Atypical Mycobacterial Infections of the Upper Extremity: Becoming More Atypical?

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Abstract

Background: Atypical mycobacterial infections are uncommon and characterized by a chronic, indolent course before diagnosis. Historically, these infections are associated with marine-related injury and/or immune dysfunction. Our institution has successfully diagnosed and treated an increasing number of these infections. The objective of this study is to review our experience with these rare infections and verify the developing trends encountered. **Methods:** A retrospective review was performed for patients with positive nontuberculous mycobacterial cultures of the upper extremity from 2000 to 2013. Patient demographics, source of transmission, symptom duration, mycobacterial species, operative and antibiotic treatments, and outcomes were recorded. **Results:** Thirty-four patients were identified. The mean symptomatic period before diagnosis was 9 months (range, 1–60 months). Fourteen patients had identifiable causes of immune dysfunction while the rest appeared immune competent. Patients were infected by *Mycobacterium marinum* (n = 14), *Mycobacterium abscessus* (n = 8), *Mycobacterium fortuitum* (n = 7), and other less common species (n = 5). Although most patients had unidentifiable causes of infection (n = 15), some could correlate infection to marine injury, lacerations, insect bites, animal bites, and tattoos. All patients received operative intervention including debridement. Antibiotics were given for a mean duration of 5 months. Ninety-seven percent had complete resolution of disease. **Conclusions:** Although *M. marinum* infections make up the majority of infections at our institution, we report a higher total incidence of nonmarinum infections. These infections are occurring in seemingly healthy individuals with no history of exposure with marine water. Successful treatment relies on having a heightened clinical awareness and adequate diagnosis.

Keywords: nontuberculous, atypical mycobacteria, marinum, hand, upper extremity

Introduction

Atypical mycobacterial infections or nontuberculous mycobacterial infections (NTM) of the soft tissues are uncommon. While studies place the incidence of *Mycobacterium marinum* at 0.05 to 0.27 per 100 000,^{3,8} the incidence of nonmarinum species is even scarcer. The overall incidence of these infections is suspected to have increased nearly 3-fold over the last decade.⁹ Because of the low prevalence, epidemiologic data on upper extremity NTM are largely lacking.⁴ A 1994 study reports 33 patients with NTM of the upper extremity, with *M. marinum* being the most frequent causative organism.⁶ Another series reviewed upper extremity *M. marinum* infections in 29 patients but did not include nonmarinum species.⁵

Historically thought to cause infection only in immunocompromised hosts, NTM are now recognized as significant pathogens in immunocompetent hosts as well. While

M. marinum is classically regarded as a species targeting the hands of immunocompromised hosts in the setting of marine trauma,⁵ little has been published documenting the clinical significance of infections caused by rapidly growing mycobacteria including *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae*.

Due to an indolent course, proper diagnosis is often delayed and stems from a high index of suspicion. Clinical presentation ranges broadly from single or multifocal lesions and abscesses to only inflammatory or nerve compression type symptoms. Pathognomonic clinical characteristics are

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often absent, prompting misdiagnosis as cellulitis, fungal or parasitic infections, gout, rheumatoid arthritis, trigger finger, foreign body reaction, median nerve compression at the wrist, or skin tumor. Delays in proper treatment are common,⁷ and inappropriate treatment with steroids and antibiotic regimens facilitate the spread of infection from skin to tenosynovium, leading to diminished hand function.^{1,2}

Our institution on the US Gulf Coast has successfully diagnosed and treated these infections, noting new patterns of infection and an increasing number of clinically pathogenic species. The purpose of this study is to review our experience with upper extremity NTM and verify the developing trends we are encountering in our patient population.

Methods

After approval by the institutional review board at the University of Texas Medical Branch, a retrospective chart review was performed. The records of patients diagnosed with a NTM infection of the upper extremity from January 1, 2000, to December 31, 2013, were retrieved.

Subjects were identified from the Division of Clinical Microbiology database of patients with a positive NTM infection. The microbiology lab identified mycobacterial species by standard criteria. First, a classic acid-fast stain is performed and if positive, a Kinyoun stain is used to confirm. Next, 2 different types of media are used including Middlebrook agar and mycobacteria growth indicator tube. These are then placed in 2 different incubators, one at 35°C to 37°C and the other at 30°C. The cooler incubator is used to grow *M. marinum* species as this species prefers a slightly lower temperature. *Mycobacterium tuberculosis* is detected by DNA sequencing via an Accuprobe (Gen-Probe, San Diego, California). Infections that were not confined to the hand, wrist, forearm, or elbow were excluded.

Patient demographics including age, gender, medical comorbidities (including conditions or treatments that may predispose to immune dysfunction), and tobacco use were collected. Charts were reviewed for duration of symptoms before diagnosis, follow-up time, mycobacterial species, suspected mechanism of transmission, operative interventions, antibiotic treatments, duration of treatment, and overall functional outcomes.

Statistical analyses were based on comparisons between the most commonly diagnosed species, *M. marinum*, *M. fortuitum*, *M. abscessus*, and *Mycobacterium avium* species. *M. chelonae*, *Mycobacterium immunogenum*, and *Mycobacterium kansasii* had insignificant sample sizes to justify inclusion and were accordingly excluded from statistical analysis. Independent *t* tests were conducted to analyze differences in mean symptom onset and mean antibiotic length between species, as well as correlation between need for extensive procedures and duration of symptoms and

Figure 1. Incidence of nontuberculous mycobacterial infections.

antibiotic course. Chi-square analyses were conducted to assess the type of antibiotic used with each species, immune suppression among hosts infected, location of infection, and the mechanism of injury relative to each species. Significance for all independent *t* tests and chi-square tests conducted was set at $P = .05$.

Results

During the years 2000 through 2013, 34 patients were identified with a positive NTM of the upper extremity. The average age of patients was 50 years, ranging from 9 to 71 years. Patients were equally distributed by gender; 17 were male and 17 female. Fourteen patients had identifiable diseases or medical treatments that were likely to predispose to an increased risk for immune dysfunction. These included multiple myeloma, solid organ transplants (heart, lung, liver), diabetes mellitus, human immunodeficiency virus, rheumatoid arthritis, lupus, and asplenia. The other 20 patients had no identifiable conditions likely to compromise their immune system and were not taking immune modulating medications. Three patients were active smokers.

The mean symptomatic period before diagnosis was 9 months, ranging from 1 to 60 months, and the mean follow-up time was 9 months, ranging from 1 to 48 months.

Patients were infected most frequently by *M. marinum*, followed by *M. abscessus*, *M. fortuitum*, and other less common strains. Less common strains included 2 cases of *M. avium* and 1 case each of *M. chelonae*, *M. immunogenum*, and *M. kansasii* (Figure 1).

A cause of infection was not identified in 15 patients. Five patients had an identifiable marine-related injury, and another 5 had a recent animal or insect bite in the same location. Three patients had an injury while gardening/performing yardwork, and a smaller subset had a previous surgical

Figure 2. Suspected source of nontuberculous mycobacterial infections.

Figure 3. Nontuberculous mycobacterial infections by anatomical location.

incision, recent tattoo in the same location, or received treatment for burn (Figure 2).

Patients infected with *M. marinum* were more likely to be immune compromised, have an identifiable marine-related injury, and a longer duration of symptoms before diagnosis ($P < .005$). Overall, the most common location for infection was the hand (which included both dorsal and volar infections), followed by the index finger, forearm, and elbow. Infections of the wrist and other fingers were less common (Figure 3). There was no association between location of infection and mycobacterial species ($P > .05$).

All patients underwent a diagnostic or therapeutic surgical intervention including incision and drainage, excisional

Table 1. Species Associated With Deep Infection Requiring More Extensive Procedure.

Species	Procedure
marinum	carpal tunnel decompression/flexor tenosynovectomy
abscessus	carpal tunnel decompression/flexor tenosynovectomy
marinum	flexor tenosynovectomy
marinum	flexor tenosynovectomy
abscessus	extensor tenosynovectomy
avium	extensor tenosynovectomy
abscessus	extensor tenosynovectomy

biopsy, sharp wound debridement, tenosynovectomy, or open carpal tunnel decompression. Seven patients underwent more extensive surgery for deeper infection such as extensor or flexor tenosynovectomy, of which 2 had concomitant carpal tunnel decompression (Table 1). There was no significant correlation between mycobacterial species and tenosynovectomy or nerve decompression. The patients who underwent the more extensive procedures did not have a longer duration of symptoms before diagnosis (mean was still 9 months) and did not require a longer course of antibiotics (mean of 5 months) ($P > .05$). One of the 2 patients who had carpal tunnel decompression had electromyography proven unilateral median nerve compression at the wrist as the main presenting symptomatology. Diagnosis of NTM in this patient was confirmed after flexor tenosynovectomy specimens were sent for further evaluation.

Every patient received antibiotic therapy that was guided in consultation with the Infectious Diseases service based on local susceptibilities, disease severity, and involved tissues. Antibiotic therapy was administered for a minimum of 1 month, with continuation past 1 month until visible cutaneous lesions resolved. The most commonly used antibiotics were clarithromycin, followed by minocycline and a combination of rifampin/ethambutol. Other less commonly used antibiotics were Amikacin and Bactrim (Figure 4). The overall mean antibiotic course was 5 months, ranging from 1 to 12 months. One patient remains on lifelong antibiotic therapy with clarithromycin secondary to multiple myeloma. Patients infected with *M. marinum* were more likely to be treated with minocycline ($P < .005$). There was no other correlation between antibiotic and mycobacterial species.

When assessing functional outcome, 33 of the 34 patients returned to premorbid baseline hand function and had complete resolution of symptoms. This was determined by reviewing the medical record for resolution of symptoms, cessation of antibiotic therapy without subsequent recurrence of symptoms, or the need for further surgical intervention. One patient outcome could not be analyzed because of death due to unrelated causes.

The years 2000 and 2013 had the highest incidence of infections, with no infection seen in the years 2002 and

Figure 4. Antibiotics used to treat nontuberculous mycobacterial infections.

Figure 5. University of Texas Medical Branch annual incidence of nontuberculous mycobacterial infections.

2008. The last 3 years of our study had steadily rising numbers of infections (Figure 5).

Discussion

This study demonstrates that NTM occur in a variety of patients, including nonsmokers and immune competent hosts. Most infections were not marine related and had no identifiable mechanism likely secondary to trivial and unrecalled injury due to the time elapsed prior to the onset of clinical symptoms. Recent studies support an increasing prevalence of these infections due to nonmarine causes such as surgical and tattoo sites.⁹ Although the most common species was *M. marinum*, there were more infections

due to nonmarine species. These are important new data that suggest not only an increasing incidence of these rapidly progressive infections but also that healthy individuals with no recollection of marine trauma are likely to be affected.

All patients received both surgical intervention and antibiotic therapy. Appropriate diagnosis and treatment led to symptom resolution and return of premorbid functional abilities. Surgical interventions were performed based on individual patient needs. All patients received antibiotic therapy that was guided in consultation with the Infectious Diseases service based on local susceptibilities, disease severity, and involved tissues. As this is a retrospective study, antibiotic therapy was not standardized by protocol for duration of therapy or mycobacterial species, and these are limitations in this study. However, all patients experienced satisfactory clinical outcomes.

Although rare, the incidence of NTM is likely increasing and still under diagnosed. Data regarding appropriate management are lacking. To date, this study represents one of the largest of its kind and includes new data regarding our experience with both *M. marinum* and nonmarine species involving the upper extremity. Because these infections run an indolent course, patients may be debilitated and kept from returning to daily activities or employment due to delay in diagnosis. To further assist with prompt diagnosis, we have since changed our practice to include a separate cutaneous biopsy specimen and lab order for atypical mycobacteria tissue culture in all patients who present with an upper extremity infection with atypical clinical features or have failed to resolve with appropriate antibiotic treatment for common pathogenic skin organisms. We believe that these changes have facilitated more timely diagnosis explaining the rise in NTM at our institution during the past 3 years.

Authors' Note

This article was presented at the American Association for Hand Surgery Annual Meeting in the Bahamas 2015 and the 6th Combined Meeting of the American Society for Surgery of the Hand and Japanese Society for Surgery of the Hand in Hawaii 2015.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Informed consent was obtained when necessary.

Declaration of Conflicting Interests

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References

1. Cheung JP, Fung B, Wong SS, Ip WY. Review article: *Mycobacterium marinum* infection of the hand and wrist. *J Orthop Surg (Hong Kong)*. 2010;18:98-103.
2. Dieudonne A, Steele R. Atypical mycobacterial infection. *Medscape*. January 7, 2015. <http://emedicine.medscape.com/article/972708-overview>. Accessed March 16, 2016.
3. Edelstein H. *Mycobacterium marinum* skin infections. Report of 31 cases and review of the literature. *Arch Intern Med*. 1994;154:1359-1364.
4. Falkinham JO III. Epidemiology of infection by nontuberculous mycobacteria. *Clin Microbiol Rev*. 1996;9:177-215.
5. Hess CL, Wolock BS, Murphy MS. *Mycobacterium marinum* infections of the upper extremity. *Plast Reconstr Surg*. 2005;115:55e-59e.
6. Kozin SH, Bishop AT. Atypical *Mycobacterium* infections of the upper extremity. *J Hand Surg Am*. 1994;19:480-487.
7. Lahey T. Invasive *Mycobacterium marinum* infections. *Emerg Infect Dis*. 2003;9:1496-1498.
8. O'Brien RJ. The epidemiology of nontuberculous mycobacterial disease. *Clin Chest Med*. 1989;10:407-418.
9. Wentworth AB, Drage LA, Wengenack NL, Wilson JW, Lohse CM. Increased incidence of cutaneous nontuberculous mycobacterial infection, 1980 to 2009: a population-based study. *Mayo Clin Proc*. 2013;88:38-45.