Journal of Infection (2012) 64, 609–612

BIA
British Infection Association

www.elsevierhealth.com/journals/jinf

CASE REPORT

Pulmonary *Mycobacterium abscessus*: A canary in the cystic fibrosis coalmine☆

Margje H. Haverkamp [a,*], Annelies van Wengen [a], Adriëtte W. de Visser [a], Klaas W. van Kralingen [b], Jaap T. van Dissel [a], Esther van de Vosse [a]

[a] *Department of Infectious Diseases, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*
[b] *Department of Pulmonary Diseases, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*

Accepted 17 February 2012
Available online 23 February 2012

KEYWORDS
Cystic fibrosis;
Cystic fibrosis transmembrane conductance regulator;
Mycobacterium abscessus;
Atypical mycobacteria;
Mendelian susceptibility to mycobacterial disease

Summary We present a case of pulmonary nontuberculous mycobacterial infection (PNTM) with *M. abscessus*. After exclusion of genetic immune disorders known to cause NTM susceptibility, we found compound heterozygosity of two mutations, F508del and R117H in CFTR. The combination of F508del with a hypomorphic CFTR mutation can cause a mild Cystic Fibrosis (CF) phenotype with delayed CF symptoms in adulthood. Although the patient was continuously treated for her lung infection by different physicians for more than twenty years, the diagnosis CF had been missed. The *forme fruste* of CF should be considered in the analysis of host factors predisposing for PNTM.

Introduction

Mycobacterium abscessus is a rapid growing nontuberculous mycobacterium (NTM), notorious for its resistance to antibiotics. NTM can cause infections which are confined to the lung (PNTM) and have many predisposing factors which are not necessarily related to HIV infection. [1] These range from structural lung diseases and endocrine pathology to genetic immune disorders (Table 1). When adult patients with PNTM were screened for cystic fibrosis (CF), 21% were diagnosed with this disease based on sweat chloride concentrations or the identification of two *CFTR* mutations. [2] In the classic form of CF (for example F508del homozygosity, high carrier rate (2–5%) in Caucasians), symptoms of the respiratory and gastro-intestinal tract appear in infancy and are due to deregulated chloride channels and viscous secretions by epithelial cells. [3] Much less known is that mild forms of CF, often with adult onset, can be caused

☆ *Patient consent*: The patient we describe in this report was no longer alive at the time of writing.

* Corresponding author. Tel.: +31 71 5262613; fax: +31 71 5266758.
E-mail address: M.H.Haverkamp@lumc.nl (M.H. Haverkamp).

0163-4453/$36
doi:10.1016/j.jinf.2012.02.010

Table 1 Predisposing factors to pulmonary nontuberculous mycobacterial disease.

Factor	Examples
Lung disorders	COPD, fibrosis due to systemic diseases, malignancy
Prior (lung) infections	HIV, tuberculosis, NTM, histoplasmosis
Genetic disorders	Cystic fibrosis, α 1-antitrypsin deficiency, ciliary motility disorder, Lady Windermere Syndrome, MSMD
Endocrine disorders	Cushing Syndrome, panhypopituitarism
Aspiration	
Hypersensitivity	

by numerous rare hypomorphic CFTR mutations. We describe a PNTM case with *M. abscessus* of an adult woman who turned out to have a *forme fruste* of CF.

Case report

In 1999, a 42-year-old childless Dutch woman was referred to our hospital after 14 years of treatment for PNTM (*Mycobacterium avium* and from 1989 *M. abscessus*) in a chest clinic in Australia. Chemotherapy (among others rifampicin, ethambutol, co-trimoxazol, doxycycline, cefoxitin, clarithromycin, amikacin) was successful in eliminating the *M. avium,* but could not remove *M. abscessus* from the sputum. In 1994 and 1995 both upper lung-lobes were removed, but *M. abscessus* grew from sputum cultures up to at least 1996. In her youth, the patient had suffered from multiple episodes of bronchitis, but was otherwise healthy and never smoked. In Australia, in 1987, she underwent a cholecystectomy for gallstones. Furthermore, the patient and her husband were enrolled in a fertility treatment program but had not followed through after she became ill.

We saw a cachectic woman who complained of fatigue, nocturnal sweating and a productive cough. She was not on antibiotics. Her BMI was 17.1. We heard diffuse rales over both lungs. Laboratory results showed an elevated white blood cell count, but no other abnormalities. A CT scan revealed post-operative fibrosis, bilateral caverns and extensive patchy anomalies in both lower lung-lobes. Sputum- but not blood-cultures grew multi-resistant *M. abscessus,* as well as *Haemophilus influenza.* Neither her Australian doctors nor we performed an HIV-test or CF screening. After initiation of clarithromycin, myambutol, and amoxicillin for *H. influenza*, the patient's condition slightly improved; sputum cultures were clear, even though *M. abscessus* had been shown to be resistant to all antibiotics tested (amikacin, ciproxin, clarithromycin, clofazimide, cycloserine, ethambuthol, INH, protionamide, rifabutin, rifampicin, streptomycin). We stopped treatment in 2002.

In 2005, we coiled the right intercostal and mammary arteries and reinitiated antibiotics (clarithromycin, rifampicin, ethambutol) because of haemoptisis and a reactivation of the *M. abscessus* infection. In sputum cultures *Pseudomonas aeruginosa* was also grown. We added ceftazidime and levofloxacin to her anti-tuberculous treatment. Unlike the *M. abscessus,* pseudomonas was no longer grown in the sputum from December 2006 onwards. We switched the antibiotic regimen to meropenem and tobramycin, urged by the widening of cavities and bronchiectasies on CT scan. Sputum cultures were negative for *M. abscessus* for a whole year until meropenem was stopped in 2008. The mycobacterium reappeared in sputum cultures and respiratory symptoms worsened despite an immediate restart of the antibiotic. The lung-function test showed severe and progressive obstructive lung disease (FEV1 600 ml (21% predicted), VC 1.5 L (44% predicted), Tiffeneau 39%). On echography of the heart, we saw both aorta and mitral valve insufficiency grade II. Within a few months, the patient's condition further deteriorated. She died in 2008 at age 51, while under evaluation for a lung transplant.

Immunological and genetic evaluation

The patient's susceptibility to NTM initially prompted us to analyze the integrity of the Interleukin-12 (IL-12)/Interferon-γ (IFN-γ) pathway. Defects in this cytokine loop, disrupting the cross-talk between macrophages and T-cells and known as Mendelian Susceptibility to Mycobacterial Disease (MSMD), predispose to Mycobacterial infections. As previously described, [4] we verified cellular expression of the receptors IFN-γR1 and IL-12Rβ1. We found normal receptor expression in our patient by flow cytometry. We stimulated whole blood samples of the patient and a control with LPS, with and without IFN-γ in order to determine IFN-γ responsiveness. TNF, IL-10 and IL-12p40 were produced in similar amounts by monocytes of the patient and of the control. Moreover, we saw normal production of IFN-γ by PHA-blasts stimulated with anti-CD3 and IL-12, indicating that IL-12R signaling is intact.

In the absence of defects in the IL-12/IFN-γ pathway, we sequenced all 27 exons of the CFTR gene and found mutations in exon 10, c.1521-1523delCTT leading to F508del, and exon 4, c.482G>A leading to R117H (Fig. 1A–C). The length of a polythymidine stretch in intron 8, which precedes the exon 9 splice acceptor site, influences the amount of functional CFTR protein with the R117H mutation.[5] We found 7 thymidines on the R117H allele (Fig. 1D). Subsequently, we sequenced *CFTR* in the patient's 4 siblings. Her father and eldest brother, whose children are adopted, both had pulmonary problems, diagnosed as 'chronic bronchitis'. This brother has bronchiectasis and was treated in adulthood for pulmonary infections with *H. influenza* and *Staphylococcus aureus* and also had allergic aspergillosis. He responded well to antibiotics. The other three siblings are healthy. In the eldest brother and in one of her sisters, we found the same compound