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Mycobacterium chelonae cutaneous infection: An opportunistic disease in an immunosuppressed patient with myasthenia gravis

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ABSTRACT

Mycobacterium chelonae can cause chronic skin, soft-tissue or bone infections.
and is often associated with the immunocompromised state.We describe a case of a 58-year-old male patient with myasthenia gravis, chronically immunosuppressed, with a four month progression of growing erythematous, nodular and hard cutaneous lesions in the left forearm, leg and foot. He was receiving immunoglobulin every four weeks (2 g/kg) and prednisolone 25 mg/day and had an important previous history of several opportunistic infections while he was receiving corticosteroids.

Histopathological examination of a biopsy showed acid-fast bacilli and tissue culture identified a *Mycobacterium* spp. within seven days of incubation, with *Mycobacterium chelonae* being identified by polymerase chain reaction assay. Antimicrobial susceptibility testing was performed showing no resistance and the patient was successfully treated during four months with ciprofloxacin, clarithromycin and trimethoprim-sulfamethoxazole with regression of the lesions, leaving some hyperpigmentation scars and without unbalancing his neurological disease.

Patients with myasthenia gravis should be closely monitored because first line treatments for *M. chelonae* infection may be associated with myasthenic crisis.

Introduction

Nontuberculous mycobacteria (NTM) are a group of organisms that are ubiquitous in the environment. *Mycobacterium chelonae* (*M. chelonae*) is a rapidly growing mycobacterium (RGM) that can cause a variety of chronic skin, soft-tissue and bone infections and is frequently associated with disseminated cutaneous disease [1–3].

The immunocompromised status is the most important contributor for NTM infections and previous corticosteroid use has been noted as one of the most relevant risk factors for *M. chelonae* infection, as well as other conditions such as hematological neoplasms and diabetes [3–5]. We describe a case of a successfully treated *M. chelonae* infection in a steroid dependent patient with myasthenia gravis.

Clinical case

A 58-year-old male diagnosed with myasthenia gravis with anti-acetylcholine receptor antibodies since 1987 presented to the Infectious Diseases outpatient consultation with growing erythematous, nodular and hard cutaneous lesions scattered in the left forearm, leg and foot. The lesions had been progressively appearing over a four-month period. They started as a single one located in the foot, with progressive involvement of the left forearm and leg and progressed with an ascending pattern to multiple lesions. He had no associated constitutional symptoms such as fever, night sweats or weight loss. One month before presentation, the patient had a trip to a rural area where he swam in a river but recalled no traumatic event.

He had been followed with Infectious Diseases consultation for one year before this event began since he was under immunosuppressive therapy with prednisolone 25 mg/day (which he started 9 years before) and intravenous immunoglobulin 2 g/kg every 4 weeks. His neurologic disease had several unstable periods, but it was under control for the last three months prior to the appearance of the lesions. The patient had a relevant history of opportunistic

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infections and diseases in the past, all related to immunosuppression: a Kaposi's sarcoma with respiratory involvement in 2012 while on azathioprine, an episode of herpes zoster ophthalmicus in 2013, a pneumonia in 2014, frequent episodes of otitis media between 2015 and 2016, occasional episodes of noncomplicated herpes simplex orolabial disease, two episodes of herpes zoster reactivation between 2000 and 2017 and an esophageal candidiasis in December 2018.

The physical examination showed erythematous and non-erythematous subcutaneous nodules that were hard, palpable and painless, with a diameter of 1.5–3 centimeters, distributed along the anterior side of the left leg and the posterior side of the left forearm (Fig. 1A and B). The histopathological examination of the skin samples revealed the presence of necrotic areas in the hypodermis and dermis surrounded by an inflammatory infiltrate of lymphocytes, macrophages and Langhans giant cells. Inside the granulomas there were central pseudocysts containing Ziehl-Neelsen stain bacilli. Periodic acid-Schiff, Gram and Grocott staining were negative. Tissue culture identified a *Mycobacterium* spp. within 7 days of incubation and *M. chelonae* was identified by polymerase chain reaction assay. A normal body CT-scan excluded disseminated disease.

Antimicrobial susceptibility testing showed no resistance to isoniazid, rifampin, pyrazinamide, ethambutol, fluoroquinolones, macrolides or aminoglycosides. A three-drug regimen with ciprofloxacin 750 mg twice daily, clarithromycin 500 mg twice daily and trimethoprim-sulfamethoxazole 960 mg twice daily was started and the patient was kept under the same immunosuppressive regimen for myasthenia gravis. After 15 days there was a clinical improvement with regression of the forearm lesions. No myasthenic crisis were documented and the disease remained stable with no need to adjust the steroid dose. During this treatment he had two other opportunistic infections: a herpes zoster infection, that was

treated with valacyclovir 1 g three times/day and a herpes simplex orolabial infection, also treated with acyclovir 400 mg, four times/day.

The patient was successfully treated for *M. chelonae* infection, with regression of the lesions during the four-months treatment, leaving some hyperpigmentation scars (Fig. 1C).

After discussion with the neurology, prednisolone was slowly tapered to the minimal effective dosage (20 mg/day) due to the cumulative opportunistic infections.

Discussion

Cutaneous infections due to NTM can be difficult to diagnose due to their wide spectrum of clinical presentations and insidious progression. The presentation may depend on the immunocompetence status. Patients affected with *M. chelonae* tend to be older and are likely to be immunosuppressed [1]. Risk factors associated with *M. chelonae* infection cases in immunocompetent patients are contact with contaminated waters and contaminated material, surgical and minimal invasive procedures, mostly cosmetic, intradermal and subcutaneous tissue injection (mesotherapy, tattoos, laser resurfacing, body piercing, insulin injection) and minor skin trauma (pedicures) [6–9].

M. chelonae infection has also been associated with immunosuppressive drugs such as adalimumab and with other anti-tumor necrosis factor monoclonal antibodies (infliximab) in combination with high prednisolone doses [10,11]. Our patient was immunosuppressed with prednisolone for a long period due to his neurological disease, which showed several periods of relapses, being difficult to manage when trying to reduce the dosage. He also reported a possible additional risk factor for atypical mycobacterial infections, since he had swum in a non-guarded rural river.

The incubation period of *M. chelonae* lasts from four to six weeks. However, it is an RGM being characterized by a rapid (within 7 days) growth on subculture which can facilitate the diagnosis. It is likely to present as multiple lesions affecting more commonly the legs [8,12].

The major types of clinical presentation are disseminated disease, localized skin and soft tissue disease (subcutaneous nodules, cellulitis, ulcers and abscesses) and osteoarticular disease (arthritis and tenosynovitis) [2,3]. Sporadic cases of keratitis associated with contact lens wear and ocular surgery, particularly LASIK, have also been rarely described [2]. When associated with the use of low doses of steroids it presents frequently in the disseminated cutaneous disease type (more than 5 lesions) [3]. Our patient had a typical presentation for a *M. chelonae* infection, with cutaneous infection and multiple lesions. However, the diagnosis was delayed for the progressive and painless evolution of the lesions until they extended into the arm.

Another important point was the fact that the patient had three more infections (esophageal candidiasis, shingles and orolabial herpes infection) at the same time he had the *M. chelonae* infection, all while he was receiving high doses of steroids. It was imperative to rethink about the immunosuppressive strategy and, after this treatment, a decision was reached to decrease the steroids dose and closely monitor the neurological disease stability.

The choice of the appropriate antimicrobial therapy in a patient with myasthenia gravis can be challenging, sometimes with the need to lower the dose of the immunosuppressive therapy without unbalancing the disease, which was difficult in this patient. First

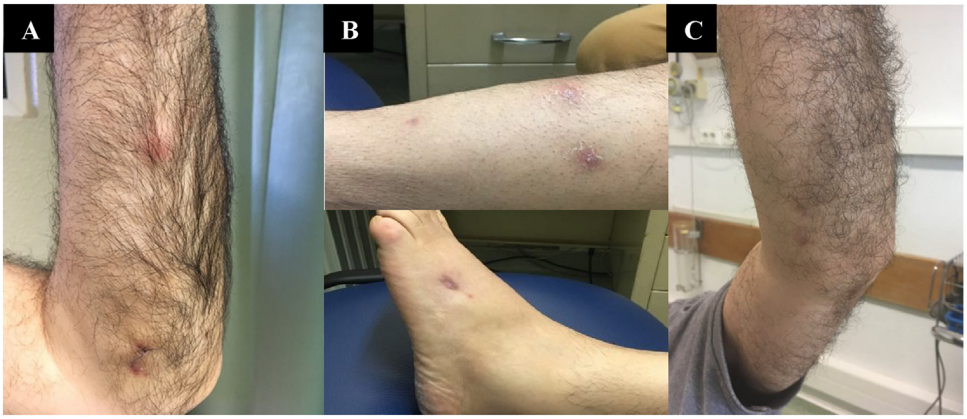

Fig. 1. A and B: Erythematous and subcutaneous nodules in the posterior side of the left forearm (A) and anterior side of the left leg and left foot (B) after 4 months of disease progression. C: Posterior side of the left forearm (as in A) after 4 months of treatment showing complete regression of the noticed lesions. C: Posterior side of the left forearm (as in A) after 4 months of treatment showing complete regression of the noticed lesions.

line antimicrobials for *M. chelonae* infections such as macrolides, aminoglycosides and fluoroquinolones can result in exacerbation of the myasthenia gravis, with the additional risk of myasthenic crisis, and should only be used if absolutely necessary and with close monitoring [12,13,14]. While treatment success of localized skin infections has been reported for *M. chelonae* with clarithromycin alone, a combination therapy of at least two susceptible agents is recommended to minimize the risk of resistance, particularly if empiric treatment is initiated. A *M. chelonae* infection in a steroid-dependent patient with myasthenia gravis that was resistant to clarithromycin and was successfully treated with linezolid has also been reported [15].

A recommended first treatment choice should be a triple combination of ciprofloxacin 750 mg bid or levofloxacin 500 mg bid associated with clarithromycin 500 mg bid and trimethoprim/sulfamethoxazole 160 mg/800 mg bid or doxycycline 100 mg bid. If there is ocular or severe disseminated infection, the addition of a fourth antimicrobial like amikacin, cefoxitin, imipenem or linezolid should be implemented [2].

In our patient, we considered the disease presentation as mild because the patient only had cutaneous involvement and a rapid clinic response with progressive regression of the lesions was achieved. Treatment should be continued for four months considering mild disease, as in our case, and extension for six months should be sought in severe cases or rare presentations, such as in keratitis [1,2].

Conclusion

This case highlights the increasing threat of unusual infectious agents in chronic immunosuppressed patients. *M. chelonae* infection has been reported in association with high dose of corticosteroids (as was the case of our patient) and patients with myasthenia gravis should be closely monitored because first line treatments for *M. chelonae* may be associated with myasthenic crisis. A multidisciplinary approach that involves good communication between the infectious disease and neurologist specialties may assist in the successful management of these particular patients.

Author contribution

All authors contributed to the paper:

Joana Granado: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article – review & editing.

Ana Cláudia Miranda: conception and design of the study, acquisition of data, analysis and interpretation of data – review & editing.

Marco Fernandes: conception and design of the study, acquisition of data, analysis and interpretation of data – review & editing.

Luis Santos: conception and design of the study, acquisition of data, analysis and interpretation of data – review & editing.

Kamal Mansinho: conception and design of the study, acquisition of data, analysis and interpretation of data – review & editing.

All authors read and approved the final version of the manuscript.

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Consent

Patient consent was obtained for publication.

Declaration of Competing Interest

None.

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