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Mycobacterium chelonae in a CF patient with anaplastic large cell lymphoma

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Abstract

A 13-year-old patient with cystic fibrosis was diagnosed with anaplastic large cell lymphoma. At the same time colonization with *Mycobacterium chelonae* was detected in sputum cultures. Despite massive immunosuppression, the patient did not show evidence of mycobacterial invasive disease. Colonisation persisted for 18 months after discontinuation of chemotherapy and was not detected in the 6 years thereafter. This case highlights the dilemma of differentiating between colonisation and infection if mycobacteria are found in CF sputum samples.

Keywords: Cystic fibrosis; Nontuberculous mycobacteria; Lymphoma; Immunosuppression

1. Introduction

Nontuberculous mycobacteria are discovered with increasing frequency in patients with cystic fibrosis (CF). The prevalence varies among centres with same centres reporting prevalence of 13% [1–3]. Most of the isolates can be classified as *Mycobacterium avium* (*M. avium*) complex, followed by *Mycobacterium abscessus* (*M. abscessus*) [2]. Other isolates are encountered less frequently. Both *M. abscessus* and *M. chelonae* are often multiresistant in in vitro tests [4,5] and have been reported to be associated with more significant pulmonary disease [6,7].

Clinical significance of mycobacteria other than tuberculosis (MOTT) detected in sputum of CF patients, especially in the context of immunosuppressive therapy, is quite unclear. There have been some reports of *M. abscessus* infection following lung transplantation, but to our knowledge no report on the effect of immunosuppressive therapy for malignancies in CF patients with mycobacteria positive sputum cultures. We here describe the clinical course of a CF patient with both lymphoma and airway colonisation with *M. chelonae*, who underwent high dose immunosuppressive chemotherapy for anaplastic lymphoma.

2. Case report

The boy was born in Sicily in 1984 and, at 8 months of age, was diagnosed with a history of recurrent bronchopulmonary infections after moving to Germany. He developed chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) infection in the first year of live and had symptoms of airway obstruction up to the age of 2 years. The following course of illness was stable without any significant problems. At first presentation to our hospital at the age of 12 years, he was doing well with a BMI of 17 and normal lung function (FEV_1 87% predicted). His sputum demonstrated chronic infection with four different strains of mucoid *P. aeruginosa*.

2 years later, he presented with symptoms of constipation to another hospital. On this occasion, the mediastinum

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was reported to be widened on X-ray and a short-term control was recommended. One month later, he was readmitted to hospital with a painful inguinal mass which was considered to be due to bacterial infection. Intravenous antibiotic therapy with ceftazidime and tobramycin administered over a 2-week period was ineffective and a biopsy was performed. Three lymph nodes were removed; histology revealed a large cell anaplastic T-cell-lymphoma. Extensive diagnostic workup showed no involvement of other lymph node regions or organ systems nor of CNS or bone marrow. A HRCT of the chest revealed bronchiectasis mainly in the right upper lobe but no evidence of mediastinal involvement.

Sputum cultures at that time continued to grow four different strains of *P. aeruginosa* as well as *M. chelonae* resistant to all available tuberculostatic drugs. Methods for mycobacteria culturing, species identification within the *M. chelonae* complex, as well as drug susceptibility testing of mycobacteria were used as recently described [8,9].

In view of the patient's stable pulmonary status, it was decided to start chemotherapy without instituting specific therapy for mycobacteria. To prevent exacerbation of his chronic *P. aeruginosa* infection, the patient was started on intravenous antibiotic therapy with ceftazidime and tobramycin, which was later switched to meropenem and tobramycin and maintained throughout immunosuppressive therapy. The patient was treated according to the NHL-BFM 95, which includes dexamethasone ($5 \times 5-10$ mg/m^2/day) and CPM (2×200 mg/m^2/day) for 5 days followed by high dose MTX (1×500 mg/m^2/day), ARA-C (4×150 mg/m^2/day), IFO (5×800 mg/m^2/day) and VP16 (2×100 mg/m^2/day) in the first block (5 days). In the second block (5 days), IFO and VP16 and ARA-C are replaced by CPM (5×200 mg/m^2/day) and DOX (2×25 mg/m^2/day). Both blocks include daily dexamethasone applications (10 mg/m^2/day). In addition to intravenous chemotherapy intrathecal therapy with prednisone, MTX and ARA-C was administered. ARA-C was discontinued after the first dose because of a toxic–allergic reaction. Otherwise, the first block was well tolerated despite neutropenia with a nadir of 220/nl for 5 days. At end of the course *M. chelonae* was still detected in sputum cultures. Remarkably, at that time acid-fast smears were as well found to be positive.

Two weeks later the second course of chemotherapy was administered that resulted in neutropenia with a nadir of 64/nl neutophils for 5 days. The patient developed mucositis and required total parenteral nutrition. In addition, he became symptomatic with fevers up to 40 °C and worsening of pulmonary symptoms. A chest CT scan showed infiltration of the right upper lobe (Fig. 1). Sputum cultures revealed *Candida albicans* as well as *Staphylococcus epidermidis*; teicoplanin plus amphotericin B was added to the antibiotic therapy with meropenem and tobramycin. The pulmonary situation was re-stabilized and there was gradual improvement of the right upper lobe infiltrates.

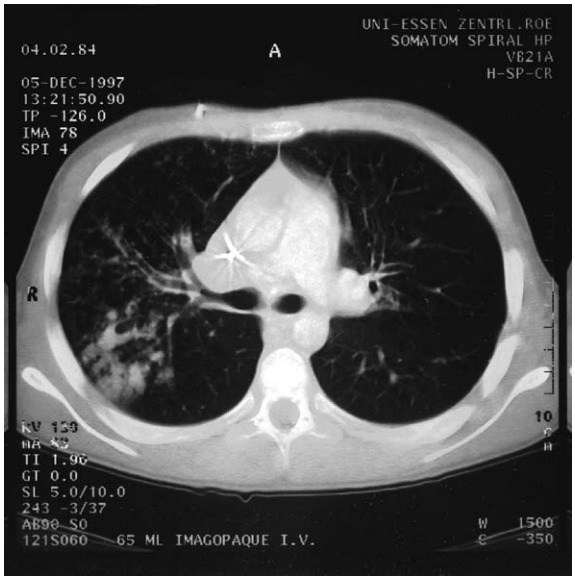

Fig. 1. CT scan at the time of neutropenia and fever showing infiltrates in the right upper lobe.

Four further sputum cultures over the subsequent 18 months yielded *M. chelonae*. During this time period, the patient received several courses of oral cefaclor for mild pulmonary exacerbations in addition to continuous colistin inhalation twice daily, but no specific therapy for mycobacteria. Subsequently, no mycobacteria were found on multiple cultures (including 2 bronchoalveolar lavage samples) for the next 6 years.

The patient is now 20 years old and clinically stable with a BMI of 20. His airways are colonized with a single *P. aeruginosa* strain. He attains normal lung function with an FEV_1 between 80% and 100% predicted. There is no evidence for recurrence of lymphoma to date.

3. Discussion

This case highlights the diagnostic dilemma in patients with CF found to be positive for mycobacteria other than tuberculosis. The patient described in this report did well despite massive immunosuppression and subsequently cleared the infection spontaneously. The scenario of upper lobe infiltrates in a febrile patient known to be colonised with mycobacteria could have prompted us to initiate treatment and we would then have attributed the improvement to the intervention. Therefore, unless there is histologic prove of caseous granulomas or tissue invasion [10], it appears to be virtually impossible to differentiate relevant infection from pure colonisation in this patient population with underlying lung disease and concomitant chronic bacterial infection [11].

CF patients have an increased risk to develop carcinoma of the gastrointestinal tract, whereas other malignancies occur at a similar rate as in the general population [12–14]. More specifically, the risk for lymphoma is not increased in

CF patients [12,13]. Against this background we classify our case as a sporadically occurred lymphoma in a patient with CF.

Immunosuppression as necessary treatment for different diseases is a known risk factor for reactivating tuberculosis from latent to active disease [15] and also for new infection with mycobacteria [10,16].

The clinical significance of detecting mycobacteria among CF patients is not yet firmly established. Criteria for relevant disease in other patient groups are: 1) clinical signs and symptoms such as chronic cough, sputum production, fatigue, malaise, dyspnea, fever, hemoptysis and weight loss; 2) multiple positive sputum or bronchial wash cultures and/or smears (3 positive cultures or 2 positive cultures and 1 positive smear or 1 positive culture and 1 highly positive smear or histopathology of biopsy shows mycobacterial features or contents NTM); and 3) compatible radiographic findings as multilobar, patchy, reticulonodular or mixed interstitial–alveolar infiltrates with upper lobe predominance in chest radiography and/or cylindrical bronchiectasis and/or multiple small (<5 mm) nodules in HRCT [2,11].

So far there are no definitive criteria defined for patients with underlying CF because clinical signs as symptoms as well as radiographic findings can overlap between those caused by CF and by NTM infection. Definite proof depends upon histological proof of the infection, which is rarely attained in these patients. Therefore, only repeated positive cultures or the combination with clinical deterioration and/or the mentioned radiographic findings that cannot be attributed to another cause are a solid basis for founded suspicion of infection with NTM. There is also some evidence suggesting that patients with positive results of acid-fast smears are more likely to be infected than colonized [7,17–19].

There are no reports related to the NTM infection in paediatric patients with lymphoma, but individual cases have been published in patients with leukaemia [20,21]. In contrast to our case, all those patients were treated with antimicrobial therapy directed against mycobacteria. In all except one patient, NTM was not detected after the therapeutic intervention. Our case highlights the known phenomenon that this transient colonisation can clear spontaneously. It is therefore difficult to define from these reports whether the therapeutic invention changed the natural course of the disease.

Immunosuppression is generally known as a risk factor for exacerbation of mycobacterial colonisation into invasive infection [15] and mycobacteria in the lung are regarded as a relative contraindication for lung transplantation in CF because of the risk of disseminating mycobacteria infection under the immunosuppressive therapy. Some authors recommend therapy of nonsymptomatic mycobacterial colonisation before starting any immunosuppressive therapy [15]. In contrast to that, Kesten and Chaparro describe two cases of new colonization with mycobacteria under immunosuppressive therapy after lung transplantation with obviously indolent disease so that no changes in immunosuppression were required [22]. They drew the conclusion that no therapy of indolent colonization is necessary. The outcome of our case and the experience of Suryanarayan et al. [21] and Levendoglu-Tugal et al. [20] also support this view.

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