Skeletal tuberculosis in children in the Western world: 18 new cases with a review of the literature

Harish S. Hosalkar · Nina Agrawal · Swapna Reddy ·
Kriti Sehgal · Edward J. Fox · Robert A. Hill

Received: 21 January 2009 / Accepted: 20 May 2009 / Published online: 19 June 2009
© EPOS 2009

Abstract

Purpose The occurrence of pediatric skeletal (extra-spinal) tuberculosis in the developed world is extremely rare. The purpose of this study was to review the cases at our institutions.

Methods We performed a retrospective review of all pediatric biopsy-proven skeletal (extra-spinal) cases of tuberculosis over a five-year period.

Results Eighteen patients of biopsy-proven tuberculosis were identified. The mean age was 12 years (range 7–20). Lesion locations included: distal humerus, ulna, scapula, acetabulum, proximal femur, proximal tibia, distal tibia,

and calcaneus. All had symptoms of pain, swelling, and stiffness. Five cases had multi-focal involvement. Twenty-four lesions were noted in 18 patients. Nineteen lesions were cystic in nature at presentation. The sedimentation rate was normal in six and purified protein derivative (PPD) was negative in five patients. All received chemotherapy. Six patients underwent surgery.

Conclusions The diagnosis of pediatric skeletal tuberculosis can be made with good correlation of clinical, radiographic, and laboratory findings. Biopsy and culture are the gold standards in diagnosis. Prognosis is good with chemotherapy and non-operative management. Surgical intervention may be needed in select cases.

H. S. Hosalkar (✉)
Department of Orthopaedic Surgery,
Hospital of the University of Pennsylvania,
3400 Spruce Street, 2 Silverstein, Philadelphia, PA 19104, USA
e-mail: hhpedpod@gmail.com

S. Reddy
Albany Medical College, 47 New Scotland Avenue,
Albany, NY 12208, USA

N. Agrawal · K. Sehgal
Children's Hospital of Philadelphia,
34th Street and Civic Center Blvd.,
Philadelphia, PA 19104, USA
e-mail: agrawal.nina@gmail.com

K. Sehgal
e-mail: kriti.sehgal@gmail.com

E. J. Fox
Pennsylvania Hospital, Garfield Duncan Building,
Suite 2C, 800 Spruce Street, Philadelphia, PA 19107, USA

R. A. Hill
Great Ormond Street Hospital for Children,
Great Ormond Street, Russell Square, London WC1N 3JH, UK

Keywords Skeletal tuberculosis · Children · Western world

Introduction

Every second, someone in the world is newly infected by tuberculosis bacilli [1]. In the year 2006, 9.2 million new cases of tuberculosis were diagnosed worldwide [1]. The World Health Organization's (WHO) Stop TB Partnership continues to stress the relevance of this disease as a response to the resurgence of tuberculosis in the 1990s and its more recent growth, which has been linked to population growth worldwide [1].

Skeletal tuberculosis accounts for 10–35% of extra-pulmonary tuberculosis and only 2% of all cases of tuberculosis [2]. While tuberculosis is a major cause of skeletal infection in many developing countries, skeletal tuberculosis in children in the developed world is noted to be rare. This containment is, in part, due to the widespread use of antibiotics in treating tuberculosis. However,

tuberculosis has risen in incidence in developed countries since 1985 due to many factors, including the acquired deficiency syndrome (AIDS) epidemic, immigration, homelessness, and intravenous drug abuse [3–7].

In their recently published annual update, the WHO reports that, while most regions are projected to halve the prevalence and death rate due to tuberculosis by 2015, the prognosis is quite different for Africa and Europe [1]. As the statistics imply, tuberculosis has become an issue even in those regions where it is seemingly under control.

Our team completed a retrospective review at two tertiary-level universities. The purpose of our study was to review the pediatric musculoskeletal (extra-spinal) cases of skeletal tuberculosis and present a succinct review of the diagnosis, symptoms, and treatment of an infrequently seen disease.

Materials and methods

Following institutional review board (IRB) approval, all consecutive cases of skeletal (extra-spinal) tuberculosis that were treated in two tertiary university hospitals over a 5-year period (2001–2006) were reviewed. The inclusion criteria were: age <18 years, occurrence of a documented bone lesion, and biopsy/microbiological evidence of tuberculosis. All of the clinical notes, laboratory findings, purified protein derivative (PPD) tests, pulmonary evaluations, biopsy results (including cultures), and available imaging modalities (plain radiographs and advanced imaging) were reviewed. The location of tuberculosis involvement and treatment offered, including chemotherapy and surgical intervention when applicable, were noted. The clinical and radiological evaluation at the final follow-up visit was recorded. The data are presented in the next section.

Results

Between 2001 and 2006, 18 pediatric patients (<18 years of age) met the inclusion criteria. All institutions are tertiary-level university hospitals and have an extremely wide referral base, therefore, making it almost impossible to come up with a denominator for the purposes of point-prevalence. There were 11 male and seven female patients. The mean age was 12 years (range 7–20 years). Only biopsy-proven cases were included in this study.

The presenting symptoms in all of the patients were persistent pain, swelling, and stiffness or lack of full motion across the involved joint/location. Only four of the 18 patients came up with a possible history of contact with a likely case of chronic cough/possible lung infection in a

family member/friend during the preceding months. All of the patients with lower extremity involvement presented with a limp. The average duration of symptoms was 6 months (range 8 weeks to 18 months). Five patients had a history of significant weight loss in the preceding months prior to presentation. These were mainly the ones with multi-focal involvement. The demographic data, symptoms at presentation, location of lesions, PPD test results, laboratory findings, and duration of anti-tuberculous therapy for all of our cases is presented in Table 1. There were a total of 24 lesions identified among the 18 patients. The most common site for lesions was around the elbow, which was present in seven of the 24 lesions. Although there was associated synovitis noted in cases where the lesion was close to the joint, there were no obvious cases of septic tuberculous arthritis with joint destruction in any of these cases. Five patients had multiple bone involvement: one had triple-bone involvement and four had double-bone involvement. Nineteen of the lesions were cystic in nature at presentation; interestingly, all 19 were strongly suspected to be bone tumors on initial diagnosis.

All patients had sputum testing and/or gastric aspirate testing for tuberculosis. In addition, seven patients had urine testing performed. None of the patients had active pulmonary or genitor-urinary tuberculosis. The erythrocyte sedimentation rate (ESR) was found to be normal in six patients and elevated in 12 patients. In those with elevated ESR, the mean was 74 mm/h with a range of 48 to 112 mm/h. Leukocytosis was evident in all cases, with marginal elevation in eight cases (between 8 and 130,000) and marked elevation in ten cases (>15,000). C-reactive protein (CRP) was in the normal range in all 18 cases. The PPD test was abnormal in 13 patients and negative in five patients. All of the patients underwent a histological diagnosis following biopsy and culture. CXR showed a suspected focus in nine of the 18 cases and was reasonably unremarkable in the remaining ten cases. None of the patients tested positive for human immunodeficiency virus (HIV) and, apart from two patients with renal insufficiency and one with diabetes, none had any obvious immunodeficiency that was detectable. Four of the 18 patients had received the Bacille Calmette-Guérin (BCG) vaccine in their infancy.

In terms of imaging studies, the most common findings were osteolytic/cystic (19/24) lesions that were well-demarcated (Fig. 1). Increased soft-tissue density, attributable to overlying soft-tissue swelling, was also noted on imaging. There is no question that, given the rarity of this infection in the developed world, all radiologists strongly suspected bone tumors as primary diagnoses.

Anti-tuberculosis chemotherapy was given to all patients upon biopsy confirmation. All patients received isoniazid and rifampin supplemented in the initial phase by ethambutol, streptomycin, or pyrazinamide. Quinolones

Table 1 The demographic data, symptoms at presentation, location of lesions, purified protein derivative (PPD) test results, laboratory findings, and duration of anti-tuberculous therapy for all of our cases is presented

Case	Age (years)	Sex	Duration of symptoms (months)	H/o close contact with tuberculosis	Location (no. of lesions)	Pain/swelling/stiffness/fever	BCG	CXR	ESR (mm)	WBC (1,000)	PPD	Anti-tuberculous therapy	Biopsy/culture
1	7	M	2	—	Distal tibia (1)	+/+/+/-	+	+	18	8	Abn	15	+
2	7	F	3	—	Proximal humerus (1)	+/+/+/-	—	—	20	15	Abn	12	+
3	8	F	3	—	Scapula (1)	+/+/+/-	+	+	70	12	Abn	12	+
4	8	M	5	—	Distal femur (1)	+/+/+/+	+	—	20	17	Abn	12	+
5	9	F	10	+	Proximal tibia (1)	+/+/+/-	—	—	52	15	Abn	09	+
6	10	F	2	—	Ulna (1), distal humerus (1)	+/+/+/+	—	+	86	11	Neg	15	+
7	10	F	8	+	Distal tibia (1)	+/+/+/-	—	—	20	16	Abn	12	+
8	11	M	2	—	Distal humerus (1), ulna (1)	+/+/+/+	—	—	18	17	Abn	12	+
9	11	M	14	—	Ulna (1)	+/+/+/-	—	+	88	9	Neg	15	+
10	12	F	3	+	Proximal tibia (1)	+/+/+/+	+	—	18	18		12	+
11	12	M	2	—	Phalanges (3)	+/+/+/-	—	+	96	10	Neg	12	+
12	13	F	6	+	Distal humerus (1)	+/+/+/-	—	+	112	13	Neg	15	+
13	14	M	12	—	Proximal tibia (1), distal tibia (1)	+/+/+/-	—	—	58	2	Abn	12	+
14	14	M	3	—	Prox humerus (1), distal humerus (1)	+/+/+/-	—	—	74	12	Abn	09	+
15	16	M	6	—	Proximal femur (1)	+/+/+/-	—	+	52	15	Abn	12	+
16	17	M	18	—	Calcaneus (1)	+/+/+/+	—	—	66	18	Abn	15	+
17	18	M	3	—	Distal femur (1)	+/+/+/+	—	+	80	19	Abn	12	+
18	18	M	6	—	Acetabulum (1)	+/+/+/-	—	+	54	12	Neg	15	+

Fig. 1 Panel of figures demonstrates various lesions of tuberculosis in diaphyses (**a**) and metaphyses (**b, c, d**) of long bones, as well as in the calcaneum (**e**). It is noteworthy that most of the lesions appear cystic in nature

were used in some cases. All of our patients received a minimum of 12–15 months of chemotherapy based on the clinical and hematological response. Two patients had 9 months of anti-tuberculosis chemotherapy, as they were non-compliant after 9 months. Both healed uneventfully and are doing well.

Six patients underwent surgical debridement (in addition to the initial biopsy) due to the lack of early response to medical therapy (within 6–8 weeks of medical treatment). Three of these lesions were treated simply with debridement and closure, while two patients had bone grafting and one patient with involvement of the acetabulum (Fig. 2)

Fig. 2 Plain radiographs of the pelvis (**a**) and right hip (lateral) (**b**) in a 20-year-old male with a 6-month history of groin pain and limp. T2-weighted coronal (**c**) and axial images (**d**) demonstrate the soft-tissue swelling, as well as the bony edema and diffuse involvement of the acetabulum. Axial computed tomography (CT) image (**e**) demonstrates the lytic lesion in the acetabulum that was biopsied (*inset*) to

reveal the classic granulomatous lesion of tuberculosis. Plain radiograph of the pelvis (**f**) five months post-curettage (with OsteoSet pellet packing) and treatment with anti-tuberculous chemotherapy reveals resolution of the lesion. Clinically, the patient was pain-free at this point and had full range of motion with no limp

had OsteoSet pellet (Wright Medical Technology, Arlington, TN) insertion. These treatments (bone-grafting/OsteoSet pellets) were based more on surgeon preference rather than on the dimensions of the lesion or evidence in the literature about any specific modality of intervention.

The average follow-up period for the patients was 34 months (range 26–60 months). All patients responded well to medical management and returned to normal function following chemotherapy and physical therapy for rehabilitation. There was complete radiological resolution in 20 of the 24 lesions within 9 months of starting chemotherapy; the other four lesions (acetabulum, one proximal femur and two distal femurs) took an average of 15 months for complete resolution at the final follow-up. No signs of recurrence were found all the way through and including the final follow-up visit. There was no evidence of significant limb-length discrepancy in any of these cases at final follow-up.

Discussion

Since 1980, a major worldwide initiative to control tuberculosis has led to a decreased incidence of the disease. More recently, however, an increased number of cases

have been reported in Europe and the United States. The potential causes of recrudescence may be due to immunomodulation [8] and possibly atypical mycobacteria in some cases. Transcontinental immigration does play a role as well. It is, therefore, important that clinicians have an increased awareness for this condition and characteristic manifested for early diagnosis. This is especially true for the pediatric population where presentation may not be typical and diagnosis can, therefore, be delayed. Skeletal tuberculosis in pediatrics, therefore, needs to be revisited.

We have presented our series of pediatric cases with skeletal (non-spinal) biopsy-proven tuberculosis over a 5-year period. Table 2 presents a comparison of common sites of infection, total number of cases, and total lesions in some of the previously published case series of pediatric skeletal tuberculosis [3, 5, 9, 10].

One of the great difficulties in diagnosing skeletal tuberculosis is the non-specific clinical presentation. The primary symptoms reported in this study were bone pain, swelling, and stiffness. Systemic symptoms may be rare, particularly in the developed world patient population, where nutritional deficiencies in general are not very common. The differential diagnosis for such symptoms is quite extensive and the chronicity of symptoms usually demands a thorough work-up to rule out the worst possible

Table 2 Comparative representation of common locations of skeletal tuberculosis infections in some previously published series [3, 5, 9, 10]

Author	Year	Age range	Total no. of cases	Total lesions	Cranium	Axial skeleton			Appendicular skeleton	
						Shoulder girdle	Spine	Pelvic girdle	Upper ext.	Lower ext.
Haygood and Williamson	1994	0.5–19	45	46	0	2	0	0	2	42
Rasool	2001	1–12	42	47	0	4	0	4	14	25
Morris et al.	2002	2–13	4	10	1	5	3	0	1	0
Dhammi et al.	2003	2–15	18	51	0	0	6	0	31	14
Hosalkar et al. (current study)	2009	7–18	18	24	0	1	0	1	12	10

scenarios, i.e., bone tumors and sarcomas. Non-disseminated tuberculosis by itself is not life-threatening and can be well controlled and treated if diagnosed early.

Laboratory findings such as leukocytosis and an elevated ESR may be present. These were seen in a majority of the patients in this study and may be important markers. CRP is usually normal given the chronic nature of inflammation and is also an important finding against acute septic arthritis and osteomyelitis. A radiographic skeletal survey may help in determining the extent of the disease. It has been reported that only 3–6% patients with bone, joint, or spinal tuberculosis have normal plain radiographs; therefore, this imaging modality is essential and very cost-effective [11]. Skeletal tuberculosis can appear as joint space narrowing, subchondral erosions, lytic lesions, or articular osteopenia on plain radiographs. The gold standard in diagnosis, however, is made with histological confirmation of a tissue sample showing tuberculous granulomas with multinucleated giant cells, epithelioid histiocytes, lymphocytes, and plasma cells.

Histology/biopsy cultures in skeletal tuberculosis are seldom positive. This is usually because the organism needs to be in specific conditions to be cultured and it sometimes takes a long incubation time for in vitro growth in the laboratory [12]. Our study, interestingly, is a retrospective case series of all biopsy/culture-positive cases of skeletal tuberculosis in the pediatric population. Therefore, in certain ways, this is a biased population of positive cases of skeletal tuberculosis.

The most common site of skeletal tuberculosis in the adult population is the spine (Pott's disease). An epidemiological study of tuberculosis in the United States reported that the spine was involved in 50% of tuberculosis patients [13]. Our cohort involved only the extra-spinal cases, as the nature of clinical practice in our institutions involves spine care as a separate subspecialty. Many of the patients in our study had localized lesions in the metaphysis. The metaphysis of long bones receives an abundant blood supply that favors the hematogenous dissemination of *Mycobacterium tuberculosis* [6, 8].

Multi-focal tuberculosis was also seen in five patients in this study. It is a rare entity, even in endemic regions, comprising only 5% of all skeletal tuberculosis cases [14]. This type of involvement is usually seen in association with pulmonary manifestations and a suppressed host immune response. Dhammi et al. reported 18 cases of multi-focal skeletal tuberculosis in India and concluded that it is a common cause of multiple skeletal lesions in developing countries where tuberculosis is widespread and nutrition is poor [9].

The treatment of skeletal tuberculosis includes administering anti-tuberculosis drugs. Many authors suggest that medical treatment alone is enough, while others believe that surgical debridement and drainage is necessary [11]. The most recent recommendations from the Centers for Disease Control and Prevention (CDC) are to give standard courses of medical treatment for a minimum 12 months in tuberculosis involving the bone and joints [15]. In some cases, the treatment may be extended for up to 24 months. The choice of drugs should be dictated by the prevalence of drug resistance.

Our indications for surgery in this group of patients include: (a) lack of early response to medical management (i.e., no evidence of early healing in 6–8 weeks), (b) severity of involvement leading to mechanical weakening of the bony skeleton. When the lesion extent is so large that a pathological fracture could occur, one may have to debate and perform bone-grafting and, in rare cases, stabilization may be necessary with instrumentation. We do not advise the routine use of any instrumentation for prophylactic stabilization in these cases, as medical management is usually successful in leading to bony union and consolidation.

Skeletal tuberculosis in children continues to be reported in the Western world. Although it may not be as common as in other nations, its diagnosis must not be missed due to a lack of familiarity. To make an accurate and timely diagnosis, physicians must be aware that skeletal tuberculosis may present simply as bone pain and decreased range of motion in the pediatric population. A good history,

thorough clinical examination, high index of suspicion, laboratory work, radiographs, and tissue biopsy may be invaluable in making the diagnosis of tuberculosis.

References

1. Dye C, Floyd K, Uplekar M (2008) WHO report 2008. Global tuberculosis control: surveillance, planning, financing. World Health Organization, Geneva, Switzerland
2. Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD (eds) (1983) Harrison's principles of internal medicine. McGraw Hill, New York
3. Haygood TM, Williamson SL (1994) Radiographic findings of extremity tuberculosis in childhood: back to the future? *Radiographics* 14:561–570
4. McDonald M, Sexton D (2006) Skeletal tuberculosis. Available online at: <http://www.uptodate.com/patients/content/topic.do?topicKey=~8NvTkw4E34ELMv>
5. Rasool MN (2001) Osseous manifestations of tuberculosis in children. *J Pediatr Orthop* 21(6):749–755
6. Teo HE, Peh WC (2004) Skeletal tuberculosis in children. *Pediatr Radiol* 34(11):853–860
7. Yao DC, Sartoris DJ (1995) Musculoskeletal tuberculosis. *Radiol Clin North Am* 33:679–689
8. Wang MN, Chen WM, Lee KS, Chin LS, Lo WH (1999) Tuberculous osteomyelitis in young children. *J Pediatr Orthop* 19(2):151–155
9. Dhammi IK, Jain AK, Singh S, Aggarwal A, Kumar S (2003) Multifocal skeletal tuberculosis in children: a retrospective study of 18 cases. *Scand J Infect Dis* 35(11–12):797–799
10. Morris BS, Varma R, Garg A, Awasthi M, Maheshwari M (2002) Multifocal musculoskeletal tuberculosis in children: appearances on computed tomography. *Skeletal Radiol* 31(1):1–8
11. Monach PA, Daily JP, Rodriguez-Herrera G, Solomon DH (2003) Tuberculous osteomyelitis presenting as shoulder pain. *J Rheumatol* 30(4):851–856
12. Watts HG, Lifeso RM (1996) Tuberculosis of bones and joints. *J Bone Joint Surg Am* 78(2):288–298
13. Bloch AB, Rieder HL, Kelly GD, Cauthen GM, Hayden CH, Snider DE (1989) The epidemiology of tuberculosis in the United States. *Semin Respir Infect* 4(3):157–170
14. Moujtahid M, Essadki B, Lamine A, Bennouna D, Zryouil B (1995) Multifocal bone tuberculosis: apropos of a case. *Rev Chir Orthop Reparatrice Appar Mot* 81(6):553–556
15. Centers for Disease Control and Prevention (CDC) (2008) Trends in tuberculosis—United States, 2007. *MMWR Morb Mortal Wkly Rep* 57:281–285