CASE REPORT

Mycobacterium celatum infection: Successful treatment with ciprofloxacin and clarithromycin

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Abstract

Mycobacterium celatum is nontuberculous mycobacterium which is rarely pathogenic in human. We describe the case of M. celatum infection in immunocompetent patient. Caucasian 64-years old female patient was referred to the outpatient service because of pulmonary hemorrhage, cough and fever up to 39^{o}C. She reported previous pulmonary tuberculosis (TB) 3 years ago. At presentation the physical examination was unremarkable. Chest computed tomographic scan showed multifocal bronchiectases and upper lobes consolidations suggestive. Empiric antibiotic therapy with amoxicillin was undertaken. At the same time the consecutive sputum samples were immediately analyzed. Smears of six from eight sputum specimens were positive for acid-fast bacilli by Ziehl-Neelsen staining. Culture from each specimen produced slow-growing mycobacterium, identified as M. celatum by mycolic acid analysis with high performance liquid chromatography. The treatment with clarithromycin and ciprofloxacin was continued for 18 months with clinical improvement. Conclusion- we present the accuracy of microbiological diagnosis of M. celatum in patient with normal immune status, which allowed successful treatment. M. celatum infection was reported in HIV infected patients or with the history of pulmonary TB prior to mycobacterial infection. Also in our patient the TB in anamnesis may indicate “hidden immunodeficiency”.

Key words

Mycobacterium celatum, High performance liquid chromatography, Clarithromycin, Ciprofloxacin

1 Introduction

The nontuberculous mycobacterial (NTM) lung disease is rare with incidence rates vary from 1.0 to 1.8 cases per 100,000 persons [1]. In Poland the incidence seems to be higher with about 4/100 000 [2, 3]. HIV infection remains the main risk factor for NTM worldwide.

Mycobacterium celatum (M.celatum) is nontuberculous mycobacterium which is rarely pathogenic in human. The first description of this slowly growing nonphotochromogenic Mycobacterium species of clinical importance was presented by Butler et al. [4]. Most cases were described in AIDS patients [5-7]. However, there are some reports on M. celatum in immunocompetent patients with various response to treatment [8-10].

The aim of this report is to describe an accurate diagnosis and successful treatment of M. celatum infection in immune-competent patient.

2 Case report

The observation was conducted from November 2009 until May 2012. 64-years old female Caucasian patient was referred to the outpatient service because of pulmonary hemorrhage. She reported cough, fever up to 39^{o}C and progressive weakness from two weeks before presentation. The onset of current symptoms was sudden and suggestive for pneumonia. Physical examination was unremarkable. Interestingly, no changes in auscultation were found. In her recent medical history no remarkable concomitant diseases were noticed. Etamsylatum and empiric antibiotic therapy with amoxicillin was undertaken. The hemorrhage was stopped, but other symptoms persisted.

Patient reported previous pulmonary tuberculosis (TB) 3 years ago. Then the classical treatment was stopped by the end by patient because of poor tolerance of antimicrobial medications. During the next years patient felt good, without any clinical signs of relapse. Presently patient refused hospitalization- the diagnostic procedures were conducted in an outpatient. The chest X ray and chest computed tomographic (CT) scan showed multifocal bronchiectases and upper lobes consolidations. In laboratory tests only elevated erythrocyte sedimentation rate (96mm/h) was observed. HIV test was negative. Having regard to the lack of improvement after empiric antibiotic therapy in patient with destructive changes in chest CT and history of tuberculosis, at the same time the consecutive sputum samples were collected and immediately analyzed. Smears of six from eight sputum specimens were positive for acid-fast bacilli by Ziehl- Neelsen staining. The first smear-positive sample was also tested by a real-time PCR assay specific for M. tuberculosis complex, Xpert MTB/RIF (Cepheid, USA) and yielded a negative result. After 3-5 weeks, culture on Loewenstein-Jensen slant from each specimen produced slow-growing mycobacterium, identified as M. celatum by mycolic acid analysis with high performance liquid chromatography (see Figure 1). The typing was confirmed by molecular method GenoType CM (HAIN Lifescience, Germany). Drug susceptibility testing failed as the growth on the control medium was negative. The treatment with clarithromycin (500mg each 12 hours) and ciprofloxacin (500mg each 12 hours) was begun. Because of side effects of ciprofloxacin reported by patient, the dose was reduced to 250mg each 12 hours. Such regimen was continued for 18 months with clinical improvement. The control test was performed 6 months after the initiation of the therapy - 3 sputum specimens yielded negative results both in staining and culture. The next control testing were done every 4 months and after termination of therapy– in total 14 sputum specimens and one bronchial washing sample investigated in 2010 and 2011 were staining- and culture-negative. No progression on CT scan were found. Unfortunately, the destructive changes previously described persisted.

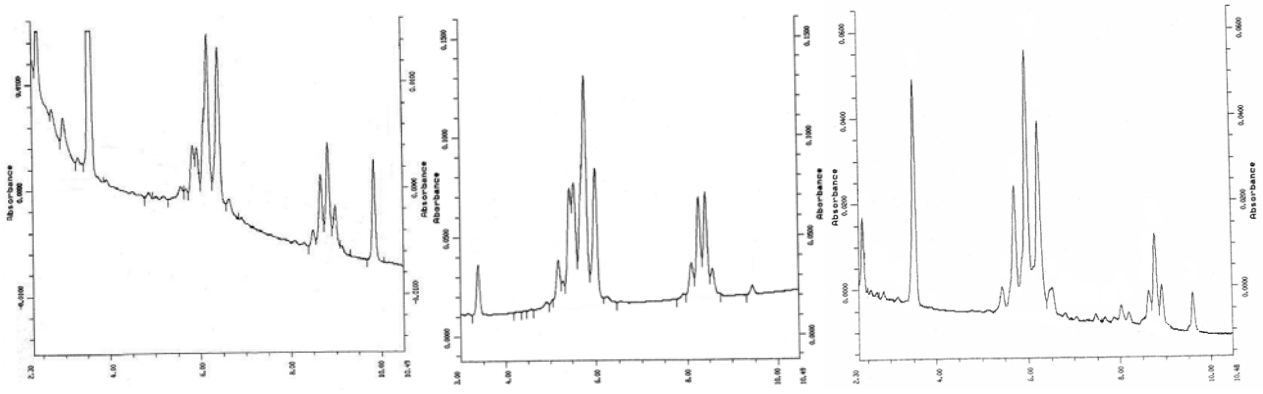

Figure 1. HPLC chromatogram of the study isolate, identified as Mycobacterium celatum. a- example of case described (Left), b- reference for Mycobacterium celatum (Middle), c- reference for Mycobacterium xenopii (Right).

3 Discussion

We present in this report the accuracy of microbiological diagnosis of rare nontuberculous mycobacteriosis caused by M. Celatum in patient with normal immune status. The careful diagnostic procedure allowed successful treatment. According to the ATS/ IDSA Statement "the nontuberculous mycobacterial (NTM) lung disease should include the following: chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan; three or more sputum specimens for acid-fast bacilli (AFB) analysis; and exclusion of other disorders, such as tuberculosis (TB)" [1]. The favorable course of treatment in our patient was a result of careful adherence to these recommendation.

Diagnosis of M. celatum infection can be challenging as the strains of this bacteria appear to be biochemically and morphologically similar to M. xenopi or species belonging to the M. avium complex [4]. A review of the literature revealed that M. celatum may be also misidentified as a member of the M. tuberculosis complex, because of false-positive results yielded by the Amplified Mycobacterium tuberculosis Direct Test (Gen-Probe, USA) [11]. Definitive identification is available by DNA sequencing or mycolic acid analysing using high performance liquid chromatography [12-15]. The second, phenotypic method is the one, which has been successfully used in our laboratory for over ten years. The library for mycobacteria identification, comprising 28 elution profiles of mycolic acids derived from reference strains, including that for M. celatum (American Type Culture Collection 51131), was prepared by Safianowska and Walkiewicz et al. [13, 14].

The protocol of microbiological diagnosis in our Laboratory was presented on the figure 2. The use of such procedure makes possible accurate recognition of M. tuberculosis complex and differential diagnosis with NTM.

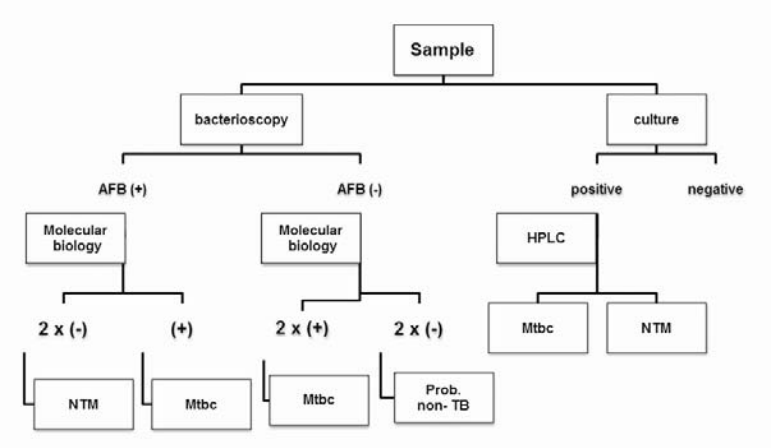

Figure 2. Microbiological diagnosis of tuberculosis. Abbreviations: AFB – Acid Fast Bacilli, HPLC – High Performance Liquid Chromatography, Mtbc – Mycobacterium tuberculosis complex, NTM – Non-tuberculous Mycobacteria, TB - tuberculosis

It is worth to notice, that the real NTM morbidity seems to be underestimated. In the careful analysis of 303 NTM positive but non- TB patients Grubek Jaworska et al. reported, that NTM caused lung disease was diagnosed in 8.9% patients [2].

The treatment of our patient was empiric according to the actual reports in the literature. Susceptibility testing of isolated M. celatum strain to second-line antibiotics failed due to stopped growth of the bacteria after the passage on antibiotic-free, control medium, which should obligatory accompany the culture on antibiotic-containing media. The successful treatment with clarithromycin and ciprofloxacine was described by others [7, 9, 10], while the resistance to isonizyd, rifampicin and ethambutol was documented [7, 8]. By Butler et al. , who first extensively described M. celatum: "Strains are completely or partially resistant to most antituberculosis drugs tested but are susceptible to a high concentration of streptomycin (10.0 µg/ml) and ciprofloxacin" [4]. Fattorini et al. described two variants of M. celatum: SO and ST. The last being more virulent than SO was susceptible to ciprofloxacin and azithromycin [16]. In our case the treatment was conducted 18

months, although the first sputum probes were both staining- and culture-negative after 12 months. The duration was prolonged because of the recurrences of cough and fever. No criteria of the duration of therapy for most pulmonary NTM pathogens is defined. In the ATS/ IDSA Statement the duration based on treatment more frequently encountered species such as Mycobacterium avium complex and M. kansasii is recommended [1]. However, the extended diagnosis, in particular in AIDS patients can cause the fatal course: in 1998 Albrecht et al. concluded, that M.celatum was a cause of serious morbidity [NLM Gatew, abstract P11.1]. Garcia et al. described the fatal course of patient with AIDS, but the treatment with rifampicin, isoniazid and pyrazinamide was used [5].

We described patient without any immune disorders, but with the previous history of tuberculosis which should be taken into account. In the cases presented by Tan et al. [10] and by Piersimoni et al. [9] patients suffered from tuberculosis and in the first approach the reactivation of process was assumed. Also in our patient the persistent mycobacterial infection caused serious destructive changes in respiratory system. These changes by themselves predispose to M.c. infection. On the other hand tuberculosis infection (if well recognized in the past) may indicate “hidden immunodeficiency”.

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