A Surgical Wound Infection Due to Mycobacterium chelonae *Successfully Treated with Clarithromycin*

ANITA SALUJA, BS
NIELL T. PETERS, MD
LORI LOWE, MD
TIMOTHY M. JOHNSON, MD

BACKGROUND. Mycobacterium chelonae *is an uncommon but recognized cause of chronic localized cutaneous infection at a site of penetrating trauma or a surgical wound.*
OBJECTIVE. *The problem faced by physicians encountering an infection by* M. chelonae *is often response to therapy, which may be highly variable.*
METHODS. *We describe an immunocompetent patient who developed a localized infection due to* M. chelonae *following surgery for a basal cell carcinoma of the lower leg.*
RESULTS. *The infection responded to treatment with clarithromycin.*
CONCLUSION. *The clinical efficacy of clarithromycin and the salient features of* M. chelonae *infection and its treatment are discussed.* © *1997 by the American Society for Dermatologic Surgery, Inc. Dermatol Surg 1997;23:539–543.*

Mycobacterium chelonae is a rapidly growing nontuberculous mycobacterium. Localized cutaneous infections with rapid growers have been described after skin injury, including injection, surgery, and minor trauma.[1] *M. chelonae* usually produces a chronic nodule or draining abscess at the portal of entry,[2] although erythema, cellulitis,[2] sporotrichoid lesions, papulopustules,[3] ulcers, and regional lymphadenopathy[4] have also been described.

Other reported infections caused by rapidly growing mycobacteria include disseminated cutaneous disease, pulmonary disease, osteomyelitis, keratitis, prosthetic valve endocarditis, lymphadenitis, meningitis, occult bacteremia, spinal epidural abscess,[1] and otitis media.[5]

Although the diagnosis of infection caused by rapid growers can be difficult, the major problem faced by physicians is not their diagnosis, but their therapy. The success of therapy for the rapidly growing mycobacteria has been highly variable in the past. Recently, clarithromycin has emerged as a possible drug of choice for treating infections caused by *M. chelonae*.[6]

We report a patient with an unusual case of *M. chelonae* infection manifested by wound erythema and mimicking a suture granuloma, presenting after Mohs excision and layered closure of a basal cell carcinoma. We also describe the clinical efficacy of clarithromycin in treating this infection.

Case Report

A previously healthy 65-year-old white woman had excision with layered closure of a basal cell carcinoma of her left lower leg. Ten weeks after surgery, she presented to the clinic with new-onset burning and erythema at the inferior portion of her surgical wound. She had no systemic symptoms. The patient's medical history was significant only for hypertension.

On examination, two small papulopustules were noted within the inferior portion of the scar. This was felt to be most consistent with a suture reaction. Two absorbable deep sutures were removed with forceps through a small #11 blade puncture and the patient was started on a 2-week course of cefuroxime to cover for possible low-grade cellulitis. Of note, the patient had received a routine prophylactic 10-day course of cephalexin following the initial excision due to location on the lower extremity.

Persistent erythema at the wound site was seen 1 month later (Figure 1). The concern was still a suture granuloma versus a cyst at the inferior part of the wound. Due to the unusual behavior of the wound, an incisional biopsy was performed. The tissue specimen was sent for histologic exam. The biopsy showed reactive epidermal hyperplasia with intradermal microabscesses and no evidence of neoplasm, compatible with a suture reaction.

On follow-up examination at 2 weeks, it was noted that the granulomatous lesion in the area of the scar had not resolved. At this time, a chronic infectious process was suspected as the patient had failed resolution with suture removal and cephalosporin therapy. Tissue stains were therefore requested on the incisional biopsy

From the University of Michigan Medical Center and Comprehensive Cancer Center (TMJ), Departments of Dermatology (AS, NTP, LL, TMJ), Otolaryngology (TMJ), Surgery (Division of Plastic Surgery) (TMJ), and Pathology (LL), University of Michigan, Ann Arbor, Michigan.
Address correspondence and reprint requests to: Timothy M. Johnson, MD, Department of Dermatology, University of Michigan, 1910 Taubman Center, Box 0314, Ann Arbor, MI 48109-0314.

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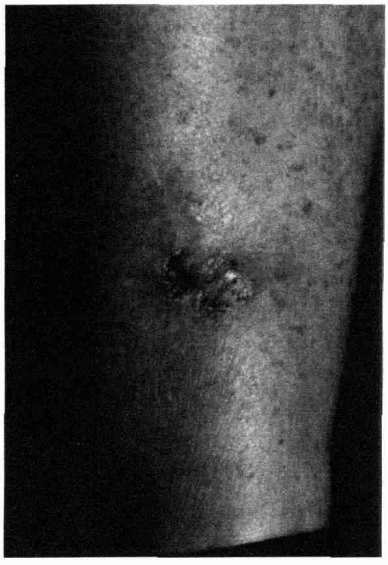

Figure 1. *Persistent granulation inflammation adjacent to an incisional biopsy site on the lower leg.*

tissue specimen. Gomori methenamine silver stain for fungi was negative. A Fite stain for acid-fast bacilli revealed numerous organisms within the dermal abscess (Figures 2 and 3). With this new information, superficial debriding of the lower leg site was performed, and a biopsy sent to microbiology for culture. The patient was started on 500 mg of oral clarithromycin twice a day for atypical mycobacterial infection.

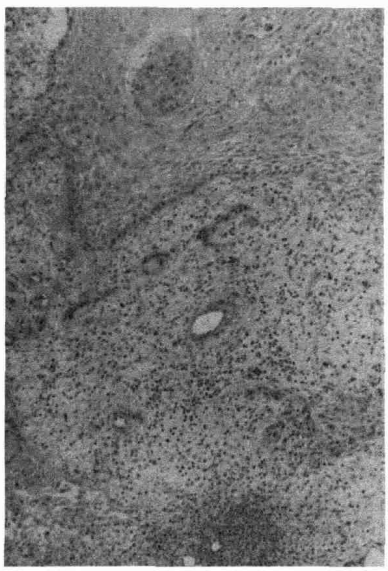

Figure 2. *There is reactive epithelial hyperplasia with a mixed dermal inflammatory infiltrate and abscess fermation (H&E, ×100).*

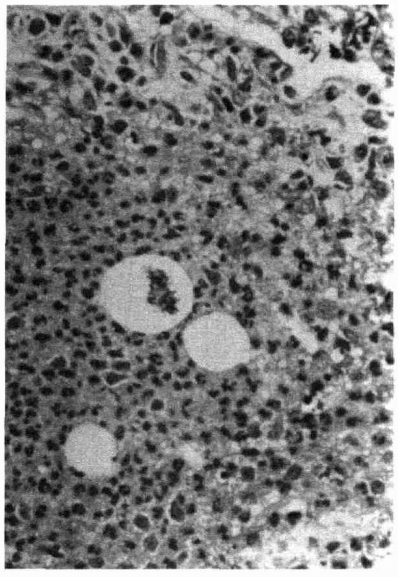

Figure 3. *Small rod-shaped acid-fast organisms are identified within a dermal neutrophilic abscess (Fite, ×400).*

The biopsy specimen was cultured on Lowenstein-Jensen slants at 30°C and 35°C. Growth of moderate amounts of acid-fast bacilli at both temperatures was noted within 2 weeks. The isolate was sent to The Michigan Department of Public Health Laboratory (Lansing, MI) for biochemical testing and high-performance liquid chromatography (HPLC). The organism was ultimately identified as *M. chelonae* (formerly *M. chelonae ssp. chelonae*).

Clinical improvement of the lesion was noted after 2 weeks of clarithromycin therapy with complete healing after 6 weeks. Clarithromycin was continued for 4 more weeks, for a total course of 10 weeks. The patient tolerated the therapy well; her only complaint being a metallic taste secondary to the antibiotic.

Eighteen months following the completion of the clarithromycin course, the patient is free of disease. No other patients in our clinic prior to or after this patient's presentation have had *M. chelonae* infection. An exhaustive history to determine the source of infection was significant only for long (30–60-minute) baths daily immediately following surgery. A definitive source for this patient's infection was not identified, although her domestic water supply may have been a possible source.

Discussion

M. chelonae was first isolated from a sea turtle in 1903 and originally speciated in 1923.[7] *M. chelonae* belongs to the Runyon group IV subtype of nontuberculous my-

cobacteria, classifying it as a rapid grower. Among the rapidly growing mycobacteria, *M. chelonae* and *M. fortuitum*, as well as the newly separate species *M. abscessus* (formerly, *M. chelonae ssp. abscessus*), are the prominent human pathogens.

The rapidly growing mycobacteria most commonly grow to visible colony size on Lowenstein-Jensen media within 7 days at temperatures ranging from 25°C to 40°C. *M. fortuitum*, *M. chelonae*, and *M. abscessus* are distinguished from the other rapid growers by their production of arylsulfastase in 1–3 days and by their inability to produce pigment with culture.[7] *M. chelonae* can be differentiated from *M. fortuitum* by a negative nitrate reduction test, negative iron uptake, and resistance to polymixin B.[1] *M. chelonae* is distinguished from *M. abscessus* by its inability to grow in the presence of 5% NaCl, its ability to use citrate as a carbon source,[7] and its resistance to cefoxitin.[8] In addition, HPLC of cell wall lipids of these organisms can aid in separating the species. These properties led to identification of *M. chelonae* in our case.

Histologic examination of atypical mycobacterial infection is often characterized by suppurative and granulomatous inflammation. Necrosis is commonly present, but caseation is minimal. Foreign-body giant cells are usually present. Acid-fast bacilli are infrequently seen, but when seen tend to appear in extracellular clumps within microabscesses.[1] The histologic pattern of atypical mycobacterial infections may simulate foreign body reactions, deep mycoses, or neutrophilic dermatoses. Our provisional diagnosis in this case was suture reaction based on our patient's history and initial histologic interpretation.

The rapid growers are free-living, ubiquitous saprophytes commonly isolated from soil, water, and dust. Infection is acquired from the environment through inoculation and not transmitted person-to-person. Incubation periods range from 1 week to 2 years, with clinical manifestations generally evident within 4–6 weeks.[2]

A review of the literature on *M. chelonae* reveals that it is a recognized cause of localized skin infection, after trauma or medical procedures, in immunocompetent hosts. In immunocompromised hosts, infection tends to be disseminated.[1,6] In a recent review of 100 cases of *M. chelonae* skin, soft tissue, and bone infections, disseminated cutaneous disease accounted for 53%, catheter infections accounted for 12%, and localized cellulitis, abscess, or osteomyelitis accounted for 35% of the infections.[8] Organ transplantation, rheumatoid arthritis, chronic renal failure, other autoimmune disorders, and corticosteroid use were risk factors for dissemination. Localized iatrogenic infections with *M. chelonae* were seen after medical injections, surgical procedures, and catheter insertions.[8]

Our patient was immunocompetent and developed disease localized to her surgical wound. No other patients undergoing surgery in our surgery unit have ever developed *M. chelonae* infection, leading us to believe that contamination of the wound did not occur from our instruments or water supply. Despite its association with immunosuppression and medical procedures, nosocomial outbreaks with *M. chelonae* have been rare.[8]

M. chelonae has been the atypical mycobacterium with the most drug resistance in the past, making infections due to it difficult or sometimes impossible to treat. Only 10–20% of infections resolve without treatment, and this resolution may take many months.[9] It is well known that the rapid growers are highly resistant to the standard antituberculosis drugs. Some success in treating *M. chelonae* infections with tobramycin, imipenem, erythromycin,[8] ciprofloxacin,[3] amikacin, doxycycline,[10] and sulfonamides[11] has been described in the past. However, high rates of resistance and relapse, persistance of lesions, and serious side effects have also been described. Resistance of *M. chelonae* to cefoxitin has been consistently demonstrated.[9,10] In addition, no reliable active oral agent has been previously found.

Recently, there have been an increasing number of reports demonstrating the clinical efficacy of clarithromycin, one of the newer macrolides, for treatment of *M. chelonae* infections.[3,6,8,12] Clarithromycin has low minimal inhibitory concentrations (MIC) versus *M. chelonae*, good oral absorption, excellent tissue concentrations, a long half life (4.7 hours), and low toxicity. It works by binding to the 50S ribosomal subunit of an organism, inhibiting its protein synthesis.[13]

In a recent study, 223 isolates of rapid growers were tested for their susceptibility to clarithromycin; 79 isolates were also tested against the other macrolides. The MIC for 90% of the strains of *M. chelonae* was 0.25 μg/mL, and 100% of the strains were inhibited by less than 1 μg/mL, well within the achievable serum levels.[12] Clarithromycin was 10 to 50 times more active than erythromycin and four- to eightfold more active than the other newer macrolides versus *M. chelonae*, although azithromycin and roxrithromycin did have acceptable MICs against most strains, as well.[12] Thus, azithromycin, very similar to clarithromycin, may be a reasonable alternative drug. In another study, 78 isolates were tested against clarithromycin. All were susceptible to 1 μg/mL and 95% were susceptible to 0.25 μg/mL, with an MIC break point of 2 μg/mL for susceptible strains and 4 μg/mL for moderately susceptible strains.[8] Also tested clinically, clarithromycin was given to patients with disseminated *M. chelonae* infections for 6 months. Eleven of 14 patients (one noncompliant patient relapsed with a resistant isolate and two died of other causes) had an excellent response to therapy, leading the authors to suggest that clarithromycin

may be the drug of choice for disseminated cutaneous disease due to *M. chelonae*.[6]

Clarithromycin has been well tolerated by patients infected with *M. chelonae*. There has been only one case report of a serious side effect causing discontinuation of the drug. This patient developed cholestatic hepatitis, which resolved after the drug was stopped.[14] Metallic taste, as noted by our patient, nausea, and mild diarrhea have also been reported.[6]

Clarithromycin has also shown good antimicrobial activity with clinical response in infections involving other atypical mycobacteria. It is a first-line agent for treating *M. avium-intracellulare* infections.[15] Success with treating *M. abscessus*,[16,17] *M. marinuum*,[18,19] and *M. kansasii*[20] has also been reported.

Optimal dosage and duration of clarithromycin therapy have not been definitively established. A 500-mg dose of clarithromycin given twice a day has proven successful thus far.[6,21] It has been suggested that therapy for rapidly growing mycobacteria should be 2–4 months for minimal localized disease with good response. Extensive disease should be treated for at least 6 months. A good margin of safety is to continue antibiotics for 4–6 weeks after complete wound healing.[9] Our patient has not had recurrence since we stopped therapy 4 weeks after resolution of the lesion.

A few cases of acquired clarithromycin resistance with monotherapy have been described.[22] However, success for single-drug therapy for limited infections with infrequent development of resistance has been shown.[23] Thus, monotherapy in these cases is appropriate. In disseminated disease, an initial induction phase of intravenous combination antibiotics prior to clarithromycin alone or with other antibiotics is justified to avoid resistance and improve bacterial killing.[23]

In the past, surgical drainage and excision was often the mainstay of therapy. However, it has also been shown that without additional antibiotic therapy, infections treated only with surgical debridement may persist for months to years.[9,10] Antimicrobial therapy is usually the preferred method of treatment. Local debridement is an important adjunctive therapy.[18]

In summary, we present a case of *M. chelonae* infection occurring in a surgical scar and mimicking a suture granuloma. With the persistence of an erythematous granulomatous lesion, we became suspicious for a chronic infectious process caused by a less common pathogen. Acid-fast bacilli were noted retrospectively in the patient's biopsy with a positive Fite stain. *M. chelonae* was later identified with biochemical testing and HPLC. We empirically treated with clarithromycin because of its reported success in other recent cases. There was complete healing after 6 weeks of therapy. Atypical mycobacteria need to be considered as possible pathogens in persistent skin and soft tissue infections. At present, clarithromycin is the drug of choice for localized infections with *M. chelonae* in the immunocompetent patient.

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Commentary

The authors of this paper share an illustrative experience with us. Although they downplay the importance of diagnosis and emphasize the management of this unusual atypical mycobacterium wound infection, the real lesson here is, in fact, just how difficult it is sometimes to figure out what is going on. When the postoperative clinical course swerves off normal and wound healing becomes either delayed, exuberant, weepy, necrotic, or otherwise altered, the clinician must put on a detective hat and try to reconcile why things have gone awry. Does the patient have an undetected medical condition or nutritional deficiency that inhibits wound healing? Are the dressings inappropriate or too occlusive? Is the patient or family clandestinely trying home remedies or poultices that are to blame? Are buried sutures, as suspected here, acting as a foreign body? Or is the culprit a wound infection?

It is in this arena, when the presentation is very unusual and the zebras are out romping, that perseverance and right-thinking pay off. A high level of suspicion must be activated if atypical mycobacterium, yeast, anaerobic bacteria, saprophytic fungi, or even algae are to be found. As was done here, appropriate biopsies must be taken and if indicated, appropriate tests pursued. These may include routine cultures, anaerobic cultures, as well as fungal and AFB cultures. Special stains to include PAS and Fite should be done.

As noted by the authors, diagnosis is part of the problem. Once accomplished the focus turns to treatment. In this case we are briefed on a new drug, clarithromycin, which appears to be an efficacious, relatively safe drug for cutaneous M. chelonae infections.

STUART J. SALASCHE, M.D.
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