



Case report

Skin and soft tissue infection by *Mycobacterium intracellulare* in an immunocompetent patient



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ABSTRACT

Nontuberculous mycobacteria (NTM) infections still represent a large group of insidious diseases hard to deal with. Traditionally, immunocompromised patients suffer from NTM infections, especially with respiratory involvement or disseminated diseases due to MAC (*Mycobacterium avium* complex). Here we report a rare case of *Mycobacterium intracellulare* infection involving skin and soft tissue, manifested as a chronic cutaneous ulcer in an immunocompetent patient with several comorbidities, including seizures. Accurate diagnosis of species was obtained with *in vitro* culture and RT-PCR (Real Time-Polymerase Chain Reaction) following a high clinical suspicion. Despite the high complexity of NTM infections, it is possible to achieve diagnostic goals through the appropriate employment of recent DNA-molecular technologies and an adequate management.

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Introduction

Nontuberculous mycobacteria (NTM) are a large group of widespread mycobacteria easily found in the environment, particularly in water, soil and animals. There is no evidence of human-to-human or animal-to-human transmission [1]. Among NTM, *Mycobacterium intracellulare* belongs to the *Mycobacterium avium* complex (MAC) together with *M. avium*. The two species are indistinguishable with classic microbiological methodology and only polymerase chain reaction (PCR) may help differentiate them. *M. avium* still represents the most frequent causative agent of disseminated disease in the immunocompromised host, whereas *M. intracellulare* is usually responsible for localized and organ-restricted diseases with special reference to respiratory diseases. *M. intracellulare* cutaneous disease is considered rare.

Case report

A 56-year-old unemployed man was admitted to the Unit of Internal Medicine at the Garibaldi Hospital in Catania (eastern Sicily) because of a deep, painful ulcer on his right foot. His clinical

history was relevant, for several comorbidities. He suffered from seizures treated with phenobarbital and carbamazepine, obesity (113 kg, BMI = 41.5), dyslipidemia treated with atorvastatin, post-surgical hypothyroidism in treatment with levothyroxine and cholelithiasis controlled with ursodeoxycholic acid. His recent clinical history started when an ulcerative lesion progressively appeared in the right front-foot, accompanied by hypoesthesia.

On admission, clinical examination showed extensive edema involving right foot, ankle and the lower part of the leg, with visible spider veins (Fig. 1), with tenderness. The patient referred no history of foot trauma.

Blood examinations showed an increase of inflammatory markers (CRP 6.9 mg/L, ESR 24 mm/h) whereas WBC count was normal, 6400 cells/ μ l. Blood cultures were negative. HIV serology was negative as well. T-cell subsets and immunoglobulins level were within the normal range.

A Computerized Tomography (CT) showed an edematous swelling of the sub-cutaneous tissue (fasciae, muscles, ligaments, adipose tissue) in the perimalleolar, tarsal and front-foot region. A Magnetic Resonance Imaging (MRI) was performed, confirming the inflammatory involvement in absence of clear-cut abscess. Subchondral edema of all the metatarsal bones was also present. Electromyography was suggestive of lumbar spinal stenosis and local compression of the right superficial peroneal nerve. A punch biopsy of the lesion was performed; and the histopathological

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Fig. 1. Skin ulcer on the right foot before therapy administration.

examination was inconclusive, showing neither necrotizing granulomatous inflammation nor multinucleate giant cells.

Nevertheless, a slice of cutaneous tissue was deparaffinised and analysed with RT-PCR amplification using primers specific for IS6110 and mpb64 of *M tuberculosis*, and 16S rRNA gene of NTM (Anyplex plus MTB/NTM detection, Seegene). The result was positive only for NTM, identifying a *M intracellulare* strain. Bacterial and fungal cultures were negative, while a Löwenstein-Jensen medium culture resulted positive after 25 days of incubation. Pigmentation production testing showed a non-chromogenic mycobacterium (Runyon III group). *In vitro* susceptibility testing showed that the isolated mycobacterium was sensitive to clarithromycin, rifampin and ethambutol. In accordance to the



Fig. 2. The skin lesion after 12 month of therapy.

drug susceptibility analysis, the patient was treated orally with rifampin 600 mg, clarithromycin 500 mg bid and ethambutol 1600 mg, three times per week for 12 months.

After three weeks of treatment, the patient reported a severe seizure attack: phenobarbital serum concentration was measured showing a sub-optimal concentration of the drug (11.3 mg/L, normal range 15–40 mg/L). Thus, following neurologic consultation, phenobarbital dosage was increased with normalization of serum concentration (19.7 mg/L).

Since then, no further epileptic attacks occurred throughout the 1-year treatment course. After 12 months, when therapy was stopped, all symptoms had subsided and subcutaneous edema disappeared. The ulcerative lesion was totally replaced by scarring tissue (Fig. 2).

Discussion

Cutaneous nontubercular mycobacteriosis are acquired either from environmental sources or from endogenous reactivation [1,2]. Cutaneous infection from *M intracellulare* has a protean clinical presentation such as abscesses, nodular lesions, erythematous plaques with yellow-crusts bases or ulcerations. Deeper infections such as panniculitis, tenosynovitis and fasciitis have also been described [3]. In our case the patient presented chronic ulcerated lesions, while CT and MRI examinations showed a deeper involvement of subcutaneous tissue up to the periosteum of the metatarsal bones. In spite of a consistent number of comorbidities, such as obesity and dyslipidemia, the patient had no evidence of an immunocompromised status: HIV test was negative, T-cell subpopulations showed no alteration in CD4/CD8 total number and ratio and immunoglobulin serum concentration was within the normal range. To prove this peculiar clinical manifestation, an ecologic study regarding differential pathogenic properties in *M avium* and *M intracellulare* demonstrated that *M intracellulare* produces biofilm more often than *M avium* [4]. This could be an explanation for the higher rate of *M intracellulare* infections in immunocompetent people rather than *M avium* infections occurring mostly in immunocompromised host. Nevertheless, in spite of a normal level of serum immunoglobulins and a normal T-cell subset count, it can be speculated that a functional abnormality of T-cell immune response could have been induced by chronic phenobarbital administration. In order to support this hypothesis, some experimental studies in mice showed that phenobarbital might decrease cytotoxic T-lymphocyte response [5]. Unfortunately, the data is controversial and too far from a prompt assumption in clinical practice [6].

Thus, in this case we presume that the infection was acquired exogenously. The patient recalled no history of skin injury or trauma, so the source of the infection has to be considered unknown. Probably, a minimal traumatic event may have determined an environmental exposure to *M intracellulare* in water or soil, which progressed towards a chronic infection due to inefficient lower limbs microcirculation. Hellinger et al. [7] reported six patients suffering of soft-tissue infections due to MAC after surgery or traumas. Other authors subsequently confirmed the traumatic origin of cutaneous MAC [8,9]. In addition, during hospital admission a chest CT scan excluded specific signs of active or prior mycobacterial disease, somewhat excluding an endogenous focus of the cutaneous infection. The patient was treated according to clinical guidelines with a macrolide-based regimen comprising two or three drugs, no aminoglycoside was administered as it is indicated for extensive MAC pulmonary disease or general symptoms [1]. The use of fluoroquinolones such as levofloxacin or ofloxacin in this specific case was discouraged mainly for two reasons: the potential adverse neurological effects such as triggering a seizure attack, and

its unknown long-term side effects and efficacy [10]. Another feasible antimicrobial treatment could be minocycline monotherapy, 100 mg twice a day for one year [3]; this treatment was not chosen as *M intracellulare* could potentially develop drug resistance when treated with monotherapy.

M intracellulare cutaneous infections still represent a rare condition, even if they are being reported more frequently, especially in Eastern Asia regions. The reason for this geographic and ethnic difference is still unknown. A Taiwanese study analysed 63 patients with a skin-soft tissue NTM infection, 6 of whom were due to MAC; none of those patients were immunocompetent [11]. Another study in Hong Kong by Ho et al. [12] considered 33 cases of cutaneous NTM infection over a ten-year period: only 3 cases were associated to MAC and 1 of 3 was immunocompetent. Other authors reported single case reports in immunocompetent patients with multiple skin localizations [13,14].

As far as we know, this is the first reported case of skin and soft tissue infection in an immunocompetent individual in Italy, which can be specifically attributed to *M intracellulare*. Landriscina et al. reported a similar case in the United States in 2014, but without distinguishing between *M intracellulare* and *M avium* [15]. In order to prevent contamination, PCR assay was performed according to the recommendations of Kwok [16]. Nevertheless, clinical amelioration of the skin ulcer after a specific anti-mycobacterial therapy demonstrates the likely correct association between the microbiological finding and the clinical result.

This case demonstrates how important the high level of suspicion should be for NTM skin-soft tissue infections when dealing with chronic skin ulcers; it also remarks the urgency of managing the undiagnosed skin ulcers by a multidisciplinary team. The clinician suspicion has to co-operate with updated microbiological procedures: in the present case, molecular assays guided physicians towards the correct diagnosis and the appropriate therapy.

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