Disseminated *Mycobacterium chelonae* infection presenting as progressive multifocal osteomyelitis: Report of two cases and a review of the literature

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Infection à *Mycobacterium chelonae* disséminée sous forme d'ostéomyélite multifocale progressive: Deux rapports de cas et revue de la littérature

**Résumé** : Deux patients ayant séjourné longtemps à l'hôpital ont développé une infection disséminée causée par *Mycobacterium chelonae*, sur une période de huit mois. Dans les deux cas, la maladie a été caractérisée par une atteinte osseuse et cutanée. Les infections ont été peu douloureuses et marquées par une destruction osseuse progressive. Ces deux cas sont présentés ici, de même qu'une revue de la littérature.
MYCOBACTERIUM CHELONAE is a member of the Mycobacterium fortuitum complex, a group of rapidly growing mycobacteria. Infections due to this organism are uncommon, usually producing local cutaneous abscesses at the site of a penetrating injury (1). Disseminated infections occur much less frequently, being seen almost universally among severely immunocompromised hosts such as those with renal transplants, hematological malignancies (2-5), or autoimmune diseases requiring corticosteroids (6). Osseous involvement has been a rare finding in these cases; however, when it occurs, a predilection for the lower extremities has been noted (7,8).

The present report describes two patients with disseminated disease due to \textit{M. chelonae}, neither of whom was severely immunocompromised. Both cases demonstrated marked osseous involvement predominantly of the upper extremities, and progressive bony destruction.

**CASE PRESENTATIONS**

**Patient 1:** A 74-year-old female was admitted to hospital with a viridans streptococcal bacteremia associated with vertebral osteomyelitis. Several years earlier, she suffered a lumbar vertebral fracture associated with osteoporosis treated with spinal fusion. She also suffered from adult onset diabetes mellitus, peripheral vascular disease, hypothyroidism, and chronic obstructive lung disease for which she was receiving prednisone 5 mg bid. On admission, she underwent surgery to remove the orthopedic ‘hardware’ of her previous spinal fusion, followed by decortication of the bone, and a three-week course of antibiotics. There was no evidence of endocarditis associated with the bacteremia. She was subsequently transferred to the long term care service pending permanent placement.

While still in hospital 18 months later, and over a period of two months, the patient began to complain of pain and swelling of her left first toe, then her foot and finally her left second finger. She appeared well and was afebrile, but the dorsum of the left foot, the heel and all toes were swollen, erythematous and tender. A similar lesion was noted on the left second finger near the proximal interphalangeal joint. In addition, a 2 cm fluctuant erythematous nodular lesion was seen on the left pretibial area. Laboratory tests revealed a white blood cell count of 9.7 x 10^9/L with a hematocrit of 0.323. Serum urea and creatinine were 7.0 mmol/L and 57 μmol/L, respectively. An aspirate obtained for culture from the pretibial lesion revealed moderate numbers of polymorphonuclear cells but no organisms on Gram’s stain, and aerobic, anaerobic and fungal cultures were negative. The patient was treated with cloxacillin for two weeks. Four weeks later, several more erythematous fluctuant, tender, raised nonulcerative lesions appeared on both hands and on the left foot. Another aspirate was taken, and a Ziehl Neelson stain revealed the presence of acid fast bacilli. Within a week, visible growth of an organism which was later confirmed as \textit{M. chelonae}, subspecies \textit{chelonae} (9), was present on sheep blood agar. A chest radiograph at this time was normal, and radiographic studies of the extremities revealed only osteoarthritic changes of several joints of the hands and osteoporosis of the left foot without any bony destruction. Mycobacterial blood cultures (Bactec system, Becton-Dickinson, Maryland) were negative.

Amikacin and cefoxitin were started pending sensitivity testing. After three weeks of treatment, no clinical improvement was noted, and imipenem was added to the regimen. Susceptibility data became available after five weeks (Table 1). Imipenem was discontinued and sulfamethoxazole was initiated. Radiographs of the hands now revealed extensive bone destruction of the left second and fourth proximal interphalangeal joints, and a pathological fracture of the right second metacarpal neck. Radiographs of the left lower extremity revealed pathological fractures of the distal fourth and fifth metatarsal shafts. Bone and gallium scans revealed multiple sites of increased uptake in both hands as well as the left elbow and distal left foot compatible with osteomyelitis and/or septic arthritis. A punch skin biopsy of a lesion on the left hand revealed a necrotizing granulomatous dermatitis with superficial and deep involvement and the presence of acid-fast bacilli in areas of necrosis.

In addition to the antibiotic therapy, several of the lesions became vesiculopustular and were incised and drained. Prednisone was tapered over a two-week period. No improvement was noted after five weeks of therapy, at which time the patient suffered a large right

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1: Intermediate sensitivity; MS: Moderate sensitivity; R: Resistant; S: Sensitive. Both cases analysed by the broth microdilution MIC test for rapidly growing mycobacteria (24) at the Centers for Disease Control and Prevention, Atlanta, Georgia.
hemispheric cerebrovascular event and died. No autopsy was obtained.

**Patient 2:** An 82-year-old male was admitted to hospital with congestive heart failure six months after the death of patient 1. The past medical history of patient 2 included adult onset diabetes mellitus, coronary artery disease, peripheral vascular disease, Paget's disease and gout. Cardiopulmonary status improved over a few days with conventional diuretic therapy, but because of an inability to care for himself, he was transferred to the long term care service in hospital (a different hospital site from patient 1).

Two months after admission, the patient complained of pain and swelling of the left hand and right index finger. Physical examination revealed a relatively well appearing man who was afebrile. Swelling and warmth with minimal erythema were observed over the dorsal surface of the left hand and right index finger. Moderate tenderness of the left second and fifth metacarpophalangeal joints with decreased range of motion was also noted. The musculoskeletal examination was otherwise normal. Laboratory examination revealed a white blood cell count of $7.3 \times 10^9/L$ with a normal differential and a hematocrit of 0.360. Serum urea and creatinine were 13.5 mmol/L and 136 μmol/L, respectively. A human immunodeficiency virus antibody test was negative. Radiographs of the hands revealed mild osteoarthritic changes, but were otherwise unremarkable. A radiograph of the chest revealed only hyperinflation and mild enlargement of the cardiopericardial silhouette. An aspirate of fluid from a lesion on the right index finger revealed moderate numbers of polymorphonuclear cells, but no organisms were seen on Gram's stain, and aerobic, anaerobic and fungal cultures were negative. A Ziehl Neelson stain revealed acid-fast bacilli. A second aspirate from the left second finger showed similar findings. Mycobacterial blood cultures (Bactec system) were negative.

The patient was initially placed on isoniazid, rifampin, pyrazinamide, and then changed to doxycycline and amikacin after two weeks. A fluctuant lesion on the left thumb was drained. All specimens yielded *M. chelonae*, subspecies *chelonae* as determined by routine biochemical testing (9). Results of susceptibility testing are shown in Table 1. Follow-up radiographs revealed bone loss involving several areas of the left hand and wrist, which progressed (Figure 1). Bone and gallium scans revealed multiple sites of increased uptake of both hands. Five weeks after antibiotics had been initiated, the patient suffered a cardiac arrest and died. No autopsy was obtained.

**DISCUSSION**

*M. chelonae* increasingly is being recognized as a human pathogen. It is an environmental saprophyte that has been isolated from soil, water and house dust (10). Two subspecies, *chelonae* and *abscessus*, have been identified (11), although recent DNA studies suggest that they should be considered as distinct species (12). *M. chelonae* was first reported as a cause of human disease by Moore and Frerichs in 1953 (13). Although more than 20 species of rapidly growing mycobacteria have been isolated (14), more than 90% of all human disease caused by these organisms is due to *M. chelonae* and *M. fortuitum* (2,3), with the majority of infections occurring in the southern coastal states of the United States (6). Localized soft tissue infection in nonimmunocompromised hosts is the most common clinical entity
encountered with this organism. Infections are usually sporadic, occurring at a site of trauma, such as a penetrating injury or surgical incision. Other entities associated with this organism include pulmonary disease (2, 15-17), prosthetic valve endocarditis (18), keratitis (18), osteomyelitis (18), and disseminated disease (2, 6-8, 18-21).

Disseminated disease due to *M. chelonae* is rare, with approximately 100 cases previously reported. It most frequently occurs without apparent trauma in severely immunocompromised patients. In an extensive review of over 50 patients with disseminated disease recently published by Wallace et al (6), only three patients were noted to have "no underlying medical condition." The most prevalent conditions occurring in association with this type of infection were autoimmune disorders requiring corticosteroid therapy (52%) and organ transplantation (25%). Other conditions reported in these patients include hematological malignancies, solid tumors and chronic renal failure.

Wallace described two clinical syndromes in patients with disseminated disease (22). Patients with underlying conditions such as renal transplantation or acute leukemia usually appear ill with fever and other constitutional manifestations. Blood and bone marrow cultures are frequently positive and mortality is high. The majority of patients with disseminated disease presents with an alternate syndrome, characterized by few or no systemic signs and negative blood cultures. These patients generally follow a more benign course and respond to therapy, but relapses are common. Common to both groups is the presence of multiple subcutaneous nodules, abscesses and cellulitis, usually on the lower extremities. Clinical involvement of visceral sites, "such as the lung, liver, spleen, or kidney, is rare" (22), as is disease involving bone (6-8).

In the present report, two patients are described with disseminated infections who presented with a syndrome characteristic of the more indolent disease noted by Wallace (22). These patients were unusual because of the absence of an overt profoundly immunocompromising condition. The course followed by these patients, which was marked by the development and progression of bony disease, also differentiates them from most of the patients recently described (6). Although the diagnosis of osteomyelitis was based on clinical grounds without biopsy, Wallace et al have shown a very strong relationship between a clinical diagnosis, based on the presence of bony erosion adjacent to the site of a soft tissue infection, and the pathological diagnosis (2). Osteomyelitis due to this organism has been well described in patients with local cutaneous disease as a result of direct extension (18); however, there have been few reports of bony involvement associated with disseminated disease. In fact, Wallace et al reported only two of 53 cases of disseminated infections due to *M. chelonae* who had an associated osteomyelitis (6).

Drabick et al (7) reported a case of disseminated infection with osseous involvement in a 75-year-old male receiving long term corticosteroids (prednisone 30 mg/day) for chronic obstructive lung disease. The patient presented with multiple nodulopustular skin lesions associated with osseous involvement over the lower extremities without significant upper extremity involvement, and was successfully treated with a three-drug regimen. Graybill et al (8) reported on a case of disseminated infection with osteomyelitis in a renal homograft patient that progressed and could not be eradicated despite bilateral leg amputation and antibiotics. One of our patients was receiving low dose corticosteroids. Although the degree of immunosuppression associated with this therapy is uncertain, a strong relationship between disseminated infections and corticosteroids has been reported (6). Both our patients demonstrated progressive disease while receiving antibiotic therapy; however, they cannot be considered treatment failures since they received inadequate antibiotic therapy based on the susceptibility profile of the organisms (Table 1). The poor outcomes likely occurred because of a delay in recognizing the infections and obtaining early sensitivity data, which is crucial with organisms showing multidrug resistance as demonstrated with these isolates. Unfortunately, clarithromycin, which has been shown to be useful in these infections (23), was not available for use at the time.

Both our cases were long term hospitalized patients who likely acquired their infections from a hospital source; however, they appear to be epidemiologically unrelated. The two patients were cared for on different hospital wards, and the second patient was admitted to hospital over six months after the first patient's death. In addition, the susceptibility results support the hypothesis that different organisms were responsible for these infections.

In summary, we have described two patients with disseminated infections due to *M. chelonae*. In contrast to most cases previously reported, neither of these two patients was severely immunocompromised, although one of the patients was receiving low dose corticosteroids. The prominence of bony destruction with progression seen in both patients was striking, and in this setting, represents a novel syndrome associated with *M. chelonae*. This report emphasizes the expanding array of diseases attributable to *M. chelonae*, and the need for early recognition and treatment guided by prompt, accurate susceptibility test results.

REFERENCES

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