

A Case of *Mycobacterium scrofulaceum* Osteomyelitis of the Right Wrist

L L Phoa,*^{MRCP, M Med (Int Med)}, K S Khong,**^{FAMS, FRCS}, T P Thamboo,***^{MBChB}, K N Sin Fai Lam,****^{FAMS, FCCP, FRCP (Ire)}

Abstract

Introduction: The objective of the case report is to highlight the possibility of osteomyelitis caused by atypical mycobacteria. Such an infection may simulate tuberculous bone infection and yet fail to respond to standard anti-tuberculous drug therapy. **Clinical Picture:** A 66-year-old man who suffered from diabetes mellitus presented with osteomyelitis of the right wrist, with extensive synovial swellings of the flexor tendon sheaths. The clinical features, radiological appearances and histology suggested a tuberculous infection, but subsequent culture grew an atypical mycobacterium, *Mycobacterium scrofulaceum*. **Treatment and Outcome:** There was good clinical improvement and control of the infection with a regime of kanamycin, ethambutol and ethionamide to which the organism was sensitive. **Conclusion:** This case illustrates the need to be aware of the possibility of infection with atypical mycobacteria in cases of suspected tuberculosis of the skeletal system which fail to respond to standard treatment.

Ann Acad Med Singapore 2000; 29:678-81

Key words: Atypical, Diabetes, Erosive, Synovectomy, Tuberculosis

Introduction

Whilst infections caused by *Mycobacterium tuberculosis* may be a common occurrence in this part of the world, those caused by atypical mycobacteria are rarely encountered. Many of the cases of atypical mycobacterial infections have been associated with underlying immunocompromised states. Similarly, although we still have a significant problem with pulmonary tuberculosis, skeletal tuberculosis is far less common. During the 3-year period from 1996 to 1998, there were 5218 cases of tuberculosis amongst Singapore residents (pulmonary and extrapulmonary); of these, 895 cases (17%) were dual pulmonary and extrapulmonary, 395 cases (7.6%) were extrapulmonary alone, and only 49 were skeletal/bone tuberculosis.¹ However, when skeletal tuberculosis is encountered, it responds very well to treatment with the standard first line anti-tuberculous drugs. In this report, we describe a patient with osteomyelitis involving the right wrist joint resulting from *M. scrofulaceum* infection. Difficulties in reaching the diagnosis and in the management are described and an awareness of this possible condition is raised.

Case Report

A 66-year-old gentleman came to hospital with a 2-month history of painless swellings over the right wrist, right index and ring finger (Fig.1). In his past medical history, he suffered from diabetes mellitus and hypertension which were well controlled. He was treated successfully for pulmonary tuberculosis 30 years previously. There was no history of any trauma or puncture wound to the right hand.

Radiographs of the right hand showed lytic lesions over the distal right radius and the base of the middle phalanx of the ring finger (Fig. 2). The chest X-ray was normal. Exploration and excisional biopsies were carried out. At operation (Fig. 3), there were extensive synovial swellings arising from the flexor sheath of the right ring and index fingers as well as the right wrist joint, with bony erosions seen at different sites. Histopathological examination showed synovium with large areas of caseous necrosis and granulomatous inflammatory reaction with epithelioid cells and giant cells (Fig. 4). Staining for acid fast bacilli was negative. No mycobacteria were subsequently cultured from the tissue.

* Registrar

**** Senior Consultant

Department of Medicine

** Senior Consultant

Department of Orthopaedics

Alexandra Hospital

*** Senior Tutor

Department of Pathology

National University Hospital

Address for Reprints: Dr K N Sin Fai Lam, Department of Medicine, Alexandra Hospital, 378 Alexandra Road, Singapore 159964.



Fig. 1. Clinical appearance of the soft tissue swellings of the right wrist at the time of first presentation.



Fig. 2. Initial postero-anterior radiograph of the right wrist showing bony erosion from without (black triangles) of soft tissue (synovial) origin (white arrows), as well as subarticular "cystic" formation (white triangles).

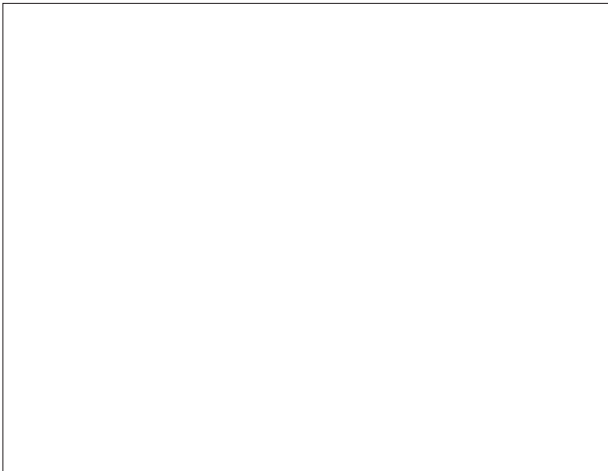


Fig. 3. Operative photographs showing thin synovial cysts containing clear fluid around tendons and eroding into the distal radius (left), and "dry" synovial tissue from the flexor tendon sheath of the ring finger communicating with the base of the proximal phalanx (right).

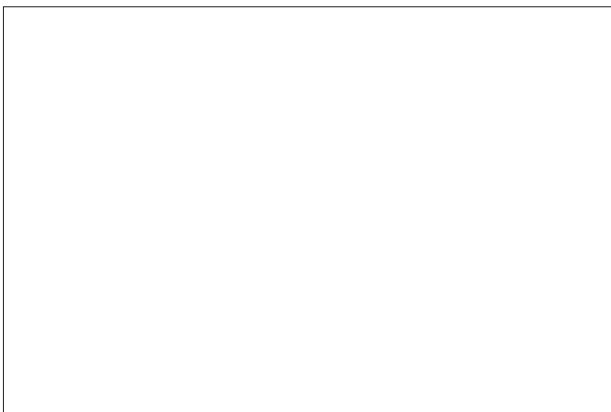


Fig. 4. Photomicrograph showing granulomatous inflammation with caseous necrosis, epithelioid cells and Langhans-type giant cells (H & E x100).

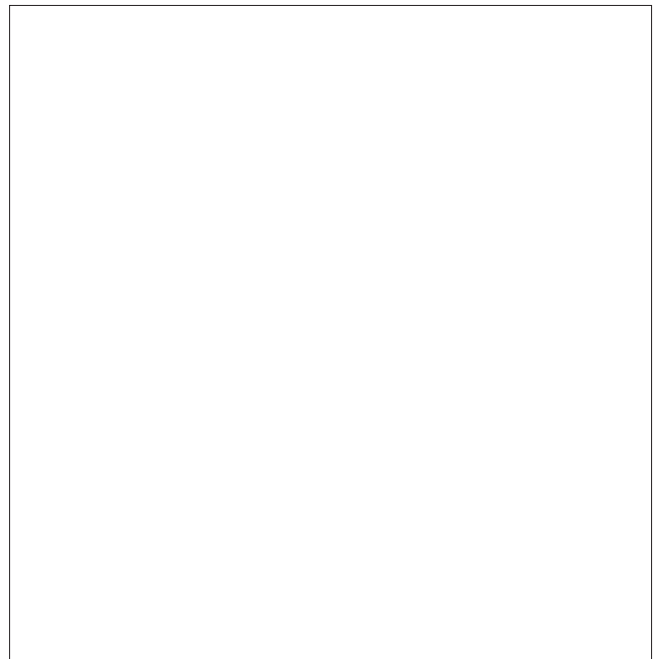


Fig. 5. Progressive collapse of right wrist joint six months after initial surgery. No further intervention was performed as the patient was asymptomatic.

Empirical treatment with anti-tuberculous drugs was started, initially with rifampicin, isoniazid and pyrazinamide. When he developed a rash to pyrazinamide, ethambutol was substituted. He tolerated treatment well and was compliant to medication. Although no mycobacterium was cultured from the tissue, anti-tuberculous therapy was continued because the clinical presentation and histology were consistent with skeletal tuberculosis.

Two months after surgery, there was a recurrence of swelling over his right wrist, associated with ulceration and sinus formation, discharging pus and with surrounding erythema. A second operation was carried out with synovectomy and curettage of the lytic lesions in both ulna and radius. Specimens were again sent for histology and bacteriology. Staining for acid-fast bacilli of the specimens was again negative.

However, after 4 months of regular anti-tuberculous treatment, the bone disease had progressed. There was radiological deterioration, and complete destruction of the right wrist joint (Fig. 5). Three months after the second surgical exploration, a positive culture of "mycobacterium other than tuberculosis" was reported by the laboratory. However, it was only a further 2 months later that the culture was found to be *Mycobacterium scrofulaceum* sensitive to kanamycin, ethambutol and ethionamide only.

The choice of drugs was based on the sensitivity results and the patient was then started on these 3 drugs. Kanamycin was taken off after 1 month and the patient was continued on ethambutol and ethionamide. There was good clinical improvement with reduction of the swelling and no further radiological deterioration. Unfortunately, the patient died 6 months later of an unrelated cardiovascular illness.

Discussion

This case demonstrates the difficulty with which the diagnosis was reached. There was obviously an inflammatory osteomyelitis at the outset with clinical swelling, radiological changes and an antecedent history of diabetes mellitus. When the histology revealed large areas of caseous necrosis with granulomatous inflammation, epithelioid cells and giant cells, it was logical to assume that skeletal tuberculosis was the cause of the osteomyelitis. Even though no mycobacteria were seen on staining or on culture of the first specimen, it was reasonable to persist with treatment with standard anti-tuberculous drugs. However, it became obvious that the infection was not being controlled and a second operation with repeat sampling was required. The definitive culture and sensitivity testing took several months, hence the delay in instituting effective treatment and the resulting bone destruction.

Mycobacterium scrofulaceum is a ubiquitous, slow growing organism, known to contaminate water supplies and unpasteurised milk.² It shares some genetic characteristics with *Mycobacterium avium* complex (MAC) and is resistant to many anti-tuberculous drugs. Aside from lymphadenitis in children, *M. scrofulaceum* is rarely a cause of human disease.³ It is responsible for less than 2% of atypical mycobacterial infections in the United States,⁴ and less than 1% of atypical mycobacterial infections in

AIDS patients.⁵ To date, there have been few reported cases of disseminated *M. scrofulaceum* infection. Most of these cases have been associated with AIDS^{6,7} or other underlying immunodeficiency states. These include advanced systemic amyloidosis, hairy cell leukaemia, chronic granulocytic leukaemia and systemic lupus erythematosus.⁶ However, extensive disseminated infection due to *M. scrofulaceum* in an immunocompetent host has also been reported.⁸

Clinical manifestations of *M. scrofulaceum* infections include pulmonary disease, lymphadenitis, granulomatous hepatitis, osteomyelitis, and subcutaneous abscesses. There is also a reported case of *M. scrofulaceum* infection presenting as lung nodules in a heart transplant recipient.⁹ Cervical lymphadenitis is perhaps the most common clinical presentation for *M. scrofulaceum*. It typically affects children between 16 months to 10 years of age. The involved lymph nodes are usually located in the submandibular or preauricular regions. *M. scrofulaceum* was the predominant aetiological agent of non-tuberculous mycobacterial (NTM) lymphadenitis when the disease was first recognised in the mid-1950s. Currently, this has largely been replaced by MAC accounting for 80% of the cases.⁷

Infections of the bones, synovia, tendon sheaths and bursa by NTM may occur following surgical procedures, trauma, and penetrating injuries in immunocompetent individuals. In many cases, as illustrated in our patient, no antecedent event can be recalled. The hand is a common site of involvement, although many of the other structures, including the spine and the sternum may be affected. After open heart surgery, osteomyelitis caused by *M. chelonae* and *M. fortuitum* has been described.^{10,11} The skeletal infections not associated with disseminated disease are usually characterised by chronicity and low grade constitutional symptoms. Clinically, skeletal infections resemble similar infections caused by *M. tuberculosis*. The most common aetiological agents of these infections are *M. kansasii*, *M. fortuitum* and MAC. Other agents may include *M. terrae* and *M. chelonae*. There is a case report of culture-positive *M. scrofulaceum* multifocal osteomyelitis in a 6-year-old boy with no underlying disease. The patient received combination drug therapy and required multiple bone excisions.¹²

It should be noted that most of the first line anti-mycobacterial agents have diminished activity against *M. scrofulaceum*, which is believed to result from the presence of a lipophilic cell wall, preventing drug penetration. The drugs with the best *in vitro* activity are second line drugs, such as ethionamide. However, these are usually associated with greater toxicity than first line anti-mycobacterial agents^{9,13} and their usage necessitates stringent monitoring.

In our patient, although a positive culture of “mycobacteria other than tuberculosis” was obtained 3 months after the specimen was processed, it required a further 2 months for accurate characterisation of the organism and sensitivity testing. This particular fastidious organism is slow growing. In addition, it is well known that mycobacterial culture from bone specimens unlike sputum cultures is notoriously difficult and variable. By then, his wrist joint was already severely destroyed. The mainstay of treatment in *M. scrofulaceum* osteomyelitis is surgical drainage and removal of infected synovium and bone. Combination chemotherapy is often concomitantly instituted. Therapy of NTM has been limited by the absence of antimicrobial agents with low toxicity and good *in vivo* therapeutic index against the organism. Besides, there is little data correlating the results of *in vivo* tests with improved clinical efficacy. The American Thoracic Society⁹ recommends the initial treatment of MAC and *M. scrofulaceum* with a 4-drug regimen of isoniazid, rifampicin, ethambutol and streptomycin; susceptibility tests would likely show resistance to several of these agents. Other agents which have been found helpful are clarithromycin, ciprofloxacin and clofazimine. Clarithromycin in particular has been shown in more recent reports to have activity against *M. scrofulaceum* as well as MAC and other non-tuberculous mycobacteria.^{6,14} In addition, the *in vitro* susceptibility to clarithromycin correlates with its clinical efficacy. However, subsequent chemotherapy should be guided by any available culture sensitivities since this organism is known to be highly resistant to many anti-tuberculous agents. The aim of instituting chemotherapy at this stage was to control the infection and to prevent dissemination of the disease. Even though rifampicin and ethambutol have been found useful in reported cases, this was not so in our patient and our subsequent choice of drugs was guided by the sensitivity results. Whether empirical therapy with clarithromycin and ethambutol prior to the sensitivity results would have made any difference to the subsequent outcome is difficult to ascertain. Nevertheless, clarithromycin, either alone¹⁵ or in combination, has been shown to eradicate infection and lead to clinical improvement. It seems reasonable therefore to treat *M. scrofulaceum* infections and perhaps other NTM infections with at least 2 drugs (including clarithromycin).⁶

This case thus illustrates the fact that atypical mycobacterial infection, though rare, should always be considered as a possibility in any patient with a clinical and histological picture of a mycobacterial infection. The limitation to early effective treatment in this case, is the slow rate of growth of this organism and more significantly, the resistance to first-line anti-tuberculous drugs (except ethambutol) as illustrated in this case.

Modern tools of rapid diagnosis such as DNA probes and

polymerase chain reaction are promising in the identification of growing colonies or early growth in automated systems.^{16,17} The application of these techniques should lead to earlier diagnosis which would make a significant difference to the eventual outcome.

REFERENCES

1. Communicable Disease Surveillance Report, Ministry of Health Singapore, 1998:9.
2. Mandel G L, Douglas R G, Bennett J F. Principles and Practice of Infectious Diseases. 3rd ed. NY: Churchill Livingstone, 1985:1918.
3. Wolinsky E. Non tuberculous mycobacteria and associated diseases. Am Rev Resp Dis 1979; 119:107-39.
4. Good R C, Snider D E Jr. From the Centres for Disease Control. Isolation of non tuberculous mycobacteria in US 1980. J Infect Dis 1982; 146:829-33.
5. Young L S, Inderfield C B, Berlin O G, Gottlieb M S. Mycobacterial infections in AIDS patients with an emphasis on MAC. Rev Infect Dis 1986; 8:1024-33.
6. Sanders J W, Walsh A D, Snider R L, Sahn E E. Disseminated *Mycobacterium scrofulaceum* infection: A potentially treatable complication of AIDS. Clin Infect Dis 1995; 20:549-56.
7. Diagnosis and treatment of disease caused by non-tuberculous mycobacteria (Official Statement of the American Thoracic Society). Am Rev Resp Dis 1990; 142:940-53.
8. Hsueh P R, Hsiue T R, Jarn J J, Ho S W, Hsieh W C. Disseminated infection due to *M. scrofulaceum* in an immunocompetent host. Clin Infect Dis 1996; 22:159-61.
9. LeMense G P, VanBakel A B, Crumbley A J III, Judson M A. *M. scrofulaceum* infection as lung nodules in a heart transplant patient. Chest 1994; 106:1918-20.
10. Hoffman P C, Fraser D W, Robicsek F, O'Bar P R, Mauney C U. Two outbreaks of sternal wound infection due to organisms of *Mycobacterium fortuitum* complex. J Infect Dis 1981; 143:533-42.
11. Szabo I. *Mycobacteria chelonae* endemy after heart surgery with fatal consequences. Am Rev Resp Dis 1980; 121:607.
12. Lincoln E M, Gilbert L A. Diseases in children due to mycobacteria other than *Mycobacterium tuberculosis*. Am Rev Resp Dis 1972; 105:683-714.
13. Wolinsky E. Mycobacteria diseases other than tuberculosis. Clin Infect Dis 1992; 15:1-12.
14. Brown B A, Wallace R J Jr, Onyi G O. Activities of clarithromycin against eight slowly growing species of nontuberculous mycobacteria, determined by using a broth microdilution MIC system. Antimicrob Agents Chemother 1992; 36:1987-990.
15. Lindeboom J A, de Lange J, van den Akker H P. Clarithromycin as a single-modality treatment in mycobacterial avium-intracellular infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87:50-4.
16. Picken R N, Tsang A Y, Yang H L. Speciation of organisms within the *Mycobacterium avium-Mycobacterium intracellulare-Mycobacterium scrofulaceum* complex (MAIS) based on restriction fragment length polymorphism. Mol Cell Probes 1988; 2:289-304.
17. Swanson D S, Pan X, Musser J M. Identification and subspecific differentiation of *Mycobacterium scrofulaceum* by automated sequencing of a region of the gene. (hsp65) encoding a 65-kilodalton heat shock protein. J Clin Microbiol 1996; 34:3151-9.