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Case report

A rare case of pulmonary mycobacteriosis caused by rifabutin resistant Mycobacterium celatum and review of the literature

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ABSTRACT

The present case demonstrates an atypical pulmonary mycobacteriosis that mimicked classical symptoms and radiology findings for tuberculosis. While T-SPOT Test and PCR analyses proved negative for tuberculosis, microscopic sputum evaluation showed acid-fast bacilli and *Mycobacterium celatum* was found in culture. Uniquely, in our case *M. celatum* was resistant to rifabutin. Therefore, after not responding to combination treatment including rifabutin, our patient was treated with ethambutol, clarithromycin and protionamide. Classical risk factors for atypical mycobacteriosis such as immunodeficiency (including medication-induced), preexisting pulmonary disease or multimorbidity were not present. We conclude that the high age of the patient (92 y) may have been the main contributing factor for the infection.

1. Introduction

Atypical mycobacteriosis, or non-tuberculosis mycobacteriosis, is an infection caused by other mycobacteria than *Mycobacterium tuberculosis-complex* and *M. leprae*. Recently, a strong increase in its incidence was reported worldwide (2,5–8,2% annually) [1]. In most mycobacteriosis cases a predisposition can be identified, such as immunosuppression (typically by HIV-infection), a preexisting tuberculosis infection, or a chronic condition such as diabetes or chronic obstructive pulmonary disease (COPD). Therefore, it is debated that the increasing incidence of mycobacteriosis is caused by a growing group of patients with a multi-morbidity and immunocompromised patients, either infected with HIV, or undergoing medicinal immunosuppression [2].

M. celatum was first isolated and described by Butler et al., in 1993 [3]. Since then, several cases were reported in the literature. Pulmonary disease has been predominantly described in HIV-positive patients [4–7]. Disseminated and/or fatal cases have been reported [6,8,9]. Besides pulmonary involvement, *M. celatum* leads to skin infections [10] and cervical lymphadenitis was reported in children [11].

Here we report a case of rifabutin resistant pulmonary *M. celatum* infection in an immunocompetent patient that mimicked pulmonary tuberculosis. To our knowledge, this is the first described clinical case of *M.celatum* resistance to rifabutin.

2. Case presentation

A 92-year-old Caucasian HIV-negative female presented with a 6-month history of a cough with yellow to brown sputum, involuntary loss of 2 kg with a generally slender body type, but no fever. The patient did not suffer from any other chronic condition and was HIV-negative. A chest radiograph showed a cavern in the right upper pulmonary lobe (Fig. 1A). In a CT scan the cavern had a 4.5 cm diameter in the right upper pulmonary lobe with accompanying infiltrations (Fig. 1B). Moreover, lymphadenopathy was found in the upper right hilum and in the mediastinum. Laboratory analyses revealed mildly elevated C-reactive protein (CRP) levels (41.3mg/L) and normal blood leukocytes. In the 1940's and 50's the patient was employed as a pediatric nurse and was exposed to patients with tuberculosis.

Indeed, microscopy analysis showed acid-fast bacilli in the sputum as well as in the bronchoalveolar lavage. However, the patient tested negative for a tuberculosis screening test, the interferon gamma release assay (T-SPOT) and *M. tuberculosis* complex DNA was not detected using amplification/PCR methods and culture analysis. Microbiological cultures revealed a *Mycobacterium spp*. infection and molecular genetic testing (GenoType Mycobacterium AS VER 1.0©, Hain-Lifescience) identified *M. celatum* [12].

Based on the above findings a standard antibiotic therapy of atypical mycobacteriosis including rifabutin, ethambutol and clarithromycin was started. Despite of the antibiotic treatment the patient is

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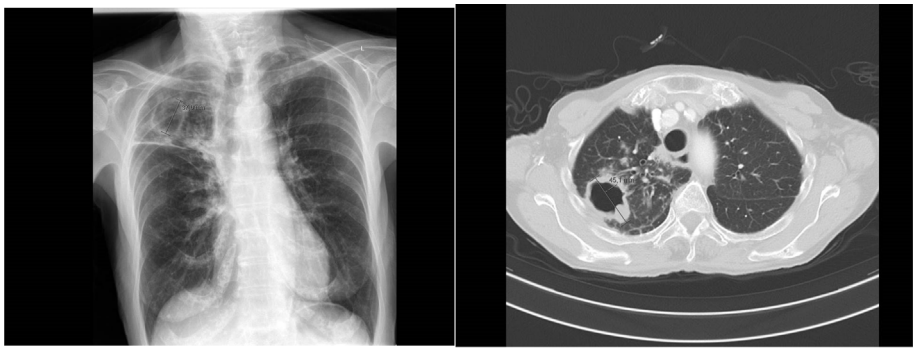

Fig. 1. A) Chest X-ray shows a cavity (3.7 cm in diameter) in the right upper lobe. B) The pulmonary cavity is even more impressive on a CT Scan with a maximum diameter of 4.5 cm.

Table 1
Drug susceptibility test of *M. celatum* isolated from the sputum and the lavage.

Antibiotic	Drug susceptibility
Clarithromycin	+
Moxifloxacin	+
Amikacin	+
Protionamid	+
Rifabutin	-
Rifampicin	-
Ethambutol	+
Isoniazid	-

treatment patient's condition aggravated as she developed fever and fatigue. Additionally, CRP concentration in blood was rising. Drug susceptibility testing revealed a resistance against rifabutin (Table 1). Consequently, antibiotic therapy was adjusted using protionamid instead of rifabutin. Within two weeks, a clinical improvement was observed: the fever subsided and CRP levels decreased. The patient was therefore dismissed from the hospital. Antibiotic therapy was scheduled to continue for one year after sputum conversion [12]. Unfortunately, the patient died at home ten weeks after the proper treatment was initiated. An autopsy was not performed due to the advanced age of the patient.

3. Discussion and review of the literature

Here we report a rare case of rifabutin-resistant *M. celatum* infection in an immunocompetent patient. Up to date, only 7 cases of pulmonary M. celatum infection have been described in immunocompetent patients. The lack of systematic studies makes the management of these cases challenging. Typically, *M. celatum* has been isolated in immunocompromised patients which makes our case, besides the rifabutin resistance, extraordinary.

In the primary diagnostics, radiological findings typical of tuberculosis-together with microscopically proven acid-fast bacilli in the sputum and bronchial lavage fluid led to a preliminary diagnosis of tuberculosis. A negative T-SPOT test and *M. tuberculosis* complex DNA test however disproved this diagnosis and were strongly suggestive of atypical mycobacteriosis, underlying importance of all mentioned methods in routine diagnostic process. Nevertheless, false positive cases of *M. tuberculosis* complex DNA test have been described using nucleic acid amplification methods causing a false diagnose and consequent therapy, due to a cross-reactivity of certain *Mycobacteria* strains with *M. tuberculosis* probe [13,14]. Microbiological culture analysis for atypical mycobacteria can however take up to six weeks, therapy against atypical mycobacteriosis should immediately be started as soon as the positive microscopical examination and negative *M. tuberculosis* complex DNA test is available.

The source of the infection remains unknown for our patient. Generally, sources of atypical *Mycobacteria* include contaminated water, soil, house dust and biofilms [15]. Interestingly, transmission of atypical *Mycobacteria* during cosmetic procedures was described [16]. Next to this, *M. celatum* causes infections in multiple animal species, which raises questions about a possible transmission potential, but at the moment there is not enough evidence to confirm or exclude a possible zoonotic risk [17–19]. Our patient lived in an urban environment, had a very stable lifestyle and did not keep any pets. She had no history of extensive or distant traveling or any close contact with potential environmental *Mycobacterium* sources such as soil, animal pasture or natural waters. The high age of the patient itself could work as an enhancing risk factor of the infection and is most likely the underlying factor of the sudden death, making therapy evaluation impossible.

Generally, antibiotic treatment of atypical mycobacteria is challenging. Therefore specific antibiotics targeted against special characteristics of atypical *Mycobacteria* such as biofilm or suspension formation are currently under development [20]. In previously described cases of pulmonary infection with atypical mycobacteria several treatment regimens were successful in immunocompetent patients (Table 2). In all described cases clarithromycin was used in a combination with one or two of these: ciprofloxacin, isoniazid, ethambutol and rifampicin. Pulmonary cavity resection was used successfully once as treatment for a pulmonary *M. celatum* infection [21]. Others have shown therapeutic success with antibiotic treatment only [22,23].

In the present case resistance to rifabutin was shown, which was not previously described in a clinical case of atypical mycobacteriosis with *M. celatum* (including cases of immunocompromised patients). Recently, an emerging increase of drug-resistance in atypical *Mycobacteria* was reported (Hitrate in PubMed: 2092), which shows the importance of antibiogram testing in every case of atypical mycobacteriosis [24]. In 7 isolates of *M. celatum* in immunocompetent patients the drug-susceptibility testing was performed in 4 cases showing various results. Rifampicin resistance, as expected, was present in all tested *M. celatum* and isoniazid resistance in two cases. Interestingly, in one case ciprofloxacin resistance was detected.

The acquired drug resistance mechanisms in *Mycobacteria* include those similar to other types of bacteria such as cell wall impermeability, active efflux of the drug or modification of either the antibiotic molecule or modification of its intracellular molecular target [25]. For example, macrolides, which used to be a first line antibiotic in the treatment of atypical mycobacteria, show a growing resistance rate. An association of this phenomenon with their use as a *M. avium* complex prevention by HIV-patients is suspected [25]. Therefore macrolides are to be used exclusively in combination with other antibiotics [26]. Rifampicin resistance reported in other than *M. celatum* atypical *Mycobacteria* was caused by mutations in the rpoB gene [27].

The present case demonstrates an atypical mycobacteriosis that

Table 2
Overview of clinical cases of immunocompetent patients with pulmonary *M. Celatum* infection. (Cla: clarithromycin, Eth: ethambutol, Cip: ciprofloxacin, Inh: isoniazid, Rif: rifampicin, Pyr: pyrazinamide).

Year	Age and gender	Medical history	Treatment Regime	Drug-susceptibility Testing	Outcome	Reference
1998	73-year-old female	Diabetes mellitus type II	Cip, Cla, Pyr, Eth	Resistant to Inh, Rif, and Pyr, sensitive to Eth	Death 10 weeks after admission	[9]
2001	61-year-old male	No chronic condition	Eth, Cla, Rif	Resistant to Pyr, Rif, Cip, sensitive to other standard antibiotics including rifabutin	Clinical improvement, positive sputum remained for more than a year after treatment initiation	[14]
2003	63-year-old female	Mild hypertensive cardiovascular disease, pulmonary tuberculosis history	Inh, Eth, Cla	Resistant to Rif	Sputum conversion after 18 months, radiological improvement	[28]
2003	79-year-old male	COPD, pulmonary tuberculosis history	Rif, Eth, Cla	Not available	Clinical improvement	[23]
2009	50-year old male	Ankylosing spondylitis (no immunosuppressants), pulmonary tuberculosis history	Cla, Cip	Not available	Clinical and radiological improvement	[22]
2010	35-year-old female	Pulmonary tuberculosis history, no chronic condition	Cla, Eth, Cip + pulmonary resection (lobectomy)	Resistant to Rif and Inh	Sputum conversion after 3 months, due to persistent pulmonary cavity a lobectomy was performed	[21]
2018	68-year-old male	COPD, peripheral vascular disease, basal and squamous cell skin cancer	Cla, Cip, and Eth	Not available	Sputum conversion after 6 months, clinical improvement	[29]
Current case	92-year-old female	No chronic condition	Cla, Eth, Prothionamid	See Table 1	Clinical improvement, however patient died after 10 weeks	

mimicked classical symptoms and radiology findings for tuberculosis. We suspect that the advanced age of the patient was the main risk factor leading to development of the infection in this case. To our knowledge this is the first clinical case describing resistance to rifabutin in *M. celatum*. In the review of the previous cases we show that the drug-resistance profile of *M. celatum* in clinical isolates varies, therefore the treatment should be based on drug-susceptibility testing.

Disclaimers

Authors declare no conflict of interest.
Patient consent was obtained.

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