TUBERCULOSIS OF THE FOOT AND ANKLE IN CHILDREN

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The University of Cape Town Research Ethics Committee has approved this study: REC REF 195/2010

Declaration

I declare that the work contained in this research report is based on my original work and has not been used for any other degree.

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Signed by candidate

Sithombo Maqungo

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Part A - Protocol

Research Proposal

TUBERCULOSIS OF THE FOOT AND ANKLE IN CHILDREN

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Introduction and aim of study

Tuberculosis is endemic in the Western Cape and it affects 40 000 people out of a population of 4 million. Six percent (2400) of cases have extra-pulmonary involvement. Four percent (100) of these present with skeletal tuberculosis. At Maitland Cottage Hospital we see 30 cases of skeletal TB every year with TB spine being the commonest presentation, and only one case of foot and ankle involvement. The literature is very sparse on this subject. Available studies have been done mostly on adult patients and the classification systems used do not relate to prognosis. The outcome in these studies is also not clearly defined.

The purpose of our retrospective study is to critically assess the long-term outcome of tuberculosis of the foot and ankle in children and to define an initial classification system that would relate to prognosis.

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Relevance of the study

The relevance of the study is to determine if radiological classification at presentation and anatomical site of involvement of tuberculosis of the foot and ankle in children relate to prognosis.

Study hypothesis

The radiological classification at presentation and anatomical site of involvement relate directly to outcome in these cases.

Study population

Clinical case notes, X-rays and CT Scans of 28 patients who presented with tuberculosis of the foot and ankle to Maitland Cottage Hospital over a 24-year period (1982-2005) will be reviewed retrospectively. All patients had an open synovial biopsy and anti-tuberculous chemotherapy.

Study design

Retrospective descriptive study.

Study method

A retrospective review of all patients who were treated for TB of the foot and ankle in Maitland Cottage Hospital over a 24-year period (1982-2005). Their records will be reviewed for the following parameters:

1. Age at presentation
2. Duration of symptoms
3. Site of involvement (clinically and radiologically)
4. Radiological classification
5. Special investigations performed
6. Histology and culture results
7. Treatment received
8. Follow up period
9. Clinical and radiological outcome

The results will be grouped into **excellent** (pain free, plantigrade foot with a normal range of movement), **good** (50% range of movement) and **poor** (less than 50% range of movement). The results will then be further looked at in order to deduce any further conclusions, especially relating to our aims.

Analysis of the study

During analysis of the results we will be looking at the following points;

- Duration of symptoms before presentation
- Anatomical site of involvement
- Radiological classification at presentation
- Special investigations performed
- Radiological appearance at follow up
- Clinical range of movement at final follow up

Report of findings

Results will be submitted for publication in peer review journals. Results will also be discussed at national or international orthopaedic conferences and research or faculty meetings.

Ethical considerations

This is purely a retrospective study utilising available clinical notes and radiographs. No intervention is to be performed on any patient outside of acceptable clinical practice. No extra risks will be entailed by any of the subjects within the study. No patients will be identified by name or hospital number and every effort will be made to protect their privacy. There are no immediate benefits to the study subjects as this is a retrospective analysis. The knowledge gained will influence the future management of similar patients seen within the context of locally available resources and expertise.

Part B – Literature Review

Introduction

Tuberculosis is an infectious disease caused by bacteria in the *Mycobacterium tuberculosis* complex. Of these the most common species to infect humans is *M. tuberculosis*. Tuberculosis has been around since very early human civilisation yet to this day it still remains the most important communicable disease in the world with 2 billion people worldwide currently infected. It is estimated that 2 to 3 million people die from tuberculosis each year[1]. Tuberculosis is endemic in the Western Cape Province of South Africa. Tuberculous involvement of the foot and ankle is an uncommon presentation of osteo-articular tuberculosis. There is scarcity of literature pertaining to foot and ankle involvement in children. Children have been included in small numbers as part of larger series containing mostly adult patients. The rarity of the site affected, uncommon presentation, difficulty in diagnosis and ability of tuberculosis to give rise to a clinical picture that closely mimics other diseases all lead to significant delays in diagnosis and initiation of appropriate treatment.

Objectives of literature review

- To gain background knowledge on the history of tuberculosis and the evolution of its treatment.
- To gain understanding of the current epidemiology of the disease and compare our local burden of disease to international trends.
- Each of the articles that include tuberculosis of the foot and ankle in children will be critically analysed for the number of cases, methods used to confirm diagnosis, classification system used, treatment received and lastly outcome measures.

Literature search methods

The literature search for this review was conducted using the electronic search engines PubMed, Google Scholar and Google. My search was limited to English text literature only. Due the paucity of articles on tuberculosis of the foot and ankle in children, I widened my search criteria to include all forms of osteo-articular tuberculosis in children as well as foot and ankle involvement in adults. I also included literature on the history and current epidemiology of tuberculosis. All relevant full-text journal articles, books, government and World Health Organisation publications that were found on this search were reviewed, as well as some references from the afore-mentioned articles.

Review

People in the pre-civilisation times lived as wanderers and did not congregate in large groups. During this era tuberculosis and other infectious diseases may have occurred sporadically but they did not occur in epidemic forms. Tuberculosis probably started to occur more frequently when people began gathering in groups and living in permanent sites such as villages but it was nevertheless still rare. Tuberculosis most likely occurred as an endemic disease in animals long before it affected humans with *Mycobacterium bovis* being the most likely pathogen. The first epidemic was reported in the 17th century and it slowly spread worldwide as a result of Europeans travelling to and colonising distant sites[2]. While some mummies from several Egyptian sites show skeletal changes suggestive of tuberculosis, Cummings[2] reports that tuberculosis was almost unknown within the interior of sub-Saharan Africa as late as 1908.
Theophille Laennec is credited with being the first person to recognise that tuberculosis, in all its forms and anatomic sites, is a single disease entity[2].
On 24 March 1882 Robert Koch described the tubercle bacillus, *Mycobacterium tuberculosis*, an organism still widely known to this day as Koch's Bacillus, and convincingly demonstrated it to be the cause of tuberculosis[2].

Rest and sunshine were initially advocated as treatment for tuberculosis with some patients spending as long as two years in hospital. In pre-chemotherapy era the ultimate mortality of patients admitted to New York State sanatoria with tuberculosis in 1938-1948 was as high as 69% for those with far advanced disease[2]. The grim prognosis of tuberculosis changed dramatically in November 1944 with the advent of Streptomycin. Isoniazid was equally and dramatically effective when it was first used in 1952. Rifampicin was introduced in 1966 and was hailed as the break-through of the time. With these dramatic therapeutic results, the era of successful chemotherapy for tuberculosis was launched. The conquest of tuberculosis seemed imminent and the worldwide incidence showed a steady decline.

Epidemiology in South Africa

Tuberculosis arrived in this country with settlers and missionaries, many of whom were already infected from the massive epidemic that had swept Europe and North America during the 17th century. Many sufferers came seeking a cure from the sun and fresh air. The previously unexposed, non-immune indigenous population of South Africa rapidly developed tuberculosis. Over the ensuing years tuberculosis then found fertile ground to rapidly become an epidemic due to poor living conditions, unjust laws that restricted people's movement, over-crowded living and working conditions, poor health service provision and the practice of banishing those with the disease to their original homes without offering them treatment. The World Health Organization (WHO) has estimated that one-third of the world's population is infected with Mycobacterium tuberculosis[3]. More than one-third of these cases are found in South and East Asia and sub- Saharan Africa. In the UN TB report of 2010[3] it is estimated that South Africa has an annual tuberculosis prevalence of 490 000 out of a population of 50 million. This number is on the rise and this alarming trend is reproduced in most countries around the world. This is directly related to the emergence of HIV/AIDS and the immigration of people from countries where tuberculosis is a serious public health problem, non-compliance with chemotherapy and an increase in the ageing population. Compounding the problem has been the emergence of multi-drug (MDR-TB) and extremely drug resistant tuberculosis (XDR-TB). Paralleling this has been a disproportionate increase in the number of extra-pulmonary tuberculosis cases. The proportion of non-respiratory cases increased from 18% in 1980 to 25% in 1998, and 20% of these involved the musculoskeletal system[4]. Children have not been immune to the ever-increasing incidence of tuberculosis, and these increases are worrisome as tuberculosis in young children is a sentinel event, indicating recent transmission of tubercle bacilli in the community. At Maitland Cottage Hospital we treat an average of 30 children with skeletal tuberculosis every year.

Osteo-articular Tuberculosis in children

Children show a higher predisposition to the development of extra-pulmonary tuberculosis compared to adults. Osteo-articular tuberculosis is described as direct infection of bones and/or joints by the tubercle bacillus. Bones and joints are involved in 1% to 3% of all tuberculosis cases[5].

Osteo-articular tuberculosis can affect the bone, joint or both. If it involves the joint it tends to be monoarticular. Tuberculous arthritis usually occurs as a result of metaphyseal tuberculous osteomyelitis crossing the epiphyseal plate into the joint[6]. This transphyseal spread is characteristic of tuberculosis and is not a feature in pyogenic arthritis. In children older than 1.5 years, the transphyseal vessels disappear and extension of infection into the epiphysis and joint becomes less common. Another route of joint infection is when the organism is deposited directly onto the joint synovium, but this occurs less commonly than via bony extension. The site of the primary infection is in most cases unknown. Concurrent pulmonary involvement is seen very rarely. Dhillon and Nagi[5] reported a series of 74 cases with tuberculosis of the foot and ankle treated over an 11 year period, and only nine patients had evidence of active or healed tuberculosis on lung radiographs. This was quite a heterogeneous group of patients however, with age ranging from 6 to 78 years. Mittal, Gupta and Rastogi[7] (1999) reported on 44 immunocompetent patients with tuberculosis of the foot and none of these had active pulmonary disease. The age range was 4 to 63 years with most patients aged between 25 and 40 years. Rasool et al[8] (1994) writing on cystic tuberculosis of bone in children presented 13 cases, and only two (15%) had concurrent chest involvement.

Teklali et al[9] (2003) reported on 106 children from Morocco with osteo-articular tuberculosis and 32 (34%) had active tuberculosis in other sites e.g. lungs, lymph nodes, skin and brain.

In these 4 studies the percentage of pulmonary co-infection ranges from 0%-34% proving once more the many different clinical scenarios tuberculosis can present with.

Spine involvement is seen in almost 50% of articular tuberculosis, followed by the hip and knee as the most commonly involved areas. In Teklali's study of the 106 children with osteo-articular tuberculosis, forty-nine (49%) percent had involvement of the hips followed by the

knee at 17 %[9]. In this study all children admitted with spine involvement were excluded. At our institution we treat on average 30 children per annum with skeletal tuberculosis with the following distribution: spine 20 cases, hip 5 cases, knee 4 cases, foot and ankle 1 case.

Distribution of site in foot and ankle involvement is also not consistent. In Mittal's cases[7], the commonest site was midtarsal joints, whereas in Dhillon's paper[5] the calcaneus was the most commonly involved bone. The age groups in both these papers are similarly matched and they come from the same country, proving once again the heterogenecity of tuberculosis. In our research manuscript attached to this literature review the commonest site of involvement is the ankle joint.

Preceding local trauma is a common finding on history but its significance is uncertain. No causal relationship has been established between trauma and tuberculosis. It has been postulated by Shams et al that this association may be due to increased vascularity and decrease in local resistance that occurs as a result of trauma and this leads to activation of dormant foci or the creation of new ones[10]. In almost all the studies I have come across the history of preceding local trauma is mentioned. The significance of local trauma would be difficult to investigate in children, as they tend to experience frequent falls with varying degrees of significance.

Diagnosis of osteo-articular tuberculosis is notoriously difficult as there are no universally accepted classic clinical and radiographic signs. The diagnosis can be made by a combination of clinical examination and confirmatory radiological and laboratory studies. World Health Organisation reports that only 7% of osteo-articular tuberculosis is diagnosed correctly at the first visit[3].

The initial symptoms are very insidious and patients often present late. The commonest presentation is that of pain early on and later followed by swelling secondary to synovitis. Virtually all the studies I have reviewed state that there is often a delay in the patient's initial appearance of symptoms and the eventual diagnosis of osteo-articular tuberculosis. This range can be anything from 5 days to 5 years and it not only varies between studies but also within cases in the same study.
Clinical examination is often non-specific but late presentation may lead to sinus formation and gross synovitis.

Mantoux skin testing is universally performed in cases of suspected tuberculosis in children. This tuberculin skin test has been in existence for over a hundred years and is still very unreliable. False positive tests can occur after a BCG (Bacille Calmette-Guerin) vaccination. A negative test does not exclude active disease as this test can be negative in patients

with a weakened immune system, malnutrition and a concomitant viral infection despite the presence of active disease.

Laboratory tests such as low haemoglobin and an elevated erythrocyte sedimentation rate (ESR) are almost universal findings. In Rasool's series of 13 children with cystic tuberculosis of bone 4 children had both a negative Mantoux test and a normal ESR[8].

Sputum testing via microscopy for acid fast bacilli (AFB) is usually the first test performed. Its use is that it can also detect other non-tuberculous bacteria, but its biggest drawback is that it does not determine which antibiotics those bacteria will be sensitive to.

Radiographically tuberculous osteitis can present in two forms, solitary cystic nodules or the more common multiple cystic form. The multicystic form was first described in the 1920's as 'Jungling's disease' or 'osteitis tuberculosa multiplex cystoides'. The terminology was however incorrect as Jungling's description was that of sarcoidosis which he considered to be a manifestation of tuberculosis. In 1952 Komins[11] proposed that the multiple cystic bone lesions of tuberculosis be renamed 'multiple pseudocystic tuberculosis' emphasizing that these lesions were not true cysts.

Solitary cystic lesions are reportedly uncommon and only a few sporadic case reports have appeared in the literature. In Rasool et al[8] 1994 series of 13 children with cystic tuberculosis of bone, ten had solitary cystic lesions and three had the characteristic multiple cystic form. Of note is that no children in this series had foot and ankle involvement. One had distal tibial metaphysis involvement but there is no mention of extension into the adjacent ankle joint

Bone lesions in tuberculosis are radiolucent, round to oval, and are situated in peripheral skeleton near metaphysis. The cysts however can occur anywhere in the skeleton. Solitary lesions may mimic bacterial and fungal infections, simple or aneurysmal bone cysts, cartilaginous tumours and osteoid osteoma[12,13]. Phemister's triad of periarticular osteoporosis, marginal erosions and narrowing of the joint space is the radiological feature of osteo-articular tuberculosis but these changes are also non-specific and it may take a while for all of these features to appear.

The value of an isotope bone scan is not well established. In theory this would be helpful in detecting other skeletal lesions. I have not found any literature that supports the routine use of this modality. In one study[6] all children who presented with osseous tuberculosis had a bone scan performed, however the results of the isotope scan are not given in the manuscript. We do not routinely perform isotope bone scans in our tuberculosis patients.

Tuberculous arthritis does not lend itself to distinctive radiographic features either. The common findings are osteopaenia early on, followed by cyst formation and eventually joint space narrowing and destruction. Kerri and Martini (1985)[14] presented 33 cases and proposed a radiological classification system. Stage 1 was described as being 'normal' with appearance of osteopaenia and soft tissue swelling. Stage 2 is 'osteomyelitic' with epiphyseal or metaphyseal cysts and a normal joint space. Stage 3 is 'arthritic' with joint space narrowing and Stage 4 adds gross anatomical disorganisation to stage 3. Again these radiographic changes are non-specific and can be seen in any arthritic process in any joint.

CT scanning can help in defining the extent of the lesions and clearly show sequestration and cortical breaks. Brew[15] used CT guided biopsies but failed to collect sufficient material for analysis.

The role of Magnetic Resonance Imaging (MRI) in diagnosis of osteo-articular tuberculosis is still under evaluation. MRI scans can demonstrate lesions in and around bone before they are evident on plain radiography. Brew[15] used it to confirm osteomyelitis centred around the talo-navicular joint and it also demonstrated synovial thickening. In Jerome et al[16] (2007) case with cuneiform involvement MRI scan showed extensive areas of altered marrow changes and bony oedema. In 2001 Hong et al[17] compared 29 patients with tuberculous arthritis with 13 who had pyogenic arthritis in an effort to assess MRI distinguishing features between the two conditions. They made two significant observations i.e.; bony erosions were more prominent in tuberculous than pyogenic arthritis and joint space narrowing was more prominent with pyogenic arthritis. They concluded however that when infection was confined to a joint MR imaging was unable to distinguish between tuberculous and pyogenic arthritis. Furthermore, in cases of arthritis involving the relatively small joints, such as the wrist or ankle, tuberculous arthritis was hardly distinguishable from pyogenic arthritis. Because of the relatively small joint cavity and narrow potential extra-articular spaces, both tuberculous arthritis and pyogenic arthritis showed irregular patterns of extra-articular spread. Abscess formations around these small joints were not common. Age range in MRI group was 13-73 years with many joints involved and the range in the pyogenic group was 3-89 years.

In 1992 Hoffman et al[18] compared the radiographic, CT and MRI findings in 25 children with spinal tuberculosis and concluded that plain radiography still provided most of the information required in diagnosing and treating spinal tuberculosis in children.

The value of ultrasonography has also not been established but it can help demonstrate joint effusion and can also direct aspiration of fluid for further laboratory testing. This tends to produce a low yield as the

organism is in synovium, and very little of it ends up in joint fluid. In our setting where tuberculosis can present acutely and resemble a picture of septic arthritis we do not do ultrasound-guided aspiration. Every patient with arthritis gets a formal arthrotomy, washout and synovial biopsy.

The only sure way to diagnose tuberculosis is by demonstration of acid fast bacilli on microscopy or culture of *Mycobacterium tuberculosis* on appropriate culture media. A major drawback for culture is that it can take up to 6 weeks for the test to yield a result.

The classic histological finding is that of granulomatous inflammation. However, this finding is also non-specific as granulomatous synovitis can be found in other infective and non-infective conditions such as mycotic infections and sarcoidosis.

Osteo-articular tuberculosis is paucibacillary in nature and therefore microscopy and culture do not always produce a positive result. Shams et al[10] state that aspiration of fluid does not always yield a positive result, as the infection is tissue based with organisms occasionally spilling into synovial fluid. Therefore AFB stains of synovial fluid are positive in only 20% of cases and culture from synovial tissue in 80% of cases.

In endemic areas it is however not essential to demonstrate AFB on microscopy or culture *M.tuberculosis*. Mittal et al[7] state that in endemic areas like India the clinical features, radiological appearance and elevated ESR are sufficient to diagnose tuberculosis and initiate treatment. It is only in areas where tuberculosis is not endemic that histopathological and/or microbiological confirmation should be mandatory[19].

Medical management with first line anti-tuberculous chemotherapy is the mainstay of treatment. The usual regimens are the three or four drug combinations of rifampicin, isoniazid, and ethambutol with or without pyrazinamide. The duration varies from region to region but is usually between 6 and 18 months, the commonest being between nine and twelve months. Sandher[20] supports treatment duration of 6 months. Before 2006 only sporadic reports of osteo-articular multi-drug resistant tuberculosis (MDR –TB) appeared in the literature[21-23] but none involved the ankle joint in a child. Baquero-Artigao and Garcia-Miguel[24] are the only ones to have reported a case of ankle involvement in a child with multi-drug resistant tuberculosis. The child in this paper did not improve after 3 months of treatment with first line anti-TB and repeat *M.tb* cultures which were sent for susceptibility patterns and showed resistance to isoniazid, rifampicin and streptomycin. Paraaminocyclic acid and cycloserine were subsequently added to her treatment and her clinical condition improved. Her treatment was planned for 2 years but she was lost to follow-up at 10 months. In our series of 28 children with foot and ankle involvement we found 2 cases with MDR-B and their drugs were modified according to

our local guidelines. No firm recommendations are available pertaining to the duration of treatment in MDR-TB and this can be up to two years and cost more than five times the cost of treatment with first line chemotherapy.
The role of surgery beyond taking a synovial biopsy is showing a diminishing trend. Wilkinson25 advised synovectomy with curettage of bone erosions in all cases of hip and knee involvement. Rasool et al[8] 1994 curetted the cyst-like cavities to remove all granulation tissue and pus. Kerri and Martini[14], and Dillon and Nagi[5] feel that the role of surgery beyond biopsy is limited because surgical synovectomy is almost always incomplete and once there is erosion of cartilage no amount of surgical synovectomy will reverse that. Dhillon and Nagi[5] used surgery to correct destroyed painful joints. Sequestrate do not need to be surgically removed as they get resorbed with medical therapy. Lee and Hoffman[26] treated 33 children with tuberculosis of the knee and only two required surgery and these were salvage procedures i.e. arthrodesis and posterior release.

In our foot and ankle series of 28 patients no children were subjected to surgery over and above synovial biopsy.

The role of joint immobilisation has also come under the microscope lately with earlier reports advocating immobilisation and later reports advocating earlier joint mobilisation as pain allows. Hoffman et al[27] found no difference in outcome in tuberculosis of the knee in children where the joint was immobilised versus those whose joints were not immobilised. These were cases that presented early, with stage 1 or stage 2 disease.

Healing can be assessed clinically, radiologically and via laboratory studies. Clinical features include decrease in pain and swelling, plus healing of sinuses. Radiographic features include a decrease in osteoporosis with appearance of focal sclerosis. Mittal et al[7] state that in patients who had loss of a phalanx healing was characterised by reconstitution of bone mass. We also experienced this phenomenon with midfoot involvement where there was bone resorption during active disease and later followed by reappearance of bone during the healing phase. It is not clear whether this is actual bone loss or severe osteopaenia. CT scans and MRI scans can also be repeated during the healing phase to monitor response to treatment. These modalities can be misleading though as the image appearance always lags behind the biologic process of repair and residual cavities may still be observed on CT scans long after the disease is healed. Laboratory testing is usually a

serial decrease in the ESR. We rely on clinical symptoms and serial ESR measurements to monitor disease response to treatment.

Ankle and foot involvement in children: Scarce literature

It was estimated in 1995 that 1.3 million children in the world develop disease caused by *M. tuberculosis* every year and the annual risk of infection with this organism is 1-2% in the developing world[4]. Extensive literature is available on tuberculosis of the foot and ankle in adults[5,7,28-32] but there is very little literature on involvement of the foot and ankle in children. Rasool et al[8] presented on 13 children with cystic tuberculosis of bone but none of their cases had foot and ankle involvement. Maltezou[33] in 2000 reviewed 102 children with extrapulmonary tuberculosis admitted to a single institution over a 17year period and only 5 had skeletal TB and of these none had foot and ankle involvement. Children have been included as part of a broader study group consisting mainly of adult subjects.

In 2010 Holland[34] reviewed 4 cases of skeletal tuberculosis that presented to the Blackburn area of England between 2006 and 2008 and found only one foot and ankle cases and this involved the talus. Sandher[35] had reviewed the same geographical area and found 2 skeletal tuberculosis cases in 17years. This is in keeping with the rising incidence of tuberculosis worldwide and with it the disproportionate rise in osteo-articular involvement.

Palozzi[36] et al reported 3 ankle cases from Italy in children aged between 14 months and 5 years. Rasool[6] found 3 patients with foot and ankle involvement out of 42 children. Our series of 28 patients is thus the largest to date.

Only few other case reports have foot and ankle involvement in children[5,7, 9,20,24,34,36,37].

Chronic monoarthrirtis is a relatively common paediatric problem and differential diagnosis includes juvenile chronic arthritis (JCA), trauma, pigmented villonodular synovitis (PVNS), foreign body synovitis, Lyme disease, viral arthritis, reactive arthritis, and arthritis associated with spondylo-arthropathies, malignancies, sarcoidosis, tuberculosis, and other chronic infections. As if this long list of differential diagnosis is not long or complex enough, tuberculosis can indeed co-exist with any of these conditions. Lui and Stephen[38] in 2008 presented a case with simultaneous pigmented villonodular synovitis (PVNS) and tuberculosis of the ankle joint.

In our setting differential diagnosis for monoarthritis is usually between JCA and tuberculosis. In JCA a definite histological finding of fibrinoid necrosis is rarely found and rheumatoid factor is positive in15% to 20% of children[39]. When culture is negative and histology non-specific it becomes very difficult to separate these two conditions.

Tuberculosis can also present acutely with a picture closely resembling that of septic arthritis or pyogenic osteomyelitis. Rasool et al[8] had 3 such cases and in our series we found one that presented with a warm, painful erythematous ankle. Four had sinuses from abscesses that were drained elsewhere.

Children tend to present with involvement of phalanges or metatarsals. If these are found then similar lesions should be sought in the contralateral foot and hands. In our series however we did not have a single case with phalangeal involvement.

Because the disease is paucibacillary by nature, sputum microscopy positive for AFB and a culture positive for *M.tuberculosis* are both rare, and the diagnosis usually is confirmed (only probably) by obtaining granulomatous tissue on biopsy. In endemic regions, radiologic appearance and elevated erythrocyte sedimentation rate are sufficient to diagnose tuberculosis and commence treatment.

Outcomes are reportedly good when the disease is identified and treated early and outcomes universally bad when the disease is picked up late with joint space narrowing[5-7,9,20,24,34,36,37]. Shanmugasundaram[40] was the first to relate initial radiographic appearance of tuberculosis of the hip to eventual outcome. This finding has since been confirmed in paediatric orthopaedic literature by Campbell and Hoffman[41] in tuberculosis of the hip, Lee et al[26] in tuberculosis of the knee, and by Dix-Peek et al[42] in tuberculosis of the elbow joint. No authors have attempted to correlate radiographic appearance at presentation and anatomic site of involvement with eventual outcome in tuberculosis of the foot and ankle in children.

Summary

Tuberculosis continues to be an important public health problem worldwide and it still eludes best and sustained efforts at control and eventual eradication. The combination of non-specific clinical and radiological signs, plus its ability to mimic other clinical entities often

leads to diagnostic and therapeutic delays. Tuberculosis has been called the great imitator for this reason[43].

The outcome is good if the disease is diagnosed early and medical treatment commenced promptly. There is paucity of literature pertaining to foot and ankle involvement in children. No one has attempted to formulate an initial anatomic classification system that relates to prognosis and the outcomes are not clearly defined.

Further avenues of research

From this literature review it has become clear that early diagnosis of tuberculosis still eludes most clinicians. Identification of early synovitis and osteopaenia remain very subjective. Even when the disease is suspected clinically, laboratory confirmatory tests cannot be relied upon to confirm the diagnosis. The tuberculin skin test has been in existence for over a hundred years and is still very unreliable.

Nucleic acid amplification tests such as polymerase chain reaction (PCR) are a relatively new development in active tuberculosis testing. These tests can detect the presence of genetic material in bacteria so they do not rely on the production of an antibody response and can be used to diagnose even latent tuberculosis. However, samples for these tests have to contain a certain number of M. *tuberculosis* bacteria for the detection to occur. This is not always possible, particularly with osteo-articular tuberculosis where sensitivity remains low. These tests are not routinely available because they are expensive and are relatively complicated to run in the laboratory and have a sensitivity of 40%. The T-SPOT.*TB* test holds several major advantages over the tuberculin skin test in that it does not require a second visit, it is not affected by BCG vaccination and it is very reliable, even in patients with weakened immune systems.

Developed by University of Oxford in England, it gives an overall measurement of the antigen load on the immune system, which can reveal the presence of subclinical disease. Because this does not rely on production of a reliable antibody response or recoverable pathogen, the technique can be used to detect conditions such as latent tuberculosis.

The future of early diagnosis of tuberculosis lies in these tests being readily available and proven in the clinical setting. Cost needs to come down as it the poorer countries that are hardest hit by the disease.

The rapid identification of drug-resistant organisms is necessary for the control of MDR-TB and a new culture medium that takes less than 6 weeks to give a result with associated sensitivity also needs to be developed.

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Part C - Manuscript

This manuscript will be submitted to the Journal of Bone and Joint Surgery, British edition. The format and referencing style is that which is required by the journal.

TUBERCULOSIS OF THE FOOT AND ANKLE IN CHILDREN

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.
This study has been approved by the University of Cape Town Research Ethics Committee REC REF 195/2010.

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Abstract

We reviewed 28 patients in order to assess the outcome of tuberculosis of the foot and ankle in children and to describe a classification that would relate to prognosis.

The average age was 5.3 years (1.5 – 12.5 years). The ankle was involved in 12 patients (43%), the midfoot in 9 patients (32%) and the subtalar joint and/or calcaneus in 7 patients (25%). Ankle joint and midfoot involvement presented with swelling and pain. Subtalar joint involvement presented with stiffness with or without a varus or valgus deformity.

Radiographs in ankle joint involvement showed osteopaenia with or without lytic lesions of the distal tibial epiphysis and/or sclerosis or lytic lesions of the dome of the talus. Midfoot involvement showed osteopaenia with or without absence of bone (cuneiforms, cuboid and navicular). Subtalar involvement showed lytic lesions of calcaneus and/or inferior neck of the talus that were not always visible on plain radiographs, but were confirmed with CT scan in 3 patients.

Open biopsy was done in all patients. Histology and/or culture was positive in 26 of 28 patients.

Treatment was with isoniazid, rifampicin and pyrazinamide for 9 months. Two patients had resistant tuberculosis and their drugs were modified accordingly.

At an average follow-up of 7.3years (4-18 years) all patients had no residual symptoms and a plantigrade foot. Ten patients (36%) had an excellent result (normal radiographs and normal range of movement), 15 patients (50%) had a good result (range of movement more than 50% of normal and/or some irregularity of bone) and 4 patients (14%) had a poor result (range of movement less than 50% of normal).

Introduction

Tuberculosis remains a major public health problem globally[1] and is endemic in the Western Cape province of South Africa with an annual prevalence of 40,000 new cases per 4 million population. Six percent of these cases present with extra-pulmonary involvement (mainly lymph nodes). Skeletal tuberculosis comprises only 4 percent of extra-pulmonary tuberculosis[2, 3]. This extrapolates to one patient with skeletal tuberculosis for every 400 patients with pulmonary tuberculosis. Due to the emergence of the Acquired Immune Deficiency Syndrome and multi-drug resistant strains of *Mycobacterium tuberculosis* there has been a significant rise of osteo-articular tuberculosis since 1985[4].

Spine, hip, knee and elbow tuberculosis in children have been extensively reported[5-9]. The few reports of foot and ankle tuberculosis mainly involve adult patients[10-12].

We reviewed 28 children with foot and ankle tuberculosis. The aims of our review were to critically assess the long-term outcome and to define a classification system that would relate to prognosis.

Patients and Methods

We reviewed the clinical records, operation notes and radiographs of twenty-eight patients treated for tuberculosis of the foot and ankle in the 24-year period from 1982 to 2005. Their average age was 5.3 years (1.5 to 12.5 years).

The ESR was elevated (>20mm/hr) in 22 patients. The Mantoux skin test was positive in 26(92.8%) and chest radiographs showed features of old or active tuberculosis in 13 patients (46.4%).

The anatomical distribution is shown in Table I. The ankle joint was involved in 12 patients (43%), the midfoot in 9(32%) and subtalar joint and/or calcaneus in 7(25%). No patients presented with metatarsal or phalangeal involvement.

The average duration of symptoms was 6 months (1 week to 2 years). The clinical presentation is shown in Table II. The commonest presentation was swelling secondary to synovitis, followed by pain. Four patients presented with a sinus due to an abscess that was drained at another institution. Two patients with subtalar joint involvement presented with a stiff valgus or varus foot. One patient presented acutely with a warm, red ankle joint mimicking a septic arthritis. All patients had a decreased range of movement.

Radiographs in ankle joint involvement showed osteopenia with or without lytic lesions of the distal tibial epiphysis, and/or sclerosis or lytic lesions of the dome of the talus (Figures 1A and 2A). Joint space narrowing was seen in 3 ankles (Fig. 3A). Midfoot involvement showed osteopenia with absence of bone (cuneiform, cuboid and navicular)(Fig. 4A). Subtalar involvement showed lytic lesions of calcaneus and/or inferior neck of talus. These lesions were not always visible on plain radiographs but were confirmed with CT scans in 3 patients (Fig. 5A and B).

An open synovial biopsy was done in all patients. Histology and/or culture were positive in 26 of the 28 cases. Histology was positive in 23 patients (82%), culture was positive in 21 patients (75%) including three of the patients with negative histology. Table III shows the positive diagnostic yield for this study compared to previous studies of hip, knee and elbow tuberculosis reported from our unit (5,6,7,8,9).

All patients were treated with rifampicin (10mg/kg), isoniazid (10mg/kg) and pyrazinamide (30mg/kg) for 9 months. Two patients with resistant disease were treated with the addition of a quinolone, ethionamide and terizidone. Patients were immobilised with a backslab and active mobilisation was permitted as soon as pain allowed. Weight-bearing was commenced as soon as there were radiographic signs of healing (usually after 3months).

All patients were followed up clinically and radiologically for an average period of 7.3 years (range 4 -18yrs). An excellent result was a pain free, plantigrade foot with a normal range of movement. A good result had a pain free, plantigrade foot with more than 50% range of movement and some joint space irregularity. A poor result had less than 50% range of movement.

Results

The results are shown in Table IV. At follow-up all patients had no residual symptoms and a plantigrade foot. Twenty-four (86%) of patients had an excellent or good result.

Of the 12 ankle joints, 9 had an excellent or good result. Erosions and large lytic lesions (mainly seen in the talus) and sclerosis of the talar dome healed with a good to excellent outcome as long as the joint space was normal at presentation (Figures 1B and 2B). The three poor results had joint space narrowing at presentation (Fig. 3B).

The main radiological feature in the midfoot was osteopaenia with suggestion of destruction of navicular, cuboid and mainly cuneiform bones. This however reconstituted at long-term follow-up. Although the joint spaces were not always clearly defined on radiographs the patients had a good functional outcome (Fig. 4B).

Six of the subtalar joints had a good or excellent outcome (Fig. 5C). The patient with a poor result had a two-year delay to diagnosis and had multi-drug-resistant-tuberculosis.

Discussion

Epidemiology

In an endemic area the differential diagnosis of a joint in a child with chronic inflammation and synovitis is essentially tuberculosis and juvenile chronic arthritis (JCA). This is especially true in the knee, ankle and subtalar joint and elbow, but not the hip joint, which is rarely involved in JCA. We treat on average 30 children with skeletal tuberculosis annually. This involves the spine in 20 patients, knee in 5 and the hip in 4. We treat on average one patient of tuberculosis of the foot and ankle per year, and one with elbow involvement every second year. Our prevalence of foot and ankle tuberculosis of 1% of skeletal tuberculosis is lower than the 10% reported from Malaysia[13] and India[11].

Diagnosis

The radiological classification of tuberculosis of the knee described by Kerri and Martini[14] can be applied to any joint with tuberculosis or chronic inflammatory joint disease. Type 1 is described as 'normal': osteopenia with or without epiphyseal hypertrophy. Type 2 is 'osteomyelitic': osteopenia with epiphyseal or metaphyseal erosions with a normal joint space. Type 3 is 'arthritic': joint space narrowing. Type 4 is also 'arthritic': gross anatomic disorganization of the joint.

We used an **anatomic classification**, because although **ankle** involvement can be adequately described by the Kerri and Martini classification, joint space narrowing in the **subtalar joint** may be difficult to quantify, if there is a valgus or varus deformity and similarly in the **midfoot** with significant osteopenia and 'absence' of bones. We do not routinely utilize CT or MRI for diagnosis in hip, knee or elbow tuberculosis. In this study however, in three of the seven feet with subtalar involvement, erosions were only visible on the CT. A stiff subtalar joint with or without varus or valgus deformity without visible erosions on plain radiographs warrants a CT.

A positive diagnostic yield (histology plus culture) in 26 of 28(92.8%) of patients is gratifying. Our laboratory uses the Lowenstein-Jensen and the automatable radiometric (Bactec) methods for culture. Two children cultured multiple-drug-resistant organisms. These patients were started on routine treatment of rifampicin, isoniazid and pyrazinamide. There was therefore an average delay of 4 weeks before the culture result became available and effective treatment could be started. Since 2008 polymerase chain reaction (PCR) is performed if Ziehl-Neelsen staining is positive. This should speed up the detection of resistant strains.

Aspiration has a much lower yield than open biopsy[15]. An open biopsy is imperative to differentiate histologically between tuberculosis and JCA, and to obtain a high as possible diagnostic yield of culture to detect multi-drug-resistant organisms.

One patient presented with an acutely swollen, red ankle joint mimicking septic arthritis. This is our experience in 10-15% of elbow and knee tuberculosis. We therefore routinely send synovium for histology, and joint fluid and synovium for tuberculosis culture during arthrotomy for septic arthritis.

Treatment

Anti-tuberculous chemotherapy gave excellent and good results in 86% of patients. We agree with Kerri and Martini[14] and Dhillon and Nagi[11] that surgery has a limited role, except to obtain a representative biopsy. Surgical synovectomy is always incomplete, is useless if the articular cartilage is already affected, and chemotherapy alone will achieve a biological synovial clearance[14].

Outcome

Shanmugasundaram[16] was the first to show that the radiological appearance of the joint at presentation was predictive of the outcome. Ankle joints with Kerri and Martini stages 1 and 2 (without joint space narrowing) had good results, while ankles with stages 3 and 4 (joint space narrowing; arthritic) at presentation had poor results. We have had similar findings in our studies of the hip, knee and elbow joints[5-9].

The Kerri and Martini classification is applicable in the ankle joint, but in the subtalar joint and midfoot the joint space can be difficult to quantify. The **anatomic classification** helps to determine the prognosis.

In the **ankle joint** the Kerri and Martini classification is predictive of the outcome. The three ankle joints with a poor outcome had joint space narrowing at presentation.

In the **midfoot** the functional outcome from this study was good, although the joint surfaces could not always be clearly defined. At presentation due the significant osteopenia and at follow-up Mittal, Gupta and Rastogi[12] describe it as a coalesced mass similar to the wrist in rheumatoid arthritis.

The **subtalar joint** can be defined if there is no varus or valgus deformity. The one poor result in this study had a varus deformity, a 2-year history and a multi-drug-resistant organism.

The duration of symptoms before treatment does not necessarily determine the outcome. Five of the patients with good results had a delay to treatment longer than 6 months, which was the average for this study. One of the 4 patients with a poor result had a delay of less than 6 months. This supports our belief that in stage 1 and 2 disease there is a protective immunity which manifests as chronic synovitis whereas in stage 3 and 4 disease there is a tissue-destroying hypersensitivity, which is not necessarily duration dependant[17]. Differences in immune response attributable to genetic and environmental factors may explain 91% of the study by Martini, Adjrad and Daoud from Algeria[10] present in stages 3 and 4, whereas 79% of the ankle and subtalar joints in our study present in stages 1 and 2.

Conclusions

Skeletal tuberculosis is known to mimic other diseases therefore a high index of suspicion should always be maintained. In an era of increasing incidence of tuberculosis in children, especially the extrapulmonary form, tuberculous arthritis should be considered in the differential diagnosis of ankle monoarthritis or foot pain. As has been shown in previous studies, radiological appearance at presentation is an accurate predictor of outcome in skeletal tuberculosis generally. In tuberculosis of the foot and ankle the anatomical site of involvement also correlates directly with

outcome. Outcome of tuberculosis of ankle and subtalar joint is good if there is no joint space narrowing at presentation.
Outcome of tuberculosis of the midfoot is functionally good even if there is no complete reconstitution of midfoot bones.
Multi-agent anti-tuberculous chemotherapy without adjunct surgical intervention apart from a biopsy is the mainstay of treatment.

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16. **Shanmugasundaram TK.** Tuberculosis of the hip. In: Shanmugasundaram TK, editor. Bone and joint tuberculosis. Madras: Kothandaram & Co; 1983. p. 59-72.
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TABLES

Table I. Anatomic distribution.

SITE	**n=28**
Ankle joint	12 (43%)
Midfoot	9 (32%)
Subtalar joint and/or calcaneus	7 (25%0

Table II. Clinical presentation.

SYMPTOM AND SIGNS	**n=28**
Decreased range of movement	28
Pain	11
Sinus	4
Varus/valgus foot	2
Acute septic arthritis	1
Swelling	22

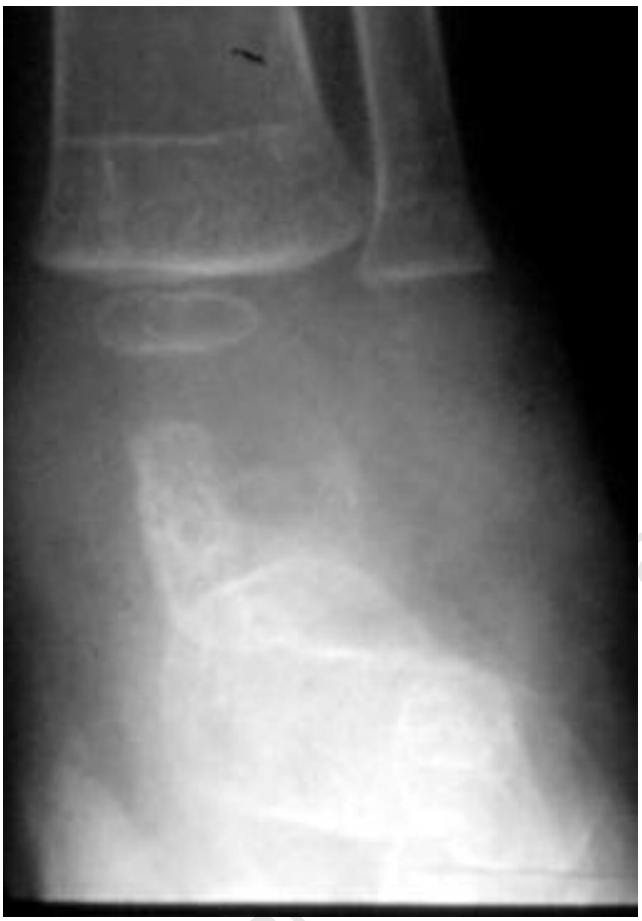
Table III. Positive diagnostic yield for foot ankle versus hip, knee and elbow tuberculosis.

	Foot and ankle n=28	**Hip, knee and elbow n=136**
Histology	82%	82%
Culture	75%	73%
Acid Fast Bacilli detected	36%	21%

Table IV. Results

Excellent	Normal radiographs and normal range of movement	9 (32%0
Good	Range of movement more than 50% and/or some irregularity of bone.	15 (54%)
Poor	Stiff joints and/or joint space narrowing and/or lack of reconstitution of midfoot bones.	4 (14%0

IMAGES



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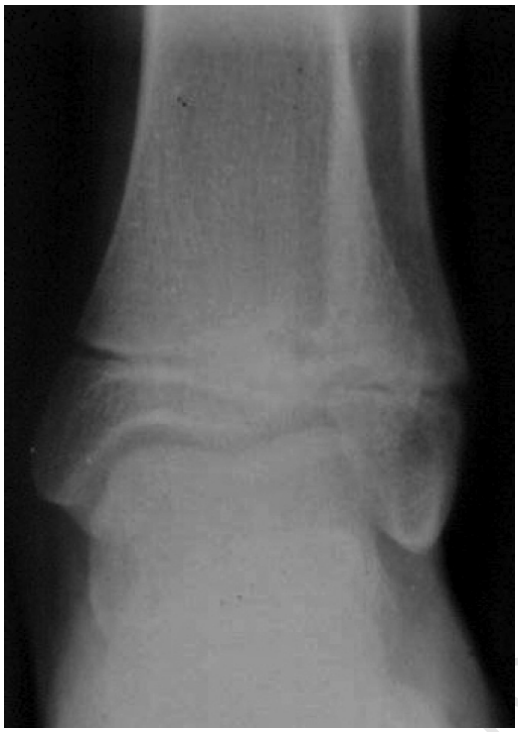

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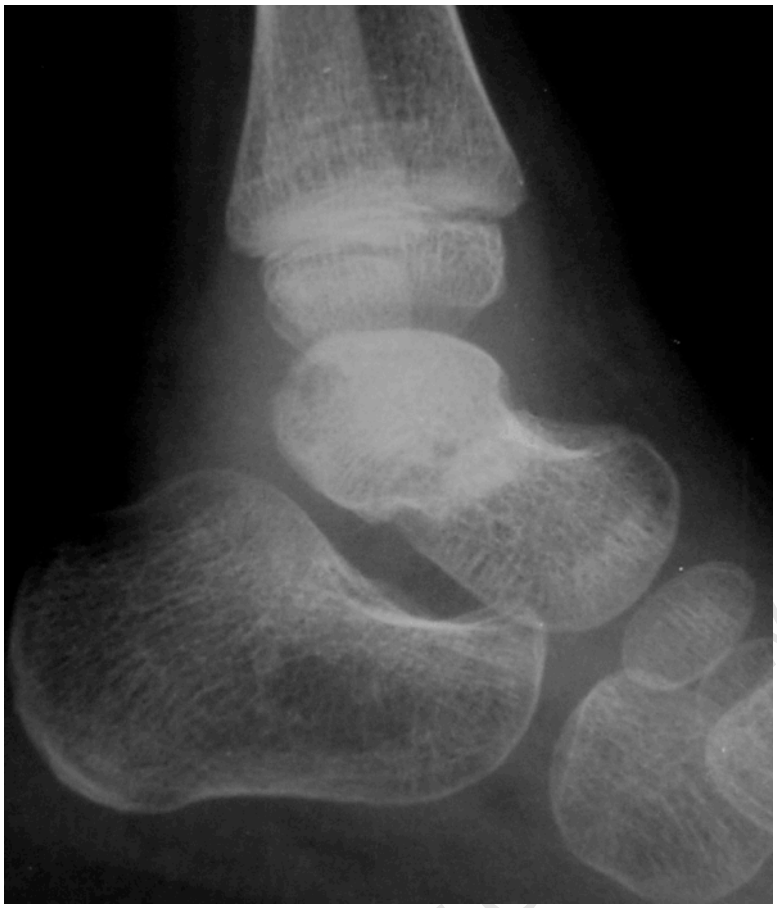

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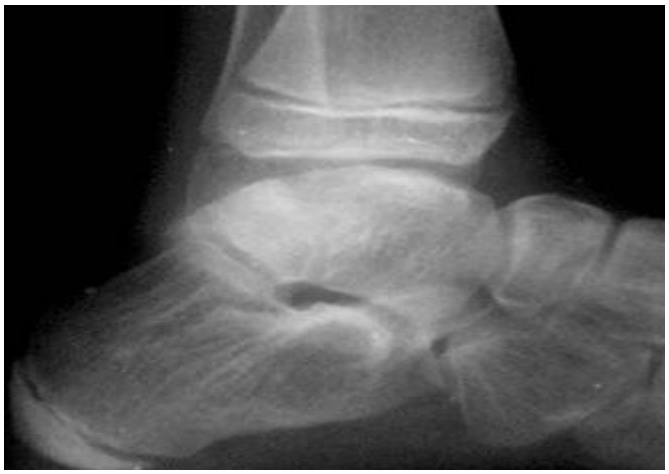

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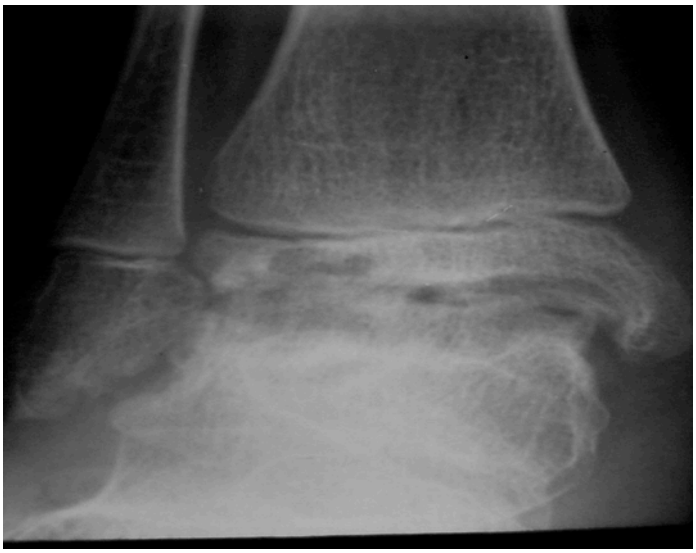

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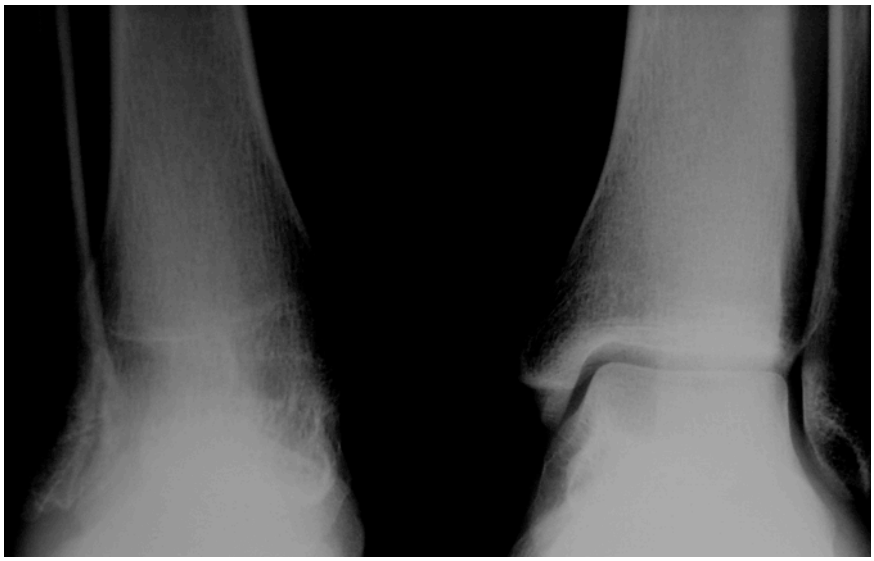

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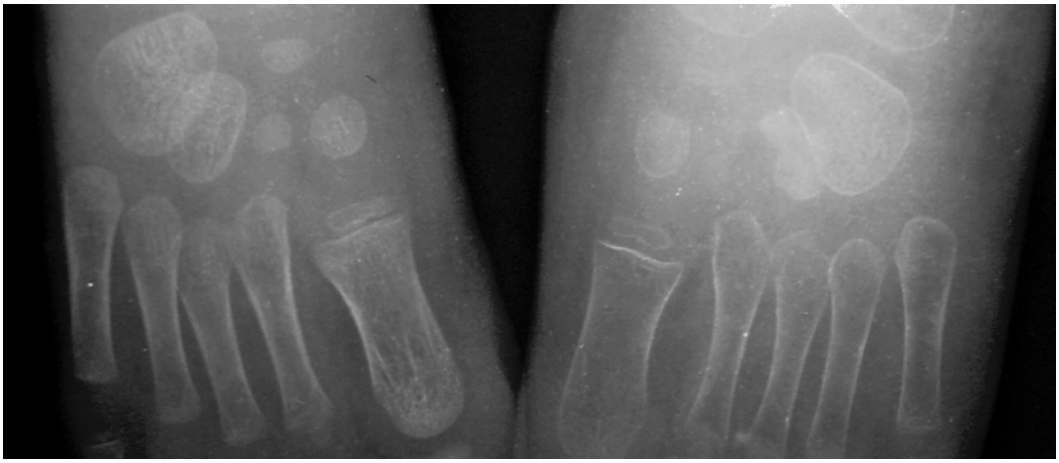

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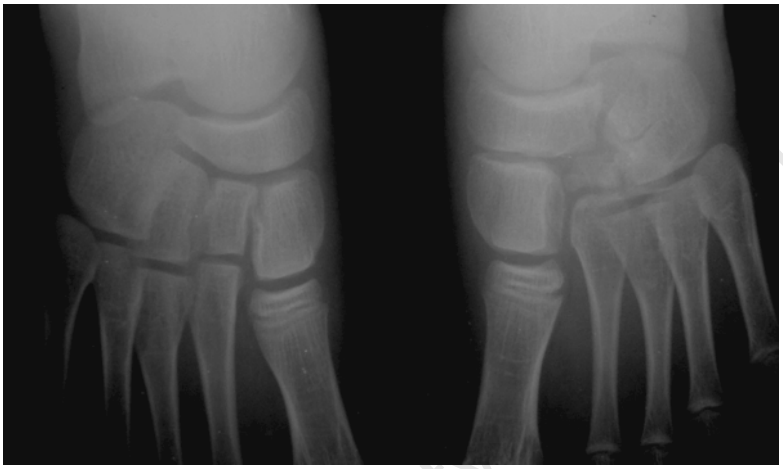

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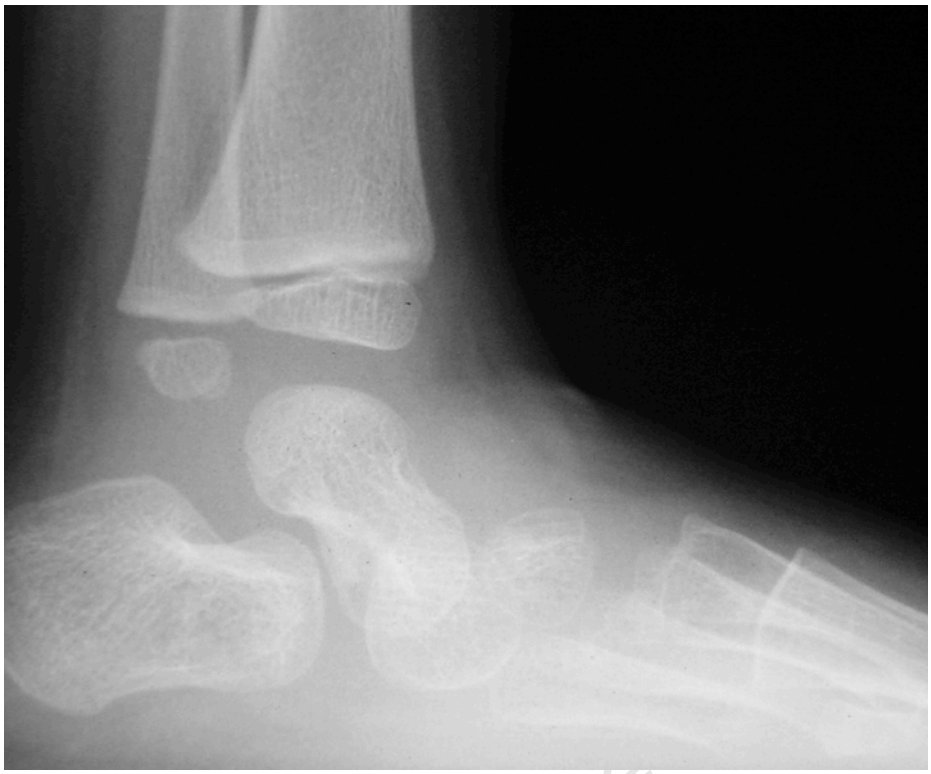

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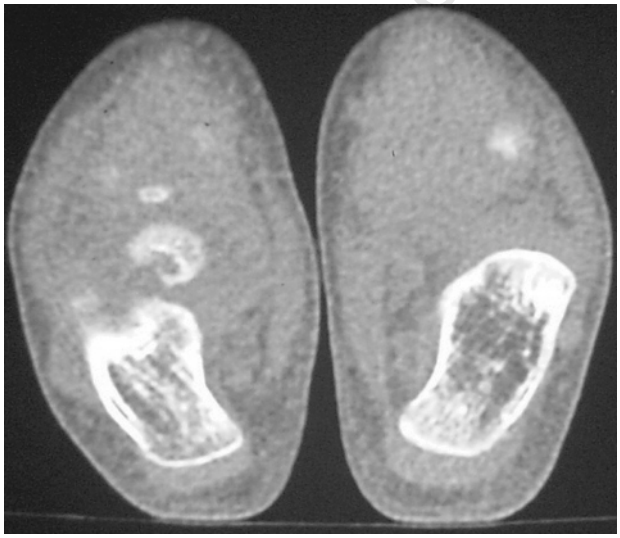

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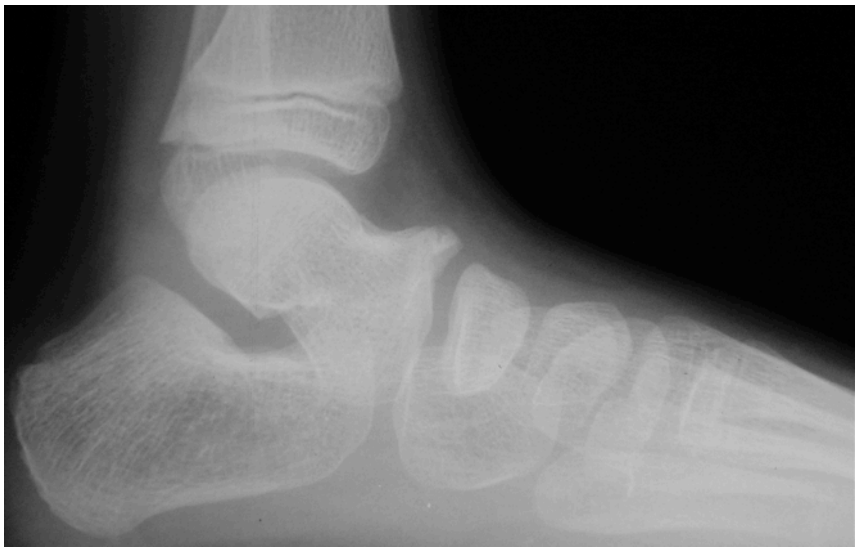

Figure 5C.

LEGEND TO FIGURES

Figure 1 A&B: A-P radiograph of ankle joint with erosion of talar dome showing an excellent result at 14-year follow up.

Figure 2 A&B: Lateral radiograph showing sclerotic talus with good outcome at 10-year follow up.

Figure 3A&B: A-P radiograph with ankle joint space narrowing and complete ankylosis at 18-year follow-up.

Figure 4 A&B: A-P radiograph of midfoot involvement showing initial bone resorption followed by reconstitution at 8-year follow-up.

Figure 5 A,B&C: Subtalar joint involvement confirmed on axial CT scan showing subtalar joint erosions and a good result at 4-year follow-up.

APPENDIX 1: PROFORMA

TB FOOT AND ANKLE

NAME: …….
FOLDER NO.……..…….
DATE OF ADMISSION: ……. DATE OF BIRTH:…….
DATE OF FINAL FOLLOW-UP:……..AGE:……..
DURATION OF FOLLOW-UP:
CLINICAL:

DURATION OF SYMPTOMS:

SYMPTOMS:
SIGNS:
X-RAYS:
E.S.R.:
MANTOUX:
CHEST X-RAY

SURGERY:
DATE OF SURGERY:
HISTOLOGY:
CULTURE:
FLUID:
SYNOVIUM:

TREATMENT:
DURATION:
DRUGS:

FOLLOW-UP:
3 MONTHS

6 MONTHS

9 MONTHS

FINAL CLINICAL: R.O.M.

X-RAY