Linezolid as a treatment option for cutaneous non-tuberculous mycobacterial infections

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Abstract

Cutaneous non-tuberculous mycobacterial (NTM) infections have rapidly increased in incidence in recent years. Currently there is no standard treatment and the variable and nonspecific ways in which cutaneous NTM infection presents makes it a therapeutic and diagnostic challenge. We describe a 67-year-old immunocompetent woman with cutaneous NTM infection after she recently underwent a root canal procedure. Although the species was not identified and she was unable to tolerate multiple antibiotics, she ultimately responded well to three months of treatment with linezolid. Given that cutaneous NTM infection can present in immunocompetent patients and that the incidence is rising, it is important for clinicians to maintain a high index of clinical suspicion, especially in patients with a recent history of surgery, trauma, or cosmetic procedures. Linezolid has coverage against non-tuberculous mycobacteria and is an effective therapeutic option for cutaneous NTM cases in which identification to the species level is not possible or when adverse effects limit therapeutic options.

Keywords: Cutaneous non-tuberculous mycobacteria, atypical mycobacteria, cutaneous infections, skin and soft tissue infections, infectious diseases, linezolid, acid-fast bacilli, dental procedure, granulomatous diseases, treatment, antibiotic susceptibility

Introduction

Mycobacteria are aerobic, acid-fast bacilli that are subdivided into three subgroups: the bacteria that cause tuberculosis (*M. tuberculosis* complex), the bacteria that cause leprosy (*M. leprae* and *M. lepromatosis*), and the non-tuberculous mycobacteria [1]. Non-tuberculous mycobacteria (NTM) are further subdivided into rapidly growing and slowly growing species. Acquisition of NTM is through environmental exposure as these organisms are ubiquitously found in the soil and water [2]. Direct inoculation is the most common method of acquisition of cutaneous NTM infection and occurs in the setting of trauma, cosmetic or surgical procedures, or indwelling medical devices [1,2].

The incidence of cutaneous infections with NTM owing to direct inoculation is rapidly increasing [1,3]. Initially, this increase was thought to relate to an increasing population of immunosuppressed patients.

However, numerous cases are being reported in healthy individuals [3]. A large population-based study found nearly a three-fold increase in incidence from the years 1980-2009; in this study, only 23% of affected patients were immunosuppressed [4]. This suggests the increasing incidence is greatly impacted by infection in immunocompetent patients.

Cutaneous NTM infection is often initially misdiagnosed and diagnosis is often delayed because of its nonspecific, variable clinical presentation. Treatment of cutaneous NTM infection is equally challenging and no universal standard of treatment exists. We report a case of cutaneous NTM infection complicated by inability to determine species and adverse drug reactions that ultimately responded well to treatment with linezolid.

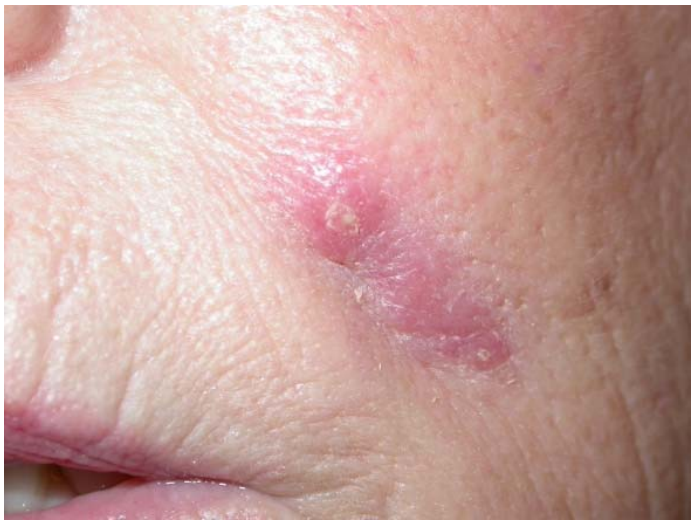

Figure 1. *Indurated, poorly defined erythematous plaque on the left nasolabial fold with a superior inflammatory nodule present.*

Case Synopsis

A 67-year old immunocompetent woman presented with a 2×1cm tumor in the left nasolabial fold two weeks after a root canal was performed near the same area. Significant previous medical history included rectal cancer, currently in remission, and histiocytoid Sweet syndrome, now resolved. The patient was afebrile with no systemic symptoms. She was treated once with intralesional corticosteroids (0.1mL triamcinolone at 2mg/mL concentration) with initial improvement but relapse of the lesion two weeks later. On repeat examination, an erythematous, indurated plaque was present on the left nasolabial fold with a superior inflammatory nodule (**Figure 1**).

A 3mm punch biopsy of the left cheek was performed to rule out infectious granuloma. On histologic examination, chronic granulomatous inflammation was seen. A lymphohistiocytic infiltrate with occasional neutrophilic abscesses and multinucleated giant cells was present throughout the dermis (**Figure 2**). Gram stain and Ziehl-Neelsen stain were positive for acid-fast gram-positive bacilli, (**Figure 3**).

The suspected causative agents at the time included *Nocardia* and mycobacteria. As *Nocardia* was highest on the differential diagnosis, the patient was initially placed on sulfamethoxazole-trimethoprim, but was switched to amoxicillin-clavulanic acid with minocycline, and then later linezolid (300mg, orally, twice daily) owing to adverse effects. Sulfamethoxazole-trimethoprim was discontinued because of a widespread urticarial reaction, amoxicillin-clavulanic acid caused intolerable gastrointestinal side effects, and minocycline was discontinued because of headaches and dizziness. Specimens for culture were sent out along with those for polymerase chain reaction (PCR), immunohistochemistry, Fite stain, Warthin-Starry (W-S) stain, and Grocott methenamine silver (GMS)

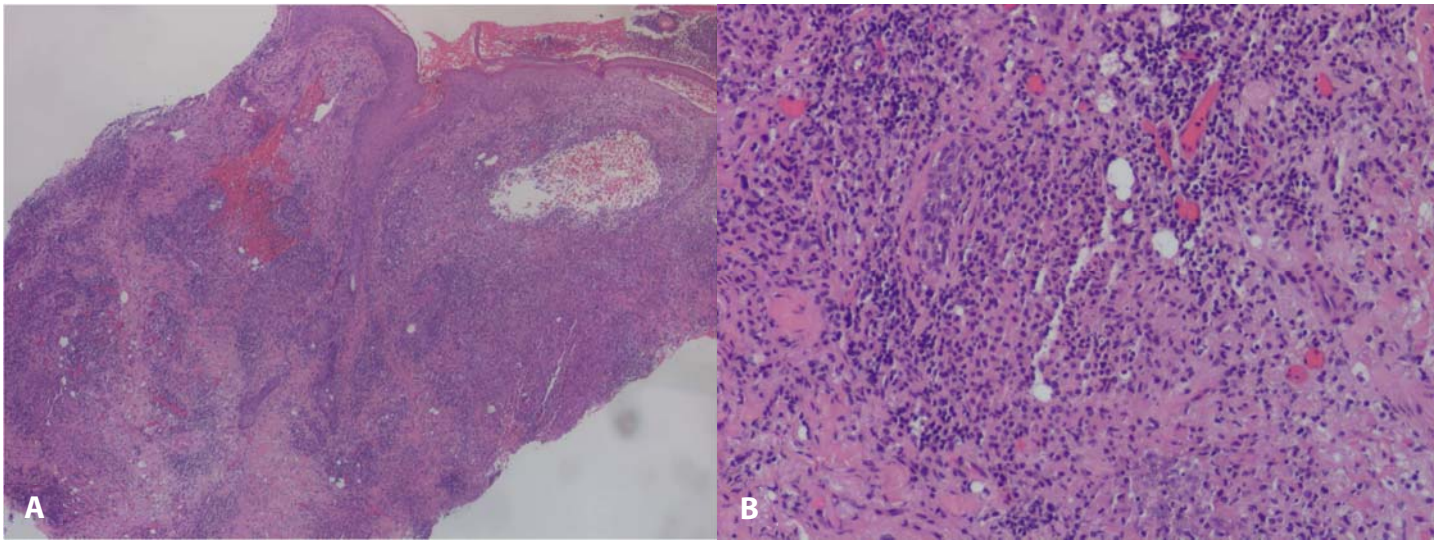

Figure 2. ***A)*** *Punch biopsy showing chronic granulomatous inflammation throughout the dermis with occasional neutrophilic microabscesses on H&E, 20×.* ***B)*** *Lymphohistiocytic infiltrate with occasional neutrophilic abscesses and multinuclear giant cells present throughout the dermis on H&E stain, 100×.*

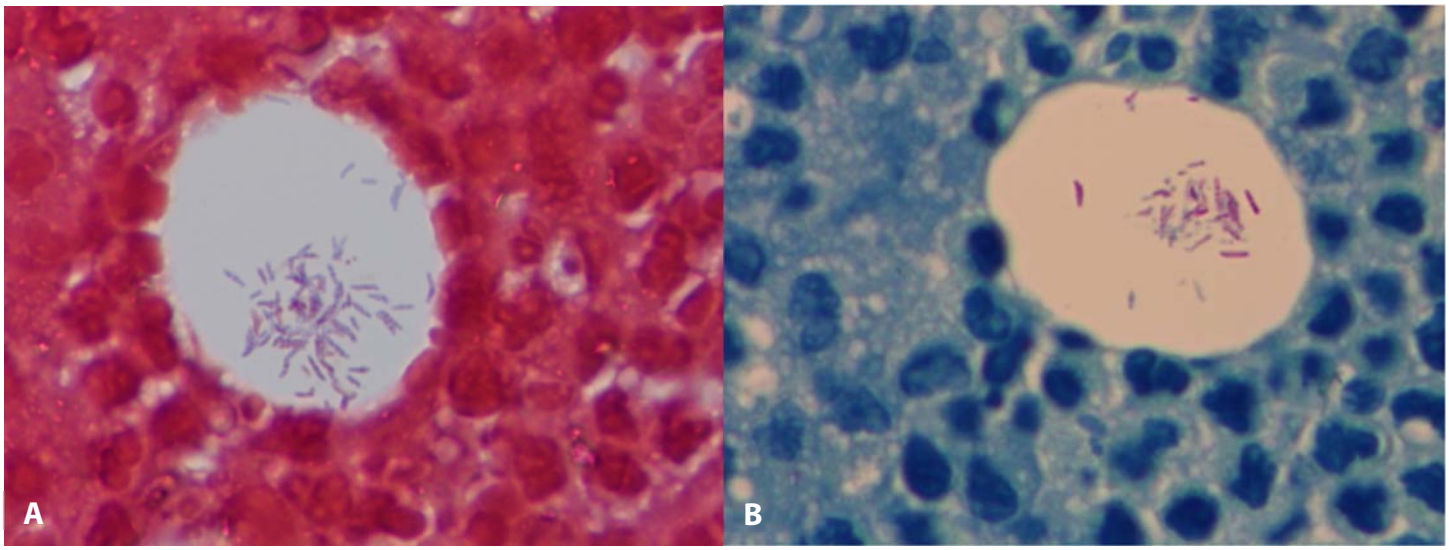

Figure 3. ***A)*** *Gram stain showing purple, gram-positive bacilli; oil immersion lens, 1000×.* ***B)*** *Ziehl-Neelsen stain showing acid-fast bacilli; oil immersion lens, 1000×.*

stain to the Center for Disease Control for identification of an etiologic agent.

Results of the PCR, W-S stain, and GMS stain were negative and no acid-fast bacilli were isolated from tissue culture after 6 weeks. However, the Fite stain demonstrated acid-fast bacilli in multiple foci and IHC was reactive for *Mycobacterium*. Because of previous intolerance to multiple antibiotics and clinical improvement with the current regimen, the decision was made to continue treatment with linezolid rather than switch to an alternative such as clarithromycin. After two months of treatment with oral linezolid 300mg twice daily, the patient self reduced her dose to 150mg twice daily owing to mild gastrointestinal upset. Oral sarecycline 60mg twice daily was added with the intent that she would take both and prevent relapse. Despite the dosage reduction she continued to improve. After 7 months of antibiotic treatment an asymptomatic 8×6mm scar remains (**Figure 4**). The patient will remain on the current regimen for one final month of treatment.

Case Discussion

Cutaneous NTM infections vary widely in clinical presentation and can be nonspecific, making diagnosis difficult or delayed. Lesions may present weeks to months after inoculation. Infection with NTM can manifest as papules, indurated, scaly plaques, cellulitis, abscesses, draining sinus tracts, subcutaneous nodules, sporotrichoid nodules, pustules, ulcers, superficial lymphadenitis, or verrucous lesions [1,3,5]. Signs and symptoms can also vary between species, further complicating diagnosis [3]. The three clinically relevant rapid growing mycobacteria are *M. fortuitum, M. abcessus,* and *M. chelonae. Mycobacteria fortuitum* generally presents in a young, immunocompetent patient as a single nodule at the site of inoculation [3]. The latter two species are more likely to present in an older, immunocompromised patient and can be multifocal

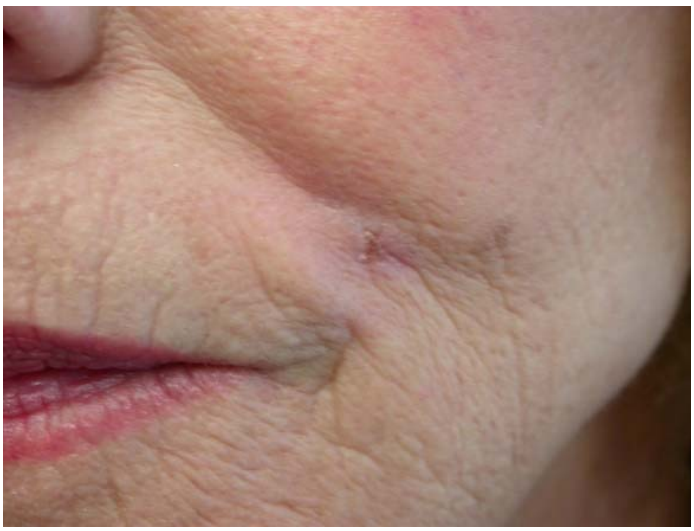

Figure 4. *After 7 months of linezolid treatment, an asymptomatic 8×6 mm scar remains.*

[3]. *Mycobacteria marinum* and *M. ulcerans*, two of the more common species of the slowly growing type, often present initially as a single papule or nodule at the site of inoculation, most often on the distal extremities, and can progress to an ulcerated lesion [3].

Although NTM are considered to be gram positive, because of their high lipid content they are not adequately detected by Gram stain and are only occasionally visualized [2,6]. The presence of mycolic acid in their lipid rich cell wall allows NTM to preferentially stain positive on acid-fast stains (**Table 1**). Characteristic features of cutaneous NTM include acid-fast bacilli on acid-fast staining along with granulomatous inflammation on histologic examination. Diagnosis can be made by identification of acid-fast bacilli using acid fast staining and with biopsy and tissue culture. However, a negative stain or tissue culture does not exclude a diagnosis of cutaneous NTM and repeat testing should be performed in highly suspicious cases [7].

Histological examination, gene sequencing, immunohistochemistry, and PCR analysis may be used for mycobacteria identification [1]. Commercial DNA probes, or high-performance liquid chromatography may be used for rapid species identification [2]. Identification of NTM to the species level is recommended for isolates as susceptibility to antibiotics varies among species [2].

Treatment often requires multidrug therapy for several months based on individual species susceptibility with surgical intervention necessary in some cases [3]. *Mycobacteria fortuitum* has shown to be susceptible to macrolides, doxycycline, fluroquinolones, amikacin, and sulfamethoxazole-trimethoprim whereas for *M. abscessus*, azithromycin is the preferred agent [1]. *Mycobacteria chelonae* has shown to be often susceptible to tobramycin, fluoroquinolones, macrolides, and cefoxitin [1]. Of note, the three clinically relevant rapidly growing mycobacteria—*M. fortuitum, M. abscessus,* and *M. chelonae*—are resistant to antituberculosis agents [1]. *Mycobacteria marinum* requires at least two drugs (a macrolide, ethambutol, rifamycin, or trimethoprim-sulfamethoxazole) with duration ranging from two to six months depending on degree of tissue involvement [1]. As for *M. ulcerans,* recommended management is currently an 8-week course of rifampin and streptomycin with surgical intervention reserved for lesions that progress despite four weeks of antibiotics, lesions with superimposed bacterial infection, or large lesions requiring skin grafting [3]. In cases of clinical suspicion, empiric treatment may be considered for cutaneous NTM infections. In such cases, clarithromycin is the recommended drug of choice as the majority of cases will be at least partially susceptible to clarithromycin treatment [7].

Linezolid is an oxazolidinone that is effective against most gram-positive bacteria. In addition, linezolid is an excellent therapeutic choice for NTM infections [10]. In vitro studies have shown potent activity of linezolid against most species of both slowly [10] and rapidly growing mycobacteria [11]. Despite this, linezolid treatment in NTM infections remains limited, partially related to lack of safety data, concern for potential hematologic side effects, and drug costs [10]. Recently, a newer oxazolidinone, tedizolid, has shown superior potency against some NTM strains in vitro, including linezolid resistant strains, and may be a promising additional treatment option for cutaneous NTM infections [12].

Table 1. *Staining characteristics of organisms in the differential diagnosis [6,8,9].*

Organism	Gram Stain	Acid-Fast (Ziehl-Neelsen) Stain	Modified Acid-Fast (Fite) Stain	Grocott methenamine silver
NTM	Positive, negative, or non-staining silhouettes	Positive	Positive	Aberrant staining*
Nocardia	Positive	Negative	Weakly positive or negative	Positive
Actinomyces	Positive	Negative	Negative	Positive

Conclusion

This case highlights the fact that cutaneous NTM infection is increasingly being diagnosed in healthy patients and remains a diagnostic and therapeutic challenge. Clinical manifestations are polymorphic necessitating a high degree of clinical suspicion. Cutaneous NTM infection should be considered in any patient with a history of recent surgery, trauma, or cosmetic procedures. Overall, there is no universal standard of treatment and even within a species multiple treatment options exist. In our patient, therapy was further complicated by adverse reactions to initial therapy choices as well as inability to determine the species of mycobacteria. Our patient ultimately tolerated and responded well to linezolid. As such, linezolid may be considered as a treatment option for cutaneous NTM infections in which the species is unable to be determined or in patients who are unable to tolerate the initially attempted antibiotics.

Potential conflicts of interest

The authors declare no conflicts of interests.

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