

Safety of Injecting Insulin Through Clothes: A Case of *Mycobacterium immunogenum* Cutaneous Infection and Review of the Literature

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PRESENTATION

L.S., a 47-year-old white woman with type 1 diabetes, a bleeding diathesis, and iron deficiency anemia, was referred to an infectious diseases physician for assessment of a painful, nonhealing skin lesion. Before the referral, her primary care physician had treated her with several courses of oral antibiotics, including cephalexin, clindamycin, and amoxicillin, without improvement. She denied a history of preceding trauma, recent foreign travel, or exposure to aquatic animals or hot tubs. When questioned about whether the lesion was at the site of insulin injection, she stated this was possible because she had injected insulin at various locations through her clothes since adolescence, as instructed.

On physical examination, the patient appeared well. Her skin examination was significant for a 5-cm erythematous, tender nodule on the anteromedial aspect of her right thigh (Figure 1). No drainage from the lesion or evidence of surrounding cellulitis was found. There was no associated lymphadenopathy, and the remainder of her physical examination was unremarkable.

Routine laboratory tests, including leukocyte count with differential, platelets, electrolytes, creatinine, and liver enzymes, were within normal ranges. Her A1C was elevated at 10.8%.

Histology of the biopsied lesion demonstrated nonspecific inflammation with negative stains for acid-fast bacilli (AFB) and fungi. Cultures, however, were positive for mycobacteria spp. after an extended incubation period of 63 days (compared to the conventional incubation period of 49 days). 16S rRNA sequencing identified the organism as *Mycobacterium immunogenum*. The antimicrobial agents the organism was susceptible to were limited to clarithromycin and tigecycline, with intermediate sensitivity to amikacin. The organism was resistant to ciprofloxacin, doxycycline, cefoxitin, imipenem, cotrimoxazole, and linezolid.

QUESTIONS

1. How did this patient acquire this infection?
2. What are the recommendations for managing this type of infection?

COMMENTARY

Non-tuberculous mycobacteria (NTM) are widely distributed in the environment, with human infection often originating from an unidentified environmental source rather than human-to-human transmission. NTM are classified by growth rate: rapid (mature growth in 7 days) or slow growers (mature growth in 2–3 weeks).

With the advent of HIV and immunosuppressive therapies, as well as improved diagnostic techniques such as high-performance liquid chromatography and 16S rRNA sequencing, NTM are increasingly being recognized as important pathogens. To date, more than 125 NTM species have been identified and are typically implicated in one of six syndromes, including pulmonary, lymph node, skin and soft tissue, bone and joint, disseminated, and catheter-related infections.

M. immunogenum was first described by Wilson et al.¹ as a rapidly growing mycobacterium and a cause of hypersensitivity pneumonitis in industrial metal grinders after being isolated from water-based metalworking fluids. Since this description, *M. immunogenum* has been implicated in a variety of infections, including cutaneous disease.

To date, there have been four additional cases of *M. immunogenum* skin infection reported in the English-language literature. The initial description of cutaneous disease reported a 55-year-old man who developed a nonhealing leg ulcer after exposure to surface water in Belize.² Additional case descriptions include a 28-year-old woman who developed a leg nodule after exposure in a hot tub,³ a wound infection after removal of a dysplastic nevus in an 82-year-old man receiving



Figure 1. *M. immunogenum* thigh nodule

immunosuppressive treatment for multiple myeloma,³ and a nodule at the site of a recent tattoo in an 18-year-old woman.⁴ Interestingly, only one of these patients was known to be immunosuppressed, attesting to the pathogenicity of this organism in causing human disease. Furthermore, a mesotherapy-associated outbreak of 19 confirmed cases of *M. immunogenum* cutaneous disease was reported from a private aesthetic clinic in Buenos Aires, Argentina.⁵

NTM-associated cutaneous infection often occurs at the site of penetrating trauma followed by contamination with soil or water containing the organism. Cutaneous NTM infection was previously associated with insulin injection sites with other rapidly growing mycobacteria such as *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium abscessus*, and *Mycobacterium peregrinum*.^{6–8}

We speculate that the practice of injecting insulin through clothing may have been a contributing factor to infection in our patient because it is possible that the organism was present on her clothing with subsequent injection into skin. This practice allows patients to administer their injections conveniently when outside the home. Safety data originate from a single

short-term, randomized study in which no adverse skin effects were demonstrated.⁹ Current guidelines for insulin injection do not make reference to injecting insulin through clothing as an option.¹⁰

The presentation of cutaneous infection includes localized cellulitis, nodules, abscesses, and ulcers. Different histopathological patterns can also be observed, including granulomatous inflammatory infiltrate, dermal or subcutaneous abscesses, diffuse dermal or subcutaneous histiocytic infiltration, acute or chronic subcutaneous tissue inflammatory infiltrates (panniculitis), or nonspecific chronic inflammation.¹¹

Because there is no pathognomonic clinical or histological appearance, culture remains the cornerstone of diagnosis. The incidence of NTM infection may be underestimated because the current recommended incubation time for mycobacteria is limited to 6–8 weeks. Growth was detected on culture within the standard incubation period at 43 days. However, a terminal Ziehl-Neelsen (ZN) stain failed to yield any AFB. The isolate was then re-incubated and, at 63 days of incubation, a terminal ZN was positive for AFB. Without the prolonged incubation period, the identification of the organism could not have been made. Thus, this case contributes to a growing body of literature suggesting that, if mycobacteria are suspected as potential pathogens, prolonged incubation periods should be considered.^{12,13}

This particularly applies to cutaneous specimens wherein the NTM of clinical concern can have optimal growth temperatures of < 30°C, including *Mycobacterium chelonae*, *Mycobacterium marinum*, *Mycobacterium ulcerans*, *Mycobacterium immunogenum*, and *Mycobacterium haemophilum*. This

can often extend the time to detection in automated systems such as the BD BACTEC MGIT 960 (BD Diagnostics, Franklin Lakes, N.J.), which incubates cultures at a stable temperature of 35–37°C.

The optimal treatment of rapidly growing NTM infections has not been established. Current recommendations include a combination of prolonged antimicrobials with surgical debridement when indicated.¹⁴ Resistance to antimicrobials is common, and treatment regimens should include at least two agents that demonstrate adequate in vitro susceptibility to avoid the development of acquired resistance. Whenever possible, a macrolide should be included in the regimen.¹⁴

Epilogue

Before initiating antimicrobial treatment, L.S. experienced clinical deterioration with progressive fever, night sweats, weight loss, and poor glycemic control. She underwent semi-urgent debridement. The operative description indicated infection to the level of fascia. Postoperatively, she was treated with tigecycline and azithromycin for a planned 6 weeks. At week 5, the tigecycline was discontinued because of gastrointestinal side effects. She remains on azithromycin with a planned duration of 6 months. Three months into treatment, she remains free of infection.

CLINICAL PEARLS

- NTM are increasingly recognized as important human pathogens.
- This case reinforces the need to consider NTM infections in cases of persistent cutaneous infection, especially in patients who are relatively immunocompromised.
- Insulin injections have been associated with NTM cutaneous infections, and injection techniques should be reviewed with patients to prevent these infections.

- In cutaneous infections in which NTM are clinically suspected, it may be important to alert the laboratory to consider re-incubation of all media at 25–30°C for an additional 2–5 weeks to optimize the growth environment. This is particularly important if the culture remains negative after a conventional incubation period of 6–8 weeks and the clinical index of suspicion remains high.

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