Successful treatment of a prosthetic joint infection due to *Mycobacterium abscessus*

Andrew Petrosoniak¹, Paul Kim², Marc Desjardins³, B Craig Lee¹

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Prosthetic joint infection due to *Mycobacterium abscessus* is uncommon and optimal therapy remains poorly defined. Following a two-stage revision, clinical and microbiological cure was achieved in a patient with a *M abscessus*-infected total hip arthroplasty. A prolonged course of directed antibacterial therapy comprising clarithromycin and cefoxitin coupled with the application of amikacin-impregnated cement likely contributed to the successful outcome.

Key Words: *Mycobacterium abscessus*, Prosthetic joint infection; Total hip arthroplasty

Mycobacterium abscessus, a rapidly growing mycobacterium (RGM) (1), is ubiquitous in soil and aqueous environments, including municipal drinking water and sewage systems (1,2). Three species of *Mycobacterium* – *M abscessus*, *M chelonae* and *M fortuitum* – cause 90% of infections due to RGM (3), with *M abscessus* being the most pathogenic (2). Phylogenetically, *M abscessus* is closely related to *M chelonae*, although each species can be differentiated by signature 16S ribosomal DNA sequences (4).

The most common clinical expression of disease caused by *M abscessus* is pulmonary and localized skin and soft tissue infections, as exemplified by the predominant mycobacteria causing nosocomial surgical site infections (2). The organism is rarely implicated in prosthetic joint infections (PJI) (5). We describe a patient with an *M abscessus* PJI in whom a microbiological and clinical cure was achieved following a two-stage prosthesis exchange coupled with a prolonged course of directed antibiotic treatment comprising clarithromycin and cefoxitin.

CASE PRESENTATION

A 70-year-old woman, with compensated hypothyroidism and a remote history of polymyalgia rheumatica, underwent an elective right total hip arthroplasty in September 2002 for degenerative joint disease. The postoperative course was uneventful. An episode of right hip pain in February 2004, attributed to right iliopsoas bursitis, required an ultrasound-guided steroid injection into the bursa, and resulted in symptomatic resolution. A plain x-ray of the right hip showed no radiological

Le traitement réussi de l'infection d'une prothèse articulaire par le *Mycobacterium abscessus*

L'infection d'une prothèse articulaire causée par le *Mycobacterium abscessus* est rare, et le traitement optimal demeure mal défini. Après un examen en deux étapes, on a pu obtenir la guérison clinique et microbiologique d'un patient dont l'arthroplastie totale de la hanche était infectée par le *M abscessus*. Un thérapie antibactérienne dirigée prolongée composée de clarithromycine et de céfoxitine, couplée à l'application d'un ciment imprégné d'amikacine, a probablement contribué à l'issue positive.

abnormality of the implant. Persistent joint pain subsequent to a fall while downhill skiing in April 2005 prompted a diagnostic ultrasound-guided aspirate of the right hip in June 2005. The joint fluid was processed for fungal, mycobacterial, and routine aerobic and anaerobic cultures. Within three days, the Mycobacterial Growth Indicator Tube (Becton Dickinson, USA) was positive with an acid-fast bacillus. A nonpigmented colony was recovered on subculture to 7H110 media. The isolate grew on MacConkey agar without crystal violet, and was nitrate negative. Susceptibility to ciprofloxacin, colistin, cephalothin and amikacin by disk diffusion for taxonomical purposes presumptively identified the isolate as a rapid grower belonging to the *M chelonae* complex. The Ontario Public Health Laboratory confirmed the identity as *M abscessus* by high-performance liquid chromatography. Susceptibility testing using a broth microdilution method (Trek Diagnostics) was performed at the National Microbiology Laboratory (Winnipeg, Manitoba). The organism was susceptible to clarithromycin, indeterminate to cefoxitin and amikacin, and resistant to ciprofloxacin and linezolid. A repeat joint aspiration performed one week later confirmed this microbiological finding.

Examination revealed an afebrile woman with a tender, nonerythematous swelling of the right thigh. Passive abduction of the right hip was restricted. There were no systemic symptoms of infection, such as fever, night sweats or involuntary weight loss. There was no serological evidence of HIV infection. Magnetic resonance imaging of the right thigh and computed tomography scan of the abdomen and pelvis with

¹Department of Medicine, ²Department of Orthopaedic Surgery, and ³Department of Laboratory Medicine, Ottawa Hospital General Campus, Ottawa, Ontario

Correspondence: Dr B Craig Lee, Department of Medicine, Ottawa Hospital General Campus, 501 Smyth Road, Ottawa, Ontario K1H 8L6. Telephone 613-737-8899 ext 72296, fax 613-737-8164, e-mail clee@ottawahospital.on.ca

contrast corroborated the clinical suspicion of an associated right iliopsoas abscess communicating with the hip joint. *M. abscessus* was isolated from the abscess fluid. Parenteral meropenem 500 mg every 6 h and oral clarithromycin 500 mg twice daily were administered as empirical antibiotic therapy. After four weeks, the regimen was modified to intravenous cefoxitin 2 g every 8 h and clarithromycin 500 mg twice daily based upon in vitro antimicrobial susceptibility tests. A reduction in the size of the abscess was paralleled by a concomitant decline in the laboratory markers of inflammation (C-reactive protein decreased from 114 mg/L in May 2005 to 26.3 mg/L in August 2005; erythrocyte sedimentation rate diminished from 76 mm/h to 46 mm/h during the same time interval).

The first stage of a two-stage revision arthroplasty was performed in August 2005, with removal of the existing components and insertion of an antibiotic-coated temporary prosthesis. The cement around the implant was impregnated with vancomycin, gentamicin and amikacin. The loculated fluid collections identified in the iliopsoas muscle by the prior magnetic resonance imaging were not encountered. *M. abscessus* was recovered from one of seven intraoperative periprosthetic tissue specimens submitted for mycobacterial culture. Cefoxitin and clarithromycin were administered, in combination, for an additional three months. An ultrasound-guided joint aspirate, conducted two weeks after the completion of antibiotic therapy, was sterile, and the C-reactive protein and erythrocyte sedimentation rate values were normal. In December 2005, 17 weeks after removal of the infected prosthesis and four weeks following the arthrocentesis, the second-stage reimplantation of her definitive prosthesis was undertaken. No histopathological abnormalities indicative of synovitis were demonstrated by frozen section examination of the joint capsule (less than five white cells/high powered field). *M. abscessus* was not isolated from multiple surgical specimens. Antibiotic therapy was stopped seven days after the second-stage revision.

Regular clinical and radiological monitoring has detected no evidence of infectious relapse after 18 months of follow-up observation.

DISCUSSION

Infections complicate prosthetic-joint replacement in 1% to 5% of cases (5), with *Staphylococcus* species as the principal pathogen (6). Two-stage prosthesis exchange combined with adjunctive antimicrobial therapy is the preferred treatment (7). Case-specific factors may allow for alternative surgical procedures such as debridement with implant retention or a one-stage exchange (6,7).

Rarely are RGM a cause of PJI. A recent literature review underscored this observation, and highlighted the scarcity of PJI due to *M. abscessus* (5). This bacterium was incriminated in only one of the 18 reported cases, with *M. fortuitum* and *M. chelonae* isolated from the majority of infected joints. The lone patient infected with *M. abscessus* was afflicted with bronchiectasis compounded by pulmonary colonization with *M. abscessus*. Immunosuppressive therapy for the concomitant rheumatoid arthritis likely predisposed the patient to the PJI. Resection arthroplasty and combination antibiotic therapy with cefoxitin and clarithromycin were unsuccessful.

The clinical and microbiological success in our patient hinged on the application of two interdependent therapeutic

principles. First, removal of the infected orthopedic implant was essential, echoing previous recommendations (5,8). The necessity for this procedure is particularly germane in view of the recognition that *M. abscessus* can display a smooth biofilm-forming phenotype (9). The capacity to form such aggregated microbial communities on prosthetic devices is a significant impediment in achieving a microbiological cure.

Second, the extended exchange interval between the first- and second-stage surgical revision (6,7) allowed for a protracted course of combination antimicrobial therapy. The optimal period, however, of antibiotic treatment for musculoskeletal *M. abscessus* infections is poorly defined. Empirical evidence supports at least four months of antimicrobial therapy for serious infections (8), guided by serial evaluation of the biochemical markers of inflammation. The subsequent documentation of a sterile joint cavity before reimplantation of the new prosthesis was also crucial in minimizing the risk of infectious relapse.

In vitro susceptibility testing has been touted as a guide in designing optimal treatment against *M. abscessus*. However, with the exception of skin and soft tissue infections, a lack of prospective controlled studies exists demonstrating a correlation between the in vitro susceptibility pattern and clinical response (8). The choice of an effective antibiotic is further complicated given that only clarithromycin, amikacin and cefoxitin are reliably active against *M. abscessus* (8). The in vitro susceptibilities of *M. abscessus* to these antimicrobials as reflected in the minimum inhibitory concentration (MIC) required to inhibit the growth of 90% of organisms are less than 0.5 µg/mL for clarithromycin, less than 16 µg/mL for amikacin and less than 64 µg/mL for cefoxitin (10,11). This dilemma was reflected in the replacement of imipenem by cefoxitin in our patient, as the MIC for imipenem is problematic due to a lack of reproducibility (8). To avoid the risk of nephrotoxicity, amikacin was not selected as an alternative drug because a lengthy period of treatment was planned. More important in achieving a successful outcome in our patient was the use of a clarithromycin-containing multidrug regimen. Although no study has established the unequivocal superiority of a particular regimen, limited data have indicated that the inclusion of this potent macrolide as the core of combination therapy has offered the best opportunity of obtaining a clinical response and is associated with a reduction in the occurrence of induced antibiotic resistance (12).

The role of the amikacin-impregnated cement spacer is a matter of debate. Experimental data have indicated a favourable elution profile and pharmacokinetics of amikacin-loaded cement in which the drug concentration in the eluent has exceeded the MIC used to define the breakpoint of amikacin against *M. abscessus* (13). Although the incorporation of antibiotic cement has emerged as the standard of care in the treatment of PJI (14), the efficaciousness of this therapeutic adjunct has not been corroborated by controlled clinical trials.

The mode for the acquisition of *M. abscessus* is unclear. The usual host determinants associated with infection due to this mycobacterium were absent (8). There was neither evidence of chronic pulmonary disease, nor exposure to immunosuppressive medication as the polymyalgia rheumatica was quiescent. Although *M. abscessus*-contaminated tap water or tap water-containing fluids have been epidemiologically linked to infections from this bacterium, this feature was not evident in

our patient. The blunt injury to the right hip incurred by her ski mishap resulted in no loss of overlying skin integrity that would pose as a potential portal of entry. Septic arthritis due to *M abscessus* is a recognized complication of intra-articular injections (15-17), raising the suspicion that the organism was introduced from the prior iliopsoas sheath steroid injection. The prolonged period from injection date until the development of symptoms renders this a remote possibility. Finally, neither multidose vials (15, 17) nor the topical antiseptic benzalkonium chloride (16), both risk factors linked to outbreaks of soft tissue abscesses and joint infections caused by RGM, were used in our patient.

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CONCLUSIONS

Our case illustrates the paramount importance of prosthesis removal coupled with an extended duration of combined directed antibiotic treatment prior to reimplantation in achieving a clinical and microbiological cure in *M abscessus* PJI. The optimum length of antimicrobial therapy before the second stage revision and the most efficacious drug regimen remain to be determined.

POTENTIAL CONFLICTS OF INTEREST: All authors: no conflicts.