ABSTRACT

Mycobacterium terrae is ubiquitous in our environment. M terrae infections most commonly involve tendon sheaths, bones, bursae, and joints. We report a case of infectious arthritis of the knee caused by M terrae in a 21-year-old man who had non-specific chronic synovitis. No organism was seen on microscopy or isolated from cultures until months later. Initially the M terrae culture was considered a contaminant and specific anti-mycobacterial treatment was not advised. The patient was commenced on suppressive therapy for persistent effusion and discomfort. Eventually, the M terrae infection was confirmed and he was commenced on clarithromycin, ciprofloxacin, and ethambutol. The triple antibiotic regimen was continued for 2 years. The knee improved but never completely settled. The patient chose to cease all antibiotic medication. The knee remained swollen and irritable, with little chance of eradicating the organism.

Key words: arthritis, infectious; mycobacteria, atypical

INTRODUCTION

Mycobacterium terrae complex (M terrae, M nonchromogenicum, and M triviale) has been classified as a non-pathogenic saprophyte, but is increasingly considered a pathogen. It is one of approximately 50 species of atypical mycobacteria or non-tuberculous mycobacteria capable of causing disease. These bacteria are ubiquitous in our environment and produce 6 major clinical syndromes: chronic bronchopulmonary disease, lymphadenitis, skin and soft tissue disease, skeletal (bone, joint, and tendon) disease, and disseminated and catheter-related infections. The most common presentation of M terrae infection is infection of tendon sheaths, bones, bursae, and joints, usually after direct inoculation. We present a case of infectious arthritis of the knee caused by M terrae in a 21-year-old man. The modes of transmission, difficulties with diagnosis, and treatment options are reviewed.

CASE REPORT

In April 1997, a 21-year-old man presented with a 10-month history of a painful, swollen left knee.
He had undergone 2 arthroscopies: the first in 1994 for a partial medial meniscectomy after a sporting injury, and the second in February 1995 for a hamstring autograft anterior cruciate ligament (ACL) reconstruction after another sporting injury. The knee was stable but persistently swollen and uncomfortable. An arthroscopy confirmed an active chronic synovitis with a possible granulomatous component. The inflammatory fluid contained no organisms or crystals. No acid-fast bacilli were seen.

He gave no history of a penetrating injury to the knee while working as a landscape gardener, and was provisionally diagnosed with an unexplained inflammatory mono-arthritis. Differential diagnoses included sarcoidosis, tuberculosis, and a foreign body synovitis. Further radiographic and serological investigations were unremarkable and he was referred for physiotherapy.

Six weeks later, the knee remained swollen and inflamed. An aspiration confirmed an inflammatory effusion with no organisms seen on microscopy. Intra-articular triamcinolone was injected and suppressive therapy with salazopyrin was commenced. 10 weeks later, *M. terrae* was isolated from the culture and the salazopyrin was ceased.

An urgent microbiological review and aspiration again yielded no mycobacteria. It was unknown whether the *M. terrae* was a commensal, pathogen or contaminant. The microbiologist was reluctant to prescribe prolonged anti-tuberculous therapy without further bacteriological and histological evidence. The patient therefore underwent a diagnostic arthroscopy and biopsy by an orthopaedic surgeon.

Repeat radiographs demonstrated a small cyst in the lateral femoral condyle, minor medial compartment wear, and features of the previous ACL reconstruction (Fig. 1). Bone scans confirmed a mild to moderate diffuse synovitis of the left knee (Fig. 2).

In December 1997, the patient underwent a further arthroscopy, synovial biopsy, and arthroscopic synovectomy for moderate synovitis (Fig. 3). Inflammatory fluid and mycobacterial cultures remained negative 12 weeks later. A histopathological examination showed an active chronic synovitis with numerous epithelioid granulomata, which was consistent with mycobacterial infection, foreign body reaction (despite no foreign material on polarisation) or sarcoidosis.

Specific anti-mycobacterial treatment was not advised as the original *M. terrae* culture was considered a contaminant. The patient was commenced on suppressive therapy with methotrexate at 6 weeks for the persistent effusion and discomfort, but this was ceased after a 6-month trial as the symptoms persisted. The patient moved out of the area and was referred to a rheumatologist for follow-up.

In July 2001, the patient was referred back with a 3-month history of a swollen left knee. The rheumatologist had isolated *M. terrae* from aspirates. Radiographs demonstrated the cystic changes in the lateral femoral condyle and marked swelling consistent with a joint effusion (Fig. 1). His blood tests remained unremarkable. The inflammatory fluid was negative on microscopy but positive on cultures 7 weeks later. He was commenced on clarithromycin and ciprofloxacin before sensitivity results became available. The organism was sensitive to clarithromycin and ethambutol but resistant to ciprofloxacin and rifampicin. Ethambutol was then added. Magnetic resonance imaging at 3 months showed an extensive erosive arthropathy with marked synovial proliferation and erosions in the femoral condyles and posteriorly along both tibial plateaux (Fig. 4).

![Figure 1](image-url)  Radiographs of the left knee in (a) April 1997, (b) October 1997, (c) May 2001, and (d) May 2001 (magnified view).
The triple antibiotic regimen was continued for 2 years until November 2003. The knee improved but never completely settled. From December 2002 onwards, improvement was minimal, with a persistent granulomatous synovitis on serial magnetic resonance imaging. In February 2005, the patient underwent synovectomy owing to ongoing pain and swelling in his knee. Once again, the straw-coloured inflammatory fluid collected did not yield any organisms on both microscopy and initial culturing. A histopathological examination revealed a chronic non-caseating granulomatous synovitis. In the early postoperative period, the patient developed a pulmonary embolus and was commenced on warfarin for a 6-month period. 12 weeks later, the cultures became positive for *M terrae*, which was sensitive to clarithromycin, amikacin, ciprofloxacin, and rifampicin. The patient was re-commenced on clarithromycin, ciprofloxacin, and ethambutol indefinitely. As the effusion remained 6 months later, linezolid (an oxazolidinone) was trialled in combination with clarithromycin and ethambutol, once the warfarin had been ceased. The linezolid was stopped because the patient developed peripheral neuropathy in his legs and clofazimine was then added. This was stopped after 3 months because...
of possible adverse effects. In November 2005, the patient chose to cease all antibiotic medication. His knee remained swollen and irritable, and there appeared little chance of eradicating the organism.

**DISCUSSION**

*M. terrae* was first isolated in 1950 from radish washings and was thus known as the radish bacillus. Based on its laboratory behaviour and culture characteristics, it was classified as non-pathogenic. In 1966, the radish bacillus was isolated from human sputum and gastric lavage samples. This soil organism occasionally inhabits human hosts' secretions as a non-pathogenic coloniser. It was designated *M. terrae* because of its ubiquitous presence in soil. In 1967, the Centers for Disease Control in the United States reported 5 clinically significant cases of *M. terrae* infection. Over 50 cases of *M. terrae* infection have been reported, involving bone and other synovial structures, lungs, skin, gut, urinary tract, lymph nodes or disseminated disease. The most common site is the tenosynovium of the hand and wrist. Two cases of *M. terrae* infection in large joints have been reported. One involved the hip in a 6-month-old infant and another involved the knee in a 57-year-old man with rheumatoid arthritis. Mycobacterial infection of larger joints is usually due to *M. tuberculosis* or other non-tuberculous mycobacteria such as *M. intracellulare-avium* complex, *M. kansasii* or *M. marinum*. Most patients are otherwise healthy with no concurrent medical illnesses or immunosuppression.

Inoculation of *M. terrae* usually occurs through direct trauma or a penetrating injury. Direct inoculation is reported in up to 75% of cases. In our patient, inoculation was either through the ACL surgery or a minor penetrating injury while working as a landscape gardener. Haematogenous spread from a distant site is possible, but has never been reported in musculoskeletal *M. terrae* infection.

Nosocomial infections of atypical mycobacteria have been reported. They are environmentally ubiquitous organisms and therefore present in most municipal water supplies. A breach of sterilisation protocols is a possible explanation, for example during arthroscopy or the ACL reconstruction. Contamination of medical equipment by tap water during the cleaning process has caused numerous outbreaks and pseudo-outbreaks of non-tuberculous mycobacteria. Inadequate cleaning of instruments, inappropriate disinfectant concentrations, outdated disinfectants, insufficient cleaning time, and the use of tap water can cause a breach in sterilisation. These bacteria are more resistant to elevated temperatures, disinfectants, and ultra-violet light because of their high lipid content and multi-layered cell walls. A rise in the prevalence of such infections has been reported when hospitals lower the temperature in the hot water systems to prevent scalding. Sterilisation equipment should be cleaned and serviced regularly, as mycobacteria can survive in biofilms inside the plastic and rubber tubing. Some atypical mycobacteria are resistant to chlorine, 2% formaldehyde and alkaline glutaraldehyde solutions, organomercurials, and other commonly used disinfectants. Our case was an isolated event with no other atypical mycobacterial infections reported during this period. The sterilisation system used during arthroscopy and ACL reconstruction was the STERRAD Sterilization Systems (Johnson & Johnson Gateway), which has not been linked to atypical mycobacterial outbreaks or pseudo-outbreaks.

*M. terrae* infection of synovial structures is difficult to diagnose because it is uncommon and non-specific and is easily mistaken for other systemic or regional rheumatological conditions. Diagnosis can be delayed by use of erroneous or ineffective treatments involving systemic or local corticosteroids, non-steroidal anti-inflammatory drugs, immunosuppressive agents, splintage, physiotherapy, or even amputation. The mean time for diagnosing *M. terrae* infection from symptom onset has been reported as 12.6 months, with more than half taking over 6 months. *M. terrae* may not be consistently isolated from tissue or synovial fluid samples; even so it is unknown whether the *M. terrae* is a commensal, pathogen or contaminant. Acid-fast bacilli are often not seen on microscopy and grown in cultures until weeks to months later. The histological appearance of synovial fluid samples is non-specific and can only provide supportive evidence.

Non-tuberculous mycobacteria should always be considered in the differential diagnosis of a chronic mono-arthritis. Chronic infections of any type should be excluded before injection of, or treatment with, corticosteroids or other immunosuppressives. The criteria for diagnosis of nontuberculous mycobacterial infection are: (1) repeated isolation of the particular organism at high concentrations over several weeks, (2) manifestation of a disease that could be caused by such an organism, and (3) lack of an associated cause for the disease.

It was unknown whether the initial *M. terrae* culture was a contaminant or a pathogen. An outbreak of 163 false positive *M. terrae* infections secondary to contaminated hospital water supply and a pseudo-outbreak of *M. terrae* secondary to contamination of
specimens in the laboratory have been reported. A single isolation of M. terrae is easily dismissed as a contaminant or non-pathogenic coloniser, because it is ubiquitous in temperate climates.

Management of M. terrae infection is controversial, with a variety of options reported: surgery alone, antimycobacterial therapy alone, monotherapy or multi-drug therapy, or a combination of surgical and antimycobacterial treatment. A combination of debridement and multiple chemotherapeutic agents for a prolonged period provides the best results. Initially, our patient responded well to drug therapy alone, thus arthroscopic synovectomy was delayed. The organism was not eliminated, however, despite prolonged antibiotic treatment and multiple arthroscopic synovectomies.

M. terrae can be multi-drug resistant when cultured. Sensitivity results may vary between laboratories because there is no standardised system for defining organism sensitivity and resistance. Sensitivities differ between in vivo and in vitro conditions. No empirical treatment regimen exists because of the paucity of in vitro testing of M. terrae isolates. No single agent or drug combination is significantly better than others, but a combination of ethambutol and rifampicin is tending toward significance. The in vitro susceptibility testing has found that ethambutol is most effective on agar plates, and in minimum inhibitory concentration studies, semisynthetic macrolides such as clarithromycin are particularly effective, as are ethambutol and aminoglycosides. Use of an empirical regimen of clarithromycin, rifampicin, and ethambutol is recommended; it can be altered based on individual sensitivity testing and should be continued for at least 12 months after the first signs of clinical benefit. This regimen is also effective for other non-tuberculous mycobacterial infections. In our case, ciprofloxacin was continued despite its in vitro resistance, because in vitro sensitivity testing is not always predictable. Linezolid and clofazimine are useful for treating other mycobacterial infections, but were not successful in our patient.

REFERENCES