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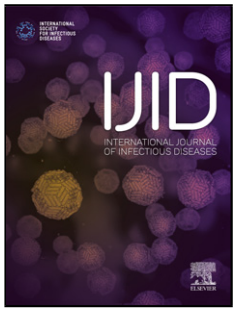

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A disseminated *Mycobacterium marinum* infection in a renal transplant HIV-infected patient successfully treated with a bedaquiline-containing antimycobacterial treatment : a case report.

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Highlights :

- *M. marinum* disseminated infections rarely occured in immunocompromised patients.
- Treatment of *M. marinum* infections requires prolonged multi-drug regimen.
- Side effects and drug-drug interaction are frequent with recommanded regimen.
- Bedaquiline may be an alternative treatment for *M. marinum* infections.

Abstract :

Background : *Mycobacterium marinum* disseminated infections rarely affected immunocompromised patients. Treatment with prolonged multi-drug regimen, exposed them to frequent drug-drug interactions and side effects.

Case report : We reported a new case of *Mycobacterium marinum* disseminated infection in a 54-year-old renal transplant HIV-infected woman. Manifestations of the infection were cutaneous and sub-cutaneous nodules, mediastinal lymphnodes and left pulmonary infiltrate. Empirical treatment for nontuberculous Mycobacteria was first initiated with rifabutin, ethambutol, and azithromycin. After identification of *M. marinum* in sputum, regarding unfavourable clinical evolution and severe adverse events, treatment was changed for doxycyclin and rifabutin. Digestive and hematologic side effects motivated a new change of antimycobacterial treatment for a combination of moxifloxacin and bedaquiline. Tolerance was satisfactory. A twelve months treatment led to cure.

Conclusion : We report the first case of *M. marinum* infection successfully treated with a bedaquiline-containing regimen. Bedaquiline could constitute an alternative to

recommended antimicrobial regimens in case of nontuberculous mycobacterial disease including *M. marinum* infection.

Keywords :

Nontuberculous mycobacteria, *Mycobacterium marinum*, treatment, bedaquiline, case report.

Introduction :

Mycobacterium marinum is a non tuberculous mycobacterium that causes skin infections often acquired from aquarium maintenance and called « fish task granuloma » (Johnson and Stout, 2015). Disseminated infections are exceptional and concerned mainly immunocompromised patients (Parent et al, 1995 ; Oh et al, 2018). Their treatment requires prolonged multi-drug regimen (Griffith et al, 2007). We reported a case of *Mycobacterium Marinum* disseminated infection in a 54 year-old renal transplant HIV-infected woman. Drug-drug interactions and adverse effects with initial recommended antimicrobial regimens led to successfull treatment with bedaquiline and moxifloxacine.

Case presentation :

A 54 year-old woman, originated from Congo Brazaville, living in France for 15 years, presented with multiple cutaneous nodules on the 15th of January 2019. The first skin lesion developed on her left leg few weeks ago. The patient had 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. She was currently on antiretroviral therapy, including raltegravir, abacavir, darunavir and ritonavir, and on immunosuppressive therapy including tacrolimus and mycophenolic acid. On admission, 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 demonstrated no recent travel abroad, and no specific exposure. Laboratory results disclosed the following : hemoglobin, 9.8g/dl ; white

blood cells, 4730/mm3 ; platelets, 212000/mm3 ; creatinine, 20 mg/l ; blood urea nitrogen, 0.79g/l ; C-reactive protein, 269 mg/l ; CD4-T-lymphocytes count, 355/mm3 ; HIV viral load<20 copies/ml. Chest radiography revealed left lung infiltrate. Our patient underwent a PET/CT scanning, revealing FDG-avid cutaneous and sub-cutaneous nodules, mediastinal lymphnodes and left pulmonary infiltrate (image 1). Biopsy of one skin lesion was performed. Histological examination showed granulomatous inflammation with necrosis. Ziehl-Neelsen staining revealed few acid-fast bacilli. Examination of three sputum samples showed acid-fast bacilli on Ziehl-Neelsen staining. Skin and sputum *Mycobacterium tuberculosis* real-time polymerase chain reaction (PCR) were negative. Quantiferon TB Gold Plus test was negative. Empirical treatment for nontuberculous mycobacteria was initiated with rifabutin (150mg once per day), ethambutol (1500 mg once per day), azithromycin (600 mg once per day). Clarithromycin was not prescribed because of major drug interaction with tacrolimus. Therapeutic drug monitoring confirmed achievement of adequate concentrations of antiretroviral, antibiotics and immunosuppressive drugs. Culture of one sputum sample finally grew in Löwenstein-Jensen medium. *Mycobacterium 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 *Mycobacterium marinum* disseminated infection was retained. After two months of treatment, the course of the disease was marked by the worsening of skin nodules, and the occurrence of visual blurring and deafness. Reported adherence to 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. Eyes examination revealed sequelae of

retinitis with no active disease. Deafness was attributed to azithromycin toxicity. Regarding unfavourable clinical evolution and antibiotics side effects, treatment was changed for a combination of doxycyclin 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. Doxycyclin and rifabutin were stopped after two weeks. Immunosuppressive treatment was modified to prevent additional hematotoxicity. Mycophenolic acid was replaced by prednisolone. After consultation of the National Consultant Center for Mycobacteria, a combination treatment with moxifloxacin and bedaquiline was recommended despite absence of available susceptibility testing. The recommended dosing of bedaquiline included a loading phase of 2 weeks with 400 mg daily dose followed by a continuation phase with 200 mg 3 times a week. QTc interval was closely monitored revealing no prolongation. Drug monitoring confirmed achievement of serum concentrations of bedaquiline and its N-modesmethyl metabolite within the therapeutic ranges. The treatment was generally well tolerated. The patient reported persistent nausea, without vomiting. The treatment was pursued 12 months, allowing cure of lung infiltrates and slow regression of cutaneous and subcutaneous lesions. No relapse of infection was observed after its discontinuation despite the maintenance of immunosuppressive treatment.

Discussion:

M. marinum infection usually manifests with cutaneous nodules or pustules that can led to ulcers or abscesses (Johnson and Stout, 2015). The lesions may extend to deeper tissues, causing tenosynovitis, osteomyelitis, or septic arthritis. Disseminated infections have been rarely reported in immunocompromised patients. Assiri A 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 case of deep structure infection is preferred (Griffith et al, 2007). Johnson MG et al. (2015) published a case-series of *M. marinum* infections and a literature review. Proportion of patients treated with antibiotics combination varied from 11 to 88% in the different reported case-series. The most common antibiotic agents used were ethambutol, rifampin, clarithromycin, azithromycin, and moxifloxacin. The median duration of treatment varied from 2 to 6 months. Change in the initial antibiotic regimen was reported in almost half of all cases due to side effects or progression of disease. Increasing data on new therapeutic agents offer alternative to recommend regimen. Among these new drugs, bedaquiline exhibited *in vitro* activity against various species of slow-growing and rapid-growing mycobacteria (Pang Y, 2017). A case series of *M. abscessus* and *M. avium* complex refractory pulmonary infections and few case reports confirmed its potential clinical activity (Philley, 2015 ; Chan, 2021 ; Erber, 2020). In our case, bedaquilin was prescribed despite no specific susceptibility testing. Our strain was assumed susceptible to bedaquiline since *M. marinum*

is a close genetic relative of *M. tuberculosis* motivating its used as a suitable model for tuberculosis drug screening (Ho et al, 2021). Our patient received bedaquiline and moxifloxacin for twelve months. No significant side effect was reported. Safety and tolerability of bedaquiline-containing regimens have been evaluated in 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 prolongation of the QT interval (Martin-Garcia et al, 2021). This risk may be increased in case of combination with other QT-interval prolonging drugs, such as moxifloxacin. In our patient, QT-interval and bedaquiline concentrations were closely monitored. Pharmacokinetic studies confirmed relationship between bedaquiline concentrations and clinical outcome or drug side effects (Tanneau, 2020). In our patients concomittant prescription of tacrolimus and ritonavir, both inhibitors of CYP3A4 enzyme which is involved in the metabolism of bedaquiline could have led to increased bedaquiline concentrations (Pandie, 2016). Pharmacokinetic studies confirmed relationship between bedaquiline concentrations and clinical outcome or drug side effects (Tanneau, 2020). They offered the possibility to predict efficacy under alternative dosing regimens, or in case of drug-drug interactions.

Conclusion :

We report to our knowledge, the first case of disseminated *M. marinum* infection successfully treated with a bedaquiline-containing regimen. Our case illustrates the interest of bedaquiline as an alternative treatment for difficult to treat nontuberculous mycobacterial infections.

Competing interests :

All authors declare no conflicts of interests.

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Consent for publication :

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

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To the editors of International Journal of Infectious Disease,

The authors report no conflict of interest concerning the manuscript submitted.

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

Image 1.