Localized Cutaneous Infections in Immunocompetent Individuals Due to Rapidly Growing Mycobacteria

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- Rapidly growing mycobacteria (RGM) cause skin infections that are refractory to standard antibiotic regimens. Although typically associated with disseminated cutaneous or other systemic infections in immunocompromised patients, RGM sometimes cause localized cutaneous infections in immunocompetent hosts. These infections are almost always associated with precedent skin trauma and inoculation, and therefore have been implicated in outbreaks involving contaminated tattoo ink and inadequately sterilized acupuncture needles. Histologic features often include suppurative granulomatous inflammation, and microorganisms are rarely visualized with stains for acid-fast bacilli. The differential diagnosis includes granulomatous fungal and non-RGM bacterial infections as well as noninfectious suppurative or sarcoidlike conditions. Because no pathognomonic histologic features exist for cutaneous RGM infections, clinical suspicion and appropriate workup are essential to reach an accurate and timely diagnosis. Most localized cutaneous RGM infections in immunocompetent individuals respond well to either clarithromycin or amikacin, in combination with surgical debridement.


Rapidly growing mycobacteria (RGM) are defined as nontuberculous species that grow on laboratory media within 7 days. There are currently 70 recognized species of RGM that are classified into 6 groups based on genetic relatedness, pigmentation, and biochemical properties. Approximately 80% of disease in humans due to RGM is caused by the nonpigmented Mycobacterium chelonae, Mycobacterium abscessus, and Mycobacterium fortuitum, with the remainder caused by RGM of the pigmented Mycobacterium smegmatis group and other rarely pathogenic groups.

Bacilli of the M smegmatis group, first discovered by Sigmund Lustgarten in the smegma of a man with a penile ulcer, were described in 1885. Fifty-three years later, a report of a strain of RGM now known to be M fortuitum isolated from a human postinjection abscess was published by da Costa Cruz. In 1953, Moore and Frerichs recovered a novel acid-fast bacillus from a knee abscess and subsequently named it M abscessus; and in 1972, Stanford et al published their findings regarding an RGM isolate from postinjection abscess outbreaks. This isolate, named M chelonae, was thought by some to be the same organism as M abscessus, but modern classification techniques have demonstrated these to be separate species.

CLINICAL FEATURES

The RGM typically cause disseminated cutaneous infections in immunocompromised hosts, but have also been implicated in lung, bone, joint, ocular, and prosthetic heart valve infections. In most cases, patients with disseminated cutaneous nontuberculous mycobacterial (NTM) infections are taking low-dose systemic corticosteroids. The most commonly implicated RGM in these instances are M chelonae or M abscessus. On rare occasion, RGM cause cutaneous infections in immunocompetent hosts. In contrast to cutaneous RGM infections in the immunocompromised, these infections are associated with precedent skin trauma, such as puncture wounds or injuries sustained in motor vehicle accidents. Patients with localized cutaneous infections caused by RGM and other NTM typically present with tender violaceous papules, plaques, nodules, or cellulitis at sites of skin penetration or trauma that, despite treatment with standard antibiotic regimens, have not regressed. Gram stain and routine cultures may be negative, and it is not until after a protracted course that NTM infection is considered. The majority of solitary lesions occur on the lower extremities, but the upper extremities, trunk, and rarely head and neck may also be involved. Additionally, there are a number of reports of cutaneous M chelonae infections in immunocompetent hosts due to subcutaneous inoculation with contaminated tattoo ink, after acupuncture, and after mesotherapy. Myalgia, fatigue, and night sweats were observed in one immunocompetent patient with tattoo-associated M chelonae infection.
Clinical Manifestations of Rapidly Growing Mycobacteria (RGM) Infections by Group

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<tr>
<th>Clinical Manifestations*</th>
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<tr>
<td><strong>Mycobacterium fortuitum group</strong></td>
<td>Localized skin and soft tissue infections, disseminated cutaneous disease (rare), bone and joint infections, lung infections (rare), central nervous system disease (rare, <em>M fortuitum</em>), keratitis, iatrogenic infections</td>
</tr>
<tr>
<td><strong>Mycobacterium chelonae/Mycobacterium abscessus group</strong></td>
<td>Localized skin and soft tissue infections, disseminated cutaneous disease, lung infections (<em>M abscessus</em> in particular), keratitis (*M chelonae, M abscessus, otitisa media (<em>M abscessus</em>), iatrogenic infections</td>
</tr>
<tr>
<td><strong>Mycobacterium mucogenicum group</strong></td>
<td>Iatrogenic infections</td>
</tr>
<tr>
<td><strong>Mycobacterium smegmatis group</strong></td>
<td>Localized skin and soft tissue infections, bone infections, lung infections (<em>M smegmatis</em>), iatrogenic infections</td>
</tr>
<tr>
<td><strong>Early-pigmented RGM</strong></td>
<td>Localized skin and soft tissue infections, bone infections</td>
</tr>
<tr>
<td><strong>Mycobacterium mageritense/Mycobacterium wolinskyi group</strong></td>
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**HISTOPATHOLOGY**

Biopsy of cutaneous RGM infections can show a variety of patterns, depending on the stage at which the biopsy is performed and the immune status of the patient. Suppurative mixed granulomatous inflammation is typically present in immunocompetent patients (Figure 1). In a report of an iatrogenic *M abscessus* outbreak, Rodriguez et al18 separated the histopathologic findings into 3 categories: nodular or diffuse inflammation with mixed granulomas containing abscesses surrounded by epithelioid and Langhans giant cells, neutrophilic abscesses with a subtle granulomatous response, and deep dermal and subcutaneous granulomatous inflammation without neutrophils. Of these patterns, the most commonly observed was the mixed pattern with a robust granulomatous response. The authors observed that broad abscesses with a weak-to-absent granulomatous response were more characteristic of biopsies from immunocompromised patients, and that acid-fast bacilli were more likely to be seen in these instances. In 82% of the biopsies, clear vacuoles surrounded by neutrophils or epithelioid cells were present, and of these nearly one-third contained clumps of acid-fast bacilli (Figure 2). These findings are corroborated by Gable et al,19 who describe a pattern of suppurative infection with a variable degree of granulomatous inflammation in 6 immunocompromised patients with cutaneous RGM infections. Of these cases, 2 had pseudocysts containing microorganisms. This pattern has been suggested to be unique to the RGM.20

Other studies characterizing the histopathologic features of NTM in immunocompetent patients show mixed results: Dodiuk-Gad et al21 reported granulomas in 36% of biopsies from immunocompetent hosts, whereas Bartralot et al22 reported granulomas in 83%. Acid-fast bacilli were observed in even fewer cases. Other patterns observed include robust tuberculoid, palisading, or sarcoidlike granulomas, as well as nongranulomatous patterns, such as necrotizing folliculitis, panniculitis, and nonspecific chronic inflammation.22

Because biopsy does not necessarily demonstrate microorganisms or granulomatous inflammatory reaction, and because RGM infections may not always be detected on standard wound cultures, a clinical suspicion for RGM or other NTM is essential for accurate and timely diagnosis. In such cases, a clinical history of skin infection that follows penetrating skin trauma, lacks response to standard antibiotics, or has negative standard wound cultures should prompt further investigation to include acid-fast bacilli stains and cultures. In cases where mycobacterial infection is suspected but the Ziehl-Neelsen stain is negative, it may be useful to perform a Fite stain, which differs in that tissue sections are deparaffinized using a mixture of mineral oil and xylene rather than xylene alone. This method is considered to be less harsh, preventing loss of the organism’s acid-fast properties, and typically is used to detect *Mycobacterium leprae*. However, no recent studies have been published that evaluate the sensitivity of modified versus standard acid-fast stains for diagnosis of cutaneous RGM infections.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for each of the granulomatous patterns encountered in cutaneous RGM infections is broad. Suppurative versus nonsuppurative granulomatous inflammations raise divergent differential diagnoses, and in both cases, the cause of the granulomas may be either infectious or noninfectious. As with any suppurative cutaneous skin infection—particularly following trauma to the skin—bacterial infection due to more commonly encountered organisms such as *Staphylococcus aureus* and *Streptococcus pyogenes* must be considered in the differential diagnosis. These cases are usually excluded by culture and successful empirical treatment. If standard wound cultures are negative and empirical treatment is unsuccessful, then RGM infection should be considered.

Suppurative granulomas are associated with a myriad of infectious conditions, including blastomyces, coccidiomycosis, paracoccidiomycosis, phaeohyphomycosis, cryptococcosis, cat-scratch disease, nocardiosis, actinomycosis, and other atypical mycobacterial infections.23,24 Additional stains for microorganisms should be considered if there is a possibility that these infectious agents are present. Periodic acid–Schiff and Gamori metheramine silver will facilitate visualization of the causative microorganisms in blastomycosis, coccidiomycosis, and paracoccidiomycosis, whereas specific histochemical stains are typically not needed for visualizing the diverse pigmented fungal organisms that cause phaeohyphomycosis, but periodic acid–Schiff and Gamori metheramine silver may still be useful. Cryptococcal microorganisms are highlighted by mucicarmine and Fontana–Masson, and Warthin–Starry highlights rare bacilli in the necrotic granulomas of cat-scratch disease.23 Nocardia

*nae infection,*21 but constitutional symptoms often are not present during localized cutaneous infections with these organisms.9
stains gram positive in a beaded pattern and is also partially acid fast. This can be confusing, as the RGM—when detected on Gram stain—will stain with a beaded pattern that may be mistaken for gram-positive bacilli. Definitive diagnosis often requires culture of the wound, particularly when other atypical mycobacterial infections such as Mycobacterium marinum are in the differential diagnosis.

Noninfectious causes of suppurative granulomas include superficial granulomatous pyoderma and ruptured cysts and follicles. Lesions of superficial granulomatous pyoderma tend to occur on the trunk but may also occur at surgical sites. A recent case report of facial superficial granulomatous pyoderma following scar revision demonstrates the potential similarity of superficial granulomatous pyoderma and RGM infection with regard to clinical presentation and histologic appearance. In this case, appropriate histochemical stains and negative cultures aided in establishing the correct diagnosis.

Sarcoidlike granulomas raise the differential diagnosis of sarcoid and foreign body giant cell reaction. However, histochemical stains and cultures will be negative in these cases, and other findings, such as a history of sarcoidosis or the presence of polarizable material or keratin debris within granulomas, would favor a diagnosis other than RGM infection.

Tuberculoid granulomas are seen in tuberculosis, leprosy, leishmaniasis, and other conditions. A Ziehl-Neelsen histochemical stain will highlight microorganisms within granulomas in M tuberculosis cutaneous infections, and wound cultures for mycobacteria should not show growth by 7 days. Mycobacterium leprae is best visualized using a Fite stain, though microorganisms are not readily visualized in tuberculoid leprosy, and a wound culture will fail to grow microorganisms. Cutaneous leishmaniasis may show amastigotes within macrophages using hematoxylin-eosin, but these organisms are not always readily visualized in biopsies of later lesions. If the clinical history suggests cutaneous leishmaniasis or leprosy, polymerase chain reaction may be useful for their detection.

LABORATORY IDENTIFICATION

Isolation of the RGM is best accomplished by culture at 28°C to 30°C. Once colonies are isolated, additional testing for definitive speciation is performed. Before the widespread use of molecular testing, biochemical and antimicrobial susceptibility tests were used to classify the RGM. For example, the M fortuitum and M chelonae/M abscessus groups are strongly positive for the arylsulfatase reaction at 3 days, in contrast to Mycobacterium wolinskyi and the M smegmatis group. Other tests, such as nitrate reduction, carbohydrate utilization, and growth in 5% NaCl, can help distinguish among species. Though historically these tests have been useful in a clinical context, molecular methods are now preferred for clinical identification. Therefore, biochemical testing is reserved as an adjunct to new species characterization and not used routinely for diagnosis.

Molecular identification methods have shown their usefulness for differentiating among RGM. These methods have the advantage of producing accurate results that are rapidly available. In one method, 2 main hypervariable domains on the 5’ end of the 16S rRNA gene (region A and region B) are analyzed for signature sequences that differentiate among species. Two of the major RGM, M chelonae and M abscessus, are identical in these regions, but differ in the 3’ end of the 16S rRNA gene. Sequence differences within the heat shock protein gene (hsp65) are very useful in differentiating among species that have a high degree of similarity in the 16S rRNA gene, including M chelonae and M abscessus. Additionally, the hsp65 gene is amenable to polymerase chain reaction restriction enzyme analysis, which does not rely on growth rates or nutritional requirements for initial identification and is relatively inexpensive. However, it is a relatively complex test that, as of 2011, has not been approved by the Food and Drug Administration and therefore requires extensive in-house validation. The utility of sequencing the rpoB gene has more recently been demonstrated in instances where neither the 16S rRNA nor the hsp65 gene differentiated among the RGM species.

TREATMENT AND PROGNOSIS

Several factors must be considered when treating NTM skin infections, such as immune status and number of cutaneous lesions. If multiple lesions are present, or if
surgical debridement would result in cosmetically or functionally unacceptable results, medical therapy alone may suffice. Although *M. chelonae* and *M. abscessus* historically have been considered to be particularly resistant to antibiotics as compared with *M. fortuitum*, more recent evidence suggests that clarithromycin is reliably active against *M. chelonae* and *M. abscessus* but not *M. fortuitum*. In cases of *M. fortuitum* infection, amikacin is the antibiotic of choice. The results of one small clinical trial published in 1993 by Wallace et al. showed that monotherapy with clarithromycin was effective in treating disseminated infection from *M. chelonae* in immunocompromised patients; however, it is questionable whether these results could be extrapolated to immunocompetent patients, as both the mechanism of infection and the hypothetical virulence of the infectious agents are likely different between the 2 groups. Regardless, monotherapy should be undertaken with caution, as development of resistance to individual groups. Regardless, monotherapy should be undertaken with caution, as development of resistance to individual agents has been reported. Moreover, Uslan et al. have noted higher levels of resistance to previously favored antibiotics of multiple different classes. Development of resistance to the cell wall synthesis inhibitors in particular is antibiotics of multiple different classes. Development of resistance to the cell wall synthesis inhibitors in particular is anticipated to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. *Arch Dermatol*. 2006;142(10):1287–1292.


