New onset erythematous nodules in an elderly woman

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Abstract

An 86-year- old woman with a history of recurrent bronchitis and giant cell arteritis presented for new onset, cyclic and migratory erythematous nodules associated with fatigue and weight loss. Although a systemic vasculitis was initially suspected, elevated inflammatory markers and symptoms persisted despite aggressive corticosteroid therapy. Excisional biopsy of one nodule showed dense suppurative and granulomatous inflammation that was rife with acid-fast bacilli. The patient was urgently admitted for empiric treatment of disseminated mycobacterial infection. Although T-SPOT Tuberculosis testing and direct mycobacterial PCR were negative, mass spectrometry demonstrated *Mycobacterium chelonae*. The patient was treated with a macrolide and quinolone combination regimen and then discharged to a rehabilitation facility.

Keywords: Mycobacterium chelonae, rapidly growing mycobacteria, disseminated infection, skin and soft tissue infections

Case Synopsis

An 86-year-old woman with a history of recurrent bronchitis, giant cell arteritis, and Alzheimer disease presented for new onset erythematous nodules.

Ten months prior to presentation, the patient was admitted to a hospital in Arizona for diplopia, headache, and jaw claudication. She was found to have an ESR exceeding 100 mm/hr and a positive temporal biopsy, leading to a diagnosis of giant cell arteritis. She was initiated on 60mg prednisone daily with rapid improvement of her symptoms. Over the next 5-6 months, she was maintained on a slow taper to 20mg. During the course of her taper, the patient began experiencing increased fatigue with reduced exercise tolerance, leading her to move to Boston to live with her daughter.

One month prior to presentation, she developed painful, warm, and erythematous skin nodules on her extremities, localizing to the upper arms, backs of the thighs, and the shins, which led to a concern for cellulitis. Despite multiple courses of antibiotics at another facility, the lesions did not improve. In addition, the nodules occurred in a cyclic and migratory pattern, emerging and subsiding over 3-4 day cycles. Her ESR was rechecked and found to be 115 mm/hr and her prednisone dose was up-titrated to 50mg daily by her rheumatologist who was concerned the skin lesions were evidence, along with the temporal biopsy, of a systemic arteritis. Administering increasing doses of prednisone only slightly decreased her inflammatory markers, and the patient's clinical condition was minimally responsive, with recurrence of skin lesions after two weeks. A consult to the dermatology service was requested.

At the time of consultation, in addition to fatigue, the patient noted a 10 lb weight loss over the preceding 3 months and global weakness. She denied fevers, night sweats, chills, cough, diarrhea, and arthralgias. Her last travel outside the country was a year prior to England and she had no risk factors for tuberculosis exposure. While she lived in Arizona, she resided in an urban area with no exposure to farm animals.

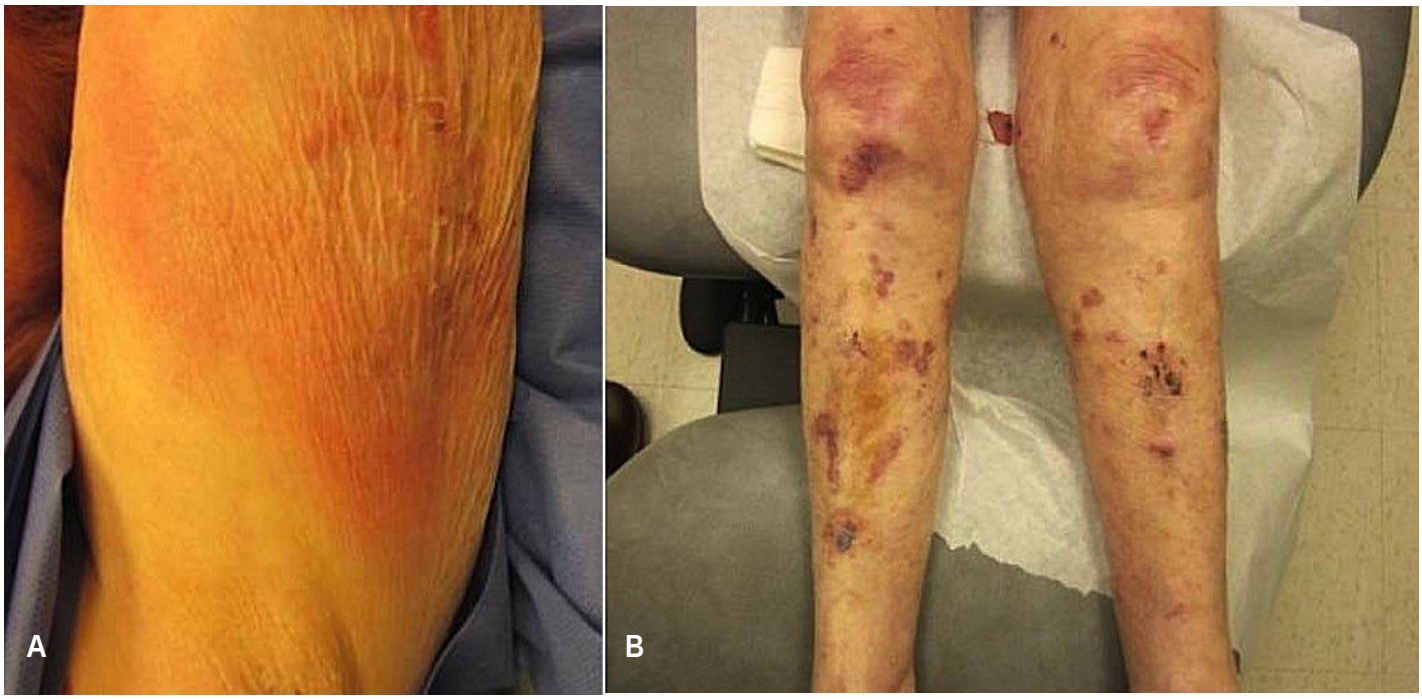
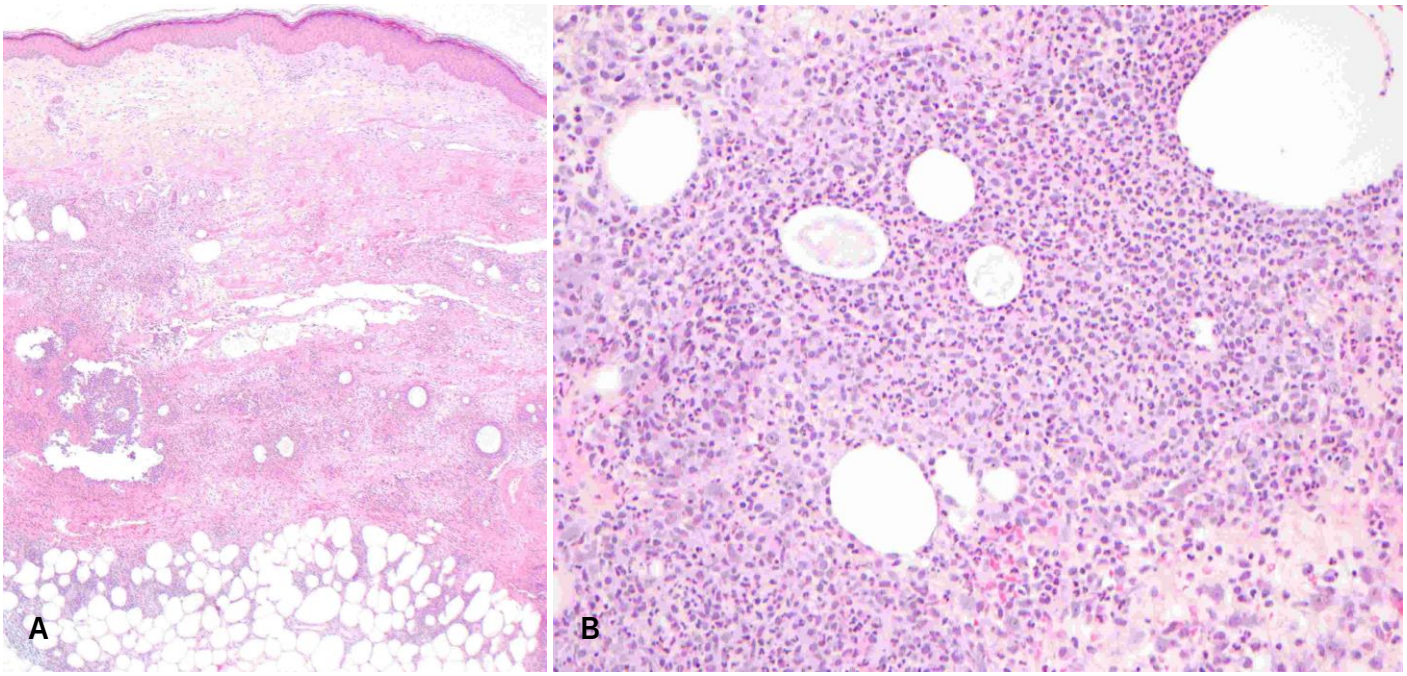


Figure 1. *Physical exam showed an erythematous, tender and warm plaque on the patient's left upper arm, and multiple violaceous nodules on the patient's lower extremities bilaterally.*

Exam revealed a 5×6 cm erythematous, tender and warm plaque along the internal aspect of her left upper arm (**Figure 1A**). The plaque was palpable with a slight subcutaneous fullness. The patient also had multiple poorly demarcated, warm and tender subcutaneous nodules, without fluctuance. Both lower extremities had multiple violaceous nodules, predominantly below the knee (**Figure 1B**). Additionally, there were multiple subcutaneous tender lymph nodes (right epitrochlear, bilateral popliteal nodes) that were 0.5–1 cm in size. No lesions on the trunk, abdomen, or chest were appreciated. Her lungs were clear to auscultation bilaterally, and the remainder of the exam was unremarkable.

An excisional biopsy of one nodule on her left thigh was obtained and sent for stains and tissue culture; the reviewing pathologist confirmed that there was dense suppurative and granulomatous inflammation on hematoxylin-and-eosin staining (**Figure 2A, B**) with numerous acid-fast bacilli (AFB) on Fite stain, consistent with an atypical mycobacterial infection (**Figure 3**).

The patient was urgently admitted for empiric treatment of suspected disseminated atypical mycobacterial infection. AFB isolator and biopsy cultures were positive. While T spot and direct mycobacterial PCR were negative, mass spectrometry identified *Mycobacterium chelonae* (*M. chelonae)*. Subsequently, testing at the Wallace Laboratory confirmed *M. chelonae* identification and demonstrated susceptibility to ciprofloxacin/ moxifloxacin, linezolid, and clarithromycin. After this, the patient's antimicrobial regimen was then transitioned to linezolid 600mg by mouth daily and clarithromycin 500mg by mouth twice daily for a planned regimen of 6 months. After treatment with linezolid and clarithromycin, serial exams demonstrated improvement in both her cutaneous lesions and lymphadenopathy. The patient was then discharged to a rehabilitation center for two weeks and maintained on her antibiotic regimen. However, approximately 2 months into antibiotic therapy, the patient's Alzheimer dementia continued to worsen; the patient became increasingly confused, anorexic, and unable to complete tasks independently. An evaluation by a neurologist and a comprehensive laboratory workup were undertaken to assess for any treatable causes of dementia, which proved negative. The patient was eventually transferred to the care of hospice services after approximately 4 months of antibiotic therapy. She was discharged to a rehabilitation facility.



Figures 2. *H&E stains demonstrated a dense infiltrate of histiocytes and prominent neutrophils in the dermis and subcutaneous tissue.* ***A)*** *100×,* ***B)*** *200×.*

Case Discussion

Although nontuberculous mycobacteria (NTM) have historically been viewed as infrequent causes of human infections, reports of disease caused by NTM are increasing [1]. Accordingly, mycobacteria are being progressively recognized as a greater public health concern [2].

In a large population-based study of NTM infection incidence, investigators observed an approximately 3-fold increase in cutaneous NTM infection incidence during the 30-year study period [1]. Furthermore, the diagnosis can easily be missed because features of NTM disease are less familiar to specialists in fields other than infectious disease [3].

The Runyon system categorizes NTM by utilizing organism morphology, growth rates, and pigmentation. Based on this system, *Mycobacterium chelonae* (*M. chelonae*) is classified under rapidly growing mycobacteria (RGM), along with two other clinically relevant species: *Mycobacterium fortuitum* and *Mycobacterium abscessus.* In addition to posing a diagnostic challenge, RGM are known to be resistant to numerous antibiotics and disinfectants [4-8]. This resistance is partially related to the ability of NTM to form biofilms [9, 10]. Furthermore, prompt identification of the offending RGM species is crucial because the specific treatment required varies depending on the exact species.

NTM are ubiquitous in the environment. Although the organisms have classically been associated with colonization of soil and water sources, mycobacterium have also been isolated from samples of animals, birds and plant matter (see sources below). Their resistance to common disinfectants, including chlorine, glutaraldehyde, and organomercurials, enables NTM to persist in chemically treated water sources [2, 4, 11]. Infections with NTM are therefore thought to occur via exposure to environmental reservoirs. To date, no incidents of human-to-human or animal-to-human transmission have been recorded [2]. Alarmingly, the potable water systems with the greatest rates of NTM colonization are those serving dental offices, hemodialysis facilities, and hospitals [5, 12-19].

Nosocomial outbreaks have occurred most commonly in the setting of plastic surgery, dialysis, and inadequately sterilized needles or injection equipment. In this setting, NTM infections have been attributed to medical or surgical instruments contaminated with water containing the organisms.

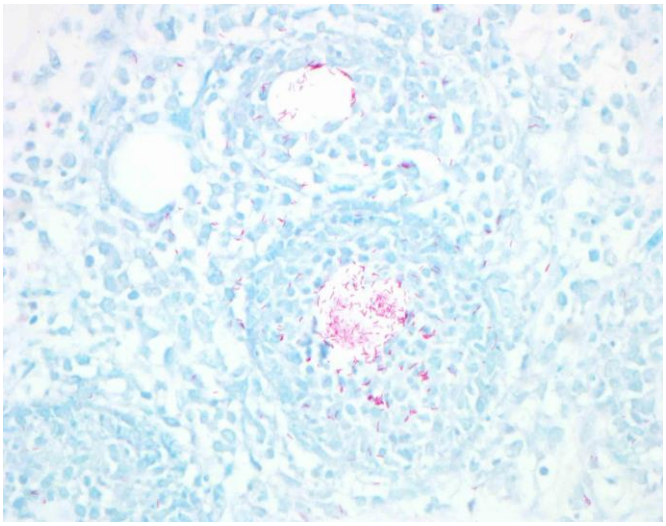


Figure 3. *Fite stain revealed many acid-fast bacilli within the suppurative area, 400x.*

Outbreaks were also previously reported with cardiac surgery, owing to either contamination of sternal wounds or porcine prosthetic valves, although this has improved significantly with enhanced sterilization techniques [20-21].

With respect to community-acquired infection, NTM were once considered uncommon causative agents. Infection in this context was often related to contamination of a traumatic wound with environmental mycobacteria [22-24]. However, NTM are emerging as frequent causes of infections related to surgical and nonsurgical cosmetic procedures including: body piercings, dermal fillers, mesotherapy, pedicures/foot spas, and tattoos [2]. The incidence of NTM skin and soft tissue infections following all of these procedures — especially pedicure-related RGM furunculosis — is increasing [21, 25]. Community NTM outbreaks have also been reported in association with acupuncture [25-27].

Although disseminated RGM infection occurs in immunocompetent hosts, it is most commonly seen in immunocompromised patients. Two key mechanisms predispose to developing disseminated RGM infection. Because cell-mediated immunity contributes significantly to the host immune response against mycobacteria, conditions that reduce cell-mediated immunity increase risk of disseminated RGM infection [28]. An additional mechanism is the dearth of tumor necrosis factor, which stimulates the granuloma formation that prevents bacterial growth [29]. Cases have been documented in immunosuppressed patients in the settings of collagen vascular disease, hematologic malignancy, or renal transplantation [28, 30].

Of the RGM species, disseminated cutaneous disease is most commonly reported with *M. chelonae* [31]. Its diagnosis is complicated by the variable presentation of skin and soft tissue infections including: abscess, localized cellulitis, catheter infections, osteomyelitis, and disseminated cutaneous infection [32]. Of these, disseminated cutaneous infection is the most frequently encountered presentation, manifesting as multiple tender, erythematous nodules [32]. In one study, this accounted for 53% of cases of skin, soft tissue, and bone infections caused by *M.* chelonae [32].

Increasing evidence is highlighting the association between corticosteroid use and NTM infection, particularly infection with disseminated *M. chelonae*. One study examined 53 cases of confirmed disseminated *M. chelonae* infection, determining that nearly every one of these patients (92%) had been receiving corticosteroid therapy (doses ranging from 5-20mg), [32]. This suggests that even low-dose corticosteroid therapy is a significant risk factor for *M. chelonae* cutaneous disease. Further complicating the matter, cutaneous NTM infection can mimic vasculitides [33], highlighting the need to exclude NTM infections as a cause of cutaneous manifestations in rheumatologic patients taking corticosteroid therapy.

Owing to a scarcity of randomized controlled trials, there remains a lack of consensus on the optimal regimen or duration for NTM infections, particularly disseminated *M. chelonae* infection [34]. Unlike *Mycobacterium tuberculosis,* NTM organisms generally demonstrate resistance to antituberculous drugs and metronidazole [35]. Because the diverse RGM species demonstrate variable susceptibilities to different antimicrobials, it is critical to identify the causative organism and conduct susceptibility testing to provide the most efficacious therapy. *M. chelonae* isolates specifically demonstrate susceptibility or intermediate susceptibility to tobramycin, clarithromycin, linezolid, imipenem, amikacin, clofazimine, doxycycline, and ciprofloxacin

[34]. To date, the only antimicrobial clinical trial for *M. chelonae* cutaneous disease examined the efficacy of clarithromycin monotherapy. This study included both patients with only localized infection, as well as patients with disseminated cutaneous disease [36]. Although approximately 91% of subjects in this study demonstrated resolution of the infection without relapse at 5 months, there are increasing reports of acquired resistance to clarithromycin monotherapy [31, 37, 38]. Currently, the recommended regimen for *M. chelonae* skin, soft tissue, and bone infections is at least 4 months of multidrug therapy; however, severe bone infections may require longer durations of therapy [34, 39]. Although there is insufficient evidence for consensus on disseminated *M. chelonae* infections, current data suggests administering a 2-3 agent multidrug parenteral therapy that typically includes a macrolide and aminoglycoside for at least 2-6 weeks depending on clinical response.; This is followed by multidrug oral therapy tailored to local susceptibility patterns for 6 months [34, 39-42]. Combination drug therapy is preferred over monotherapy to minimize the risk of developing resistance.

The portal of entry through which our patient initially acquired the infection remains unclear because she lacked exposure to any of the typical healthcare or cosmetic procedure settings. Given that she was on prolonged prednisone therapy, a likelier explanation is infection through environmental exposure. Prior to mass spectrometry identifying the NTM species, the patient was empirically treated with imipenem 500mg IV Q6H, clarithromycin 500mg PO BID, and amikacin 15mg/kg IV daily combination therapy. This was chosen to broadly cover for the RGM, particularly *M. abscessus*, which is widely considered the most pathogenic species within the RGM category [35].

Conclusion

Given that the incidence of cutaneous NTM infections appears to be increasing, it is of growing importance that clinicians become more familiar with their presentation and risk factors. As this case demonstrates, it is important to maintain NTM infections in the differential diagnosis when evaluating inflammatory lesions in the setting of immunosuppression.

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