruction of bone and cartilage which is mostly seen in children. The second type is a proliferating type with predominant cellular proliferation with minimal caseation which is less commonly seen in children. The tuberculous granuloma is the extreme form of the caseating type.

Cultures, Genotype and Drug sensitivity:

TB culture is considered as the gold standard in diagnosing Tuberculosis and also, detecting drug sensitivity. Commonly used culture media are Lowenstein Jensen medium, BACTEC Mycobacterium Growth Indicator Tube 960 (MGIT 960) and Bi-layered medium for rapid isolation of M.Tuberculosis. Cultures usually takes 6-8 weeks with L-J medium and have high specificity while it takes 3 weeks for MGIT tube which has high sensitivity. When microbacterial studies are positive, drug sensitivity test has to be done. The anti-bacterial drug sensitivity ranges from about 30-80% for single drug sensitivity to about 9 to 25% in MDR cases. Also, as osteoarticular TB is paucibacillary, culture yield is poor as reported by Indian studies [20].

Molecular methods– GeneXpert detects M. TB as well as drug resistance for Rifampicin. GeneXpert will give faster results as early as within 2 hours. It can detect M. TB DNA and, it can also detect Rifampcin resistance and, helps in starting treatment immediately in MDR TB. Sensitivity of GeneXpert in musculoskeletal TB is 60-70% whereas specificity is 100%.

The New diagnostic tool GeneXpert MTB/RIF ultra or Xpert ultra has improved sensitivity compared to GeneXpert in detection of TB and RIF resistance in both pulmonary and extrapulmonary TB. However it has to be noted that it has the disadvantage of lower specificity than GeneXpert. It is negative in TB mimics and non- tubercular mycobacteria and this helps in differentiating them in AFB smear positive cases. It is important as non-tubercular mycobacterial infections are increasing in some parts of the world.

Single tube nested PCR (STNPCR) has shown sensitivity and specificity in detecting the Koch's bacillus and advantage of STNPCR is minimal contamination compared to conventional PCR. It gives promising results as it is non-invasive, and samples can be collected in outpatient clinics [21].

Pyrosequencing is a rapid but expensive method for the detection of resistance to rifampicin, isoniazid, streptomycin, ethambutol, ofloxacin, and amikacin in M.TB. The results are available as early as six hours.

Interferon gamma release assay– Quantiferon –TB indicates cellular response to microbial antigens. ATT based on these tests is not warranted.

Most current molecular methods detect resistance to rifampicin, some others detect resistance to Isoniazid. So, Resistance to other drugs may not be known. It is always advisable to do culture- based resistance tests along with molecular tests [22].

Treatment

Main treatment of musculoskeletal TB is ATT (Antitubercular chemotherapy). In the initial stages, rest, analgesics, immobilization and braces can be given [1]. Once inflammation and pain are controlled, patients should be encouraged to start mobilizing joints to prevent permanent

deformities. Tubercular osteomyelitis, if advanced, requires protection with splinting to prevent pathological fractures. Most of the patients will require nutritional therapy also. Duration of ATT for musculoskeletal tuberculosis is a topic of debate. Current literature suggests ATT for a period of 12-18 months with increased duration for paediatric age group, who are immunocompromised and, those with connective tissue diseases [2]. As per RNTCP guidelines 2016 – ATT is to be given for 12 months with a long- term follow-up of at least 24 months [2]. GeneXpert Mycobacterium tuberculosis guides in the choice of ATT and drug resistant TB. ATT is given through DOTS under RNTCP for 12 months in each case and monitoring is done at regular intervals [2]. According to paediatric TB management guidelines 2022 by NTEP, Fixed drug combination tablets have replaced combi packs and patient wise boxes. NTEP has introduced a fixed drug combination including multidrug therapy for TB. It is safe, simplified, avoiding errors in missing one or more combination drugs, thus reducing risk of emergence of drug resistant strains.

There are two types of Paediatric FDCs available under NTEP-
Formulation: Dispersible and flavored.

Intensive Phase (IP): 3 Drugs FDC Dispersible Tablets (DT) (H 50, R 75, Z 150)

For Continuation Phase (CP): 2 Drug FDC DT (H 50, R 75)

There are two types of Adult FDCs available under NTEP, which are used in older children:

For Intensive Phase: 4 FDC (H 75, R 150, Z 400, E 275)

For Continuation Phase: 3FDC (H 75, R 150, E 275)

In Daily dosing schedule, drug dosages according to weight are incorporated. Children should be monitored closely for treatment progress and response to the disease . There are two components of follow-up i.e, clinical follow-up and laboratory follow-up. After completion of treatment children should be followed up every 6months until 2years to detect early detection of relapse of disease [22].

Role of surgery: Surgical procedure is indicated to obtain samples and to establish diagnosis especially in cases who are not responding to treatment. Bacterial sensitivity can also be detected from samples, so that appropriate antibiotics can be given. Sometimes emergency surgery can be carried out to decompress bulky abscesses and, in case of spinal TB with gross neurological deficit at presentation or, neurological deficit interfering with patient mobilization. Surgery is indicated in correcting post tubercular deformity correction like kyphotic and scoliotic deformities both in acute and late stages. Surgery may be indicated to correct deformities of lower limbs and to restore joint function which are affected by TB sequalae. In patients with neurological manifestations/deformities of joints – surgery combined with prolonged ATT is indicated and it will provide satisfactory results [17]. Radical currettage and, antituberculous chemotherapy followed by a period of immobilisation and rehabilitation will give excellent results [23].

Conclusion

Musculoskeletal tuberculosis should be kept as a differential diagnosis when managing a case of musculoskeletal infection in children because of its non- specific presentation. Imaging such as MRI and advanced microbiological analysis aids in arriving correct diagnosis. Multidrug chemotherapy is mainstay of treatment. Radical curettage, if indicated and antituberculous chemotherapy followed by a period of immobilisation and rehabilitation will give excellent results.

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Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her 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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