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Case Report

A disseminated *Mycobacterium marinum* infection in a renal transplant HIV-infected patient successfully treated with a bedaquiline-containing antimycobacterial treatment: A case report

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ABSTRACT

Background: Disseminated *Mycobacterium marinum* infections occur rarely, in immunocompromised patients. Treatment with a prolonged multi-drug regimen exposes patients to drug–drug interactions and side effects.

Case report: We report a case of disseminated *M. marinum* infection in a 54-year-old renal transplant, HIV-infected woman. Manifestations of the infection were cutaneous and subcutaneous nodules, mediastinal lymph nodes and left pulmonary infiltrate. Empirical treatment for non-tuberculous mycobacteria was initiated with rifabutin, ethambutol and azithromycin. After identifying *M. marinum* in sputum, due to unfavourable clinical evolution and severe drug-related adverse events, treatment was changed to doxycycline and rifabutin. Digestive and haematologic side effects motivated a change in antimycobacterial treatment to a combination of moxifloxacin and bedaquiline. Tolerance was satisfactory, and the patient was cured after 12 months of treatment.

Conclusion: We report (to the authors' knowledge) the first case of disseminated *M. marinum* infection successfully treated with a bedaquiline-containing regimen. Bedaquiline could be an alternative to recommended antimicrobial regimens in cases of non-tuberculous mycobacterial disease, including *M. marinum* infection.

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Introduction

Mycobacterium marinum is a non-tuberculous mycobacterium that causes skin infections. It is often acquired from aquarium maintenance and is known as fish tank granuloma (Johnson and Stout, 2015). Disseminated infections are exceptional and mainly occur in immunocompromised patients (Parent et al., 1995; Oh et al., 2018). Treatment requires a prolonged multi-drug regimen (Griffith et al., 2007). We report a case of disseminated *M. marinum* infection in a 54-year-old renal transplant, HIV-infected woman. Drug–drug interactions and adverse effects with the initial recommended antimicrobial regimens led to successful treatment with bedaquiline and moxifloxacin.

Case presentation

A 54-year-old woman, originating from Brazaville, Congo and living in France for 15 years, presented with multiple cutaneous nodules on 15 January 2019. The first skin lesion developed on her left leg a few weeks prior. The patient had a history of stage C3 HIV-infection diagnosed in 2004, complicated with cytomegalovirus retinitis in 2005, HIV-related nephropathy leading to end-stage renal insufficiency and dialysis in 2008, and HIV-related encephalitis in 2018. She received a renal allograft in 2014. At the

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time of presentation, she was on antiretroviral therapy, including raltegravir, abacavir, darunavir and ritonavir, and immunosuppressive therapy including tacrolimus and mycophenolic acid. On admission, her body temperature was 37.5 °C. Physical examination revealed multiple painful erythematous cutaneous nodules distributed over her face and upper and lower extremities. No other abnormal sign was found. Detailed history revelated no recent travel abroad or specific exposure. Laboratory results were: haemoglobin, 9.8 g/dl; white blood cells, 4730/mm^3; platelets, 212 000/mm^3; creatinine, 20 mg/l; blood urea nitrogen, 0.79 g/l; C-reactive protein, 269 mg/L; CD4-T-lymphocytes count, 355/mm^3; HIV viral load <20 copies/ml. Chest radiography revealed a left lung infiltrate. Our patient underwent a positron-emission tomography-computed tomography scan, revealing F-fluoro-2-deoxy-d-glucose-avid cutaneous and subcutaneous nodules, mediastinal lymph nodes, and a left pulmonary infiltrate (Figure 1). A biopsy of 1 skin lesion was performed. Histological examination showed granulomatous inflammation with necrosis. Ziehl-Neelsen staining revealed acid-fast bacilli in 3 sputum samples. Skin and sputum real-time polymerase chain reaction (PCR) and QuantiFERON TB Gold Plus test did not detect *M. tuberculosis*.

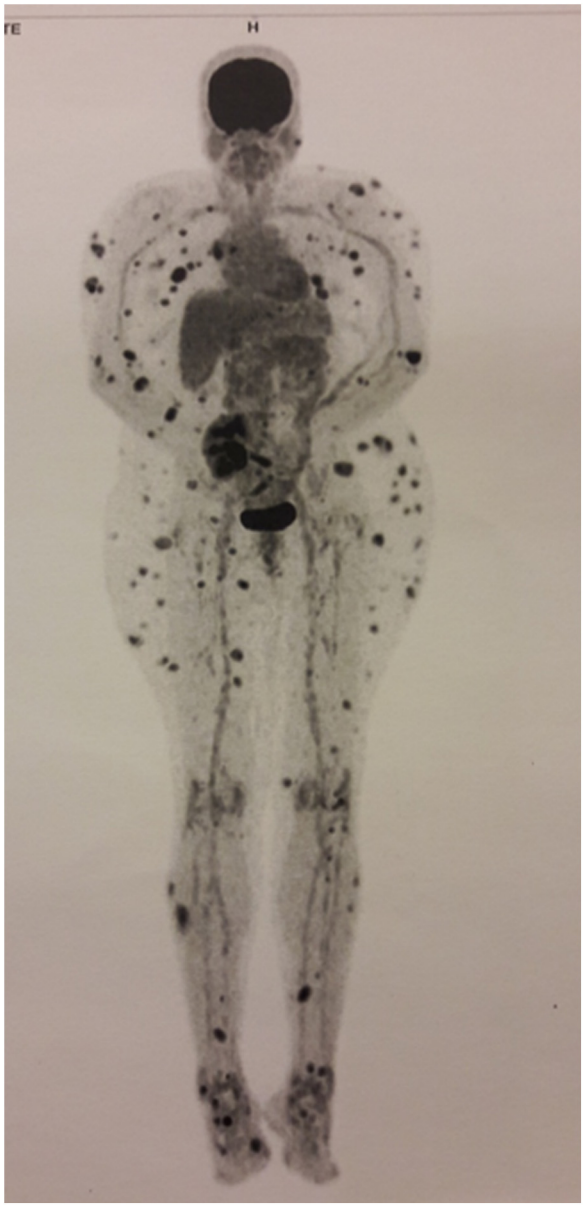

Figure 1. PET/CT scanning, revealing FDG-avid cutaneous and sub-cutaneous nodules, mediastinal lymphnodes and left pulmonary infiltrate.

Empirical treatment for non-tuberculous mycobacteria was initiated with rifabutin (150 mg once per day), ethambutol (1500 mg once per day) and azithromycin (600 mg once per day). Clarithromycin was not prescribed because of a major drug interaction with tacrolimus. Therapeutic drug monitoring confirmed the achievement of adequate concentrations of antiretroviral, antibiotics and immunosuppressive drugs. A culture from 1 sputum sample grew in Löwenstein-Jensen medium. *M. marinum* was identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Antimicrobial susceptibility testing showed sensitivity to amikacin, clarithromycin, doxycycline, ethambutol, moxifloxacin, rifabutin, rifampicin and trimethoprim-sulfamethoxazole. The diagnosis of disseminated *M. marinum* infection was retained. After 2 months of treatment, the course of the disease was marked by the worsening of skin nodules, visual blurring and deafness. Reported adherence to the antimicrobial treatment was good. Serum concentrations of antibiotics remained within therapeutic range. Worsening of skin lesions was attributed to a probable immune reconstitution inflammatory syndrome. Examination of the patient's eyes revealed sequelae of retinitis with no active disease. Deafness was attributed to azithromycin toxicity. Due to this unfavourable clinical evolution and antibiotics side effects, treatment was changed for a combination of doxycycline and rifabutin. Our patient developed severe digestive side effects leading to a significant impairment of her renal function. Biologic tests revealed cholestatic hepatitis and neutropenia. Doxycycline and rifabutin were stopped after 2 weeks. Immunosuppressive treatment was modified to prevent additional haematotoxicity. Mycophenolic acid was replaced by prednisolone. After consultation with the National Reference Centre (Hôpital de la Pitié Salpétrière, Paris, France) for Mycobacteria, a combination treatment with moxifloxacin and bedaquiline was recommended despite the absence of susceptibility testing. The recommended dosing of bedaquiline included a loading phase of 2 weeks with 400 mg daily followed by a continuation phase of 200 mg 3 times per week. Corrected QT interval was closely monitored revealing no prolongation. Drug monitoring confirmed the achievement of serum concentrations of bedaquiline and its N-modes methyl metabolite within the therapeutic range. The treatment was generally well-tolerated. The patient reported persistent nausea without vomiting. The treatment was pursued for 12 months, allowing the cure of lung infiltrates and slow regression of cutaneous and subcutaneous lesions. No relapse of infection was observed after treatment discontinuation despite the maintenance of immunosuppressive treatment.

Discussion

M. marinum infection usually manifests with cutaneous nodules or pustules that can lead to ulcers or abscesses (Johnson and Stout, 2015). The lesions may extend to deeper tissues, causing tenosynovitis, osteomyelitis or septic arthritis. There are only a few reports of disseminated infections in immunocompromised patients. Assiri et al. (2019) published a case report of *M. marinum* infection in a renal transplant patient and reviewed 11 cases in solid organ transplant recipients, including 4 disseminated infections.

Optimal antibiotherapy of *M. marinum* infections is not established. According to the guidelines of the American Thoracic Society and the Infectious Disease Society of America, a combination of clarithromycin and ethambutol, with the addition of rifampicin in the case of deep structure infection, is preferred (Griffith et al., 2007). Johnson and Stout (2015) published a case series of *M. marinum* infections and a literature review of other

case series. The proportion of patients treated with combination antibiotics was 11%–88% across the different case series. The most common antibiotic agents used were ethambutol, rifampin, clarithromycin, azithromycin and moxifloxacin, with a median duration of treatment 2–6 months. A change in the initial antibiotic regimen was reported in almost 50% of cases due to side effects or disease progression. Increasing data on new therapeutic agents offers alternatives to recommended regimens. Among these new drugs, bedaquiline exhibited in vitro activity against various species of slow-growing and rapid-growing mycobacteria (Pang et al., 2017). A case series of *M. abscessus* and *M. avium* complex refractory pulmonary infections and a few case reports have confirmed its potential clinical application (Philley et al., 2015; Chan et al., 2021; Erber et al., 2020). In our case, bedaquiline was prescribed despite no specific susceptibility testing. Our strain was assumed to be susceptible to bedaquiline because *M. marinum* is a close genetic relative of *M. tuberculosis*, hence its use as a model for tuberculosis drug screening (Ho et al., 2021). Our patient received bedaquiline and moxifloxacin for 12 months. No significant side effect was reported. The safety and tolerability of bedaquiline-containing regimens have been evaluated in a large cohort of patients infected with multidrug-resistant tuberculosis (Borisov et al., 2017). The most frequent adverse events reported were nausea, arthralgia, vomiting and dizziness. Prescription of bedaquiline has been associated with QT-interval prolongation (Martin-Garcia and Esteban, 2021), a risk that may be increased when it is used in combination with other QT-interval prolonging drugs, such as moxifloxacin. In our patient, QT-interval and bedaquiline concentrations were closely monitored. Concomitant prescription of tacrolimus and ritonavir, both inhibitors of the CYP3A4 enzyme which is involved in the metabolism of bedaquiline, could have increased bedaquiline concentration (Pandie et al., 2016). Pharmacokinetic studies confirming the relationship between bedaquiline concentrations and clinical outcomes or drug side effects (Tanneau et al., 2020) offered the possibility to predict efficacy under alternative dosing regimens and drug–drug interactions.

Conclusion

To the authors' knowledge, ours is the first case report of disseminated *M. marinum* infection successfully treated with a bedaquiline-containing regimen. Our case illustrates the potential of bedaquiline as an alternative treatment for difficult-to-treat non-tuberculous mycobacterial infections.

Competing interests

All authors declare no conflicts of interest.

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Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the consent form is available for review by the Editor of this journal.

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