Case Report: Pulmonary Infection with *Mycobacterium Abscessus*

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**Abstract**

In the last decades growing incidence of nontuberkulous mycobacterium (NTM) in HIV negative patients was registered. Chronic respiratory disease is definitely representing a strong risk factor. In the routine practice lung infections by NTM are often overlooked, resulting in delayed diagnosis. The treatment is not standardized and we are still lacking evidence based trials. Especially, rapid growing NTM, from which *M. abscessus* is the most widespread, are presenting a real challenge. Here, we report a case of pulmonary nontuberkulous mycobacterial (NTM) infection with *M. abscessus*. Although the patient was continuously treated after being diagnosed, further progression, unfortunately, could not be prevented.

**Keywords:** Pulmonary infection; Nontuberkulous mycobacterium (NTM); *Mycobacterium abscessus*; Cavitary pulmonary lesion

**Introduction**

Historically, pulmonary infection due to mycobacterium has been well known as tuberculosis. Later, other mycobacterium species were identified, they are referred to as atypical mycobacterium, mycobacterium others than tuberculosis (MOTT) or nontuberculous mycobacterium (NTM). They are aerobic, non-motile organisms that appear positive with acid-fast alcohol stains and are ubiquitous in the environment with the heaviest concentration found in soil and water [1]. The growing number of patients potentially infected by these organisms resulted in increased interest, and the arrival of AIDS was a crucial point in the study of NTM [2].

Over 150 different species of NTM has been identified, and been further divided into slow- and rapid growing groups. The most common of the slow-growing is *M. avium* complex (MAC) and from rapid-growing *M. abscessus* [1]. In the last decades growing incidence of NTM was registered. It can be explained with the improvement of identification methods but also with the spreading of NTM due to the increase in the number of susceptible and especially immunosuppressed patients [2].

According to the report of Kendall and Winthrop from 2013 the prevalence of NTM in USA varies between 4.1 and 14.1 per 100,000 person-years [3]. In the patients over 65 years of age the prevalence is 47 per 100,000 years and women are found more likely to suffer from NTM than men [4].

C. Andrejak, who investigated the epidemiology of NTM in Denmark between 1997 and 2008, found the mean annual age-standardized incidence rate of patients with at least one NTM-positive specimen to be 2.44 per 100,000 person-years (1.36 for colonization and 1.08 for disease). Five-year mortality after definite NTM disease was 40.1% [5].

Another population-based case-control study by Andrejak provides evidence that chronic respiratory diseases, like asthma, bronchiectasis, previous tuberculosis and particularly COPD, is a strong risk factor for NTM disease. Also the risk is clearly associated with use, dose and type of ICS [6].

In routine practise lung infections by NTM often mimicking symptoms of the chronic respiratory disease, this leads to delayed diagnosis and increased mortality.

**Case Report**

A 54-year-old man with a history of chronic obstructive pulmonary disease (COPD) was referred from general practitioner to our respiratory unit for evaluation, because of the frequent exacerbations. The patient had dyspnoea on exertion and cough without expectoration. He had a smoking history of 160 pack-years. Pulmonary function tests showed reduced expiratory flow limitation: the forced expiratory volume in one second (FEV1) was 1.17 L/s (34% of the predicted value) and the forced vital capacity (FVC) was 3.68 L/s (86% of the predicted value). The patient’s blood samples showed a normal white blood cell count and C-reactive protein (CRP) level. Chest radiography presented emphysema (Figure 1). Computer tomography of the chest (Chest-CT) revealed giant bullous emphysema mostly in the right upper lobe and upper part of the right lower lobe with limited left side dominant bilateral consolidation in the upper lobes (Figure 2).

The patient was already receiving maximal therapy for severe COPD with tiotropium, formoterol and budesonide. Because of the consolidation in the left upper lobe, we decided to follow up with Chest-CT scan after 2 months, which showed progression of the consolidation. Unfortunately, the patient was not agreeing with bronchoscopic intervention and did not have expectoration, making it impossible to obtain samples for microbiological diagnostic.

One year after his first referral he was admitted to our hospital with fever and expectoration. A laboratory evaluation revealed a white blood cell count of 15,300/cm$^3$ and CRP level of 20.2 mg/dl. On examination, he was found to have a temperature of 39.6°, an oxygen saturation of 95% at rest on room air. He had lost 10 kg over the last 12 months and was emaciated, with a body mass index of 17 kg/m$^2$. Chest auscultation presented inspiratory coarse crackles in the upper part of the left lung.
Pulmonary function tests revealed further expiratory flow limitation: the forced expiratory volume in one second (FEV1) was 0.64 L/s (18% of the predicted value) and the forced vital capacity (FVC) was 2.73 L/s (60% of the predicted value).

Chest radiography showed a new cavitary lesion in the apical part and consolidation in anterior part of the upper lobe of the patient’s left lung (Figure 3). We faced 5 major differential diagnoses: tuberculosis, lung cancer, lung abscess, aspergillosis and nontuberculous mycobacteria (NTM) infection. Empiric antibiotic therapy with penicillin and metronidazole was initiated. At the same time the patient was undertaken 18-Fludeoxyglucose positron emission tomography scanning (18-FDG-PET-CT) under suspicion of lung cancer and bronchoscopic examination in order to obtain microbiological and pathological samples. On PET scanning the lesion in the upper left lobe was highly hypermetabolic (Figure 4).
Bronchoscopy did not reveal any endobrochial occlusion, but macroscopic signs of chronic inflammation. Pathological examination of the samples from bronchial washing and brushing from the upper left lobe presented normal cells. Microbiological specimens were obtained by bronchial wash and had shown negative PCR for mycoplasma, chlamidien, legionella, pneumocystis and negative Aspergillus galactomannan antigen. The diagnostic solution was provided by the bronchial washing smear, which was found to be positive for acid-fast bacilli. PCR for mycobacterium complex was negative; PCR for NTM was not performed. But cultivation of the bronchial wash samples verified growth of M. abscessus. No other pathologic microorganisms or fungi were isolated. Additional blood samples showed negative HIV test.

The M. abscessus isolate was found to be susceptible to amikacin, clarithromycin, azithromycin, imipenem/cilastatin and ciprofloxacin. We initiated treatment with azithromycin 500 mg/day and amikacin 15 mg/kg/day. We preferred azithromycin instead of clarithromycin because it seems to have lower rate of gastrointestinal side effects comparing to clarithromycin.

The clinical response was not really satisfying, so we commenced intravenous therapy with imipenem/cilastatin (1000 mg/day). In 4 weeks of the described treatment, the patient’s condition slowly improved. Laboratory test revealed near-normalization of the white blood cells and CRP. He was discharged from the hospital and came to our unit for amikacin infusions 3 times per week (15 mg/kg/day) and continued his medication with azithromycin 500 mg/day.

However, the treatment was only partially successful in slowing the progression of the NTM infection; it came in the next months again to deterioration. The patient developed chronic respiratory failure and got prescribed continuous home oxygen therapy. We added moxicillin 400mg/day urged by the widening of cavities, documented on Chest CT scan (Figure 5).

He received the following treatment over the next 16 months, with short term clinical response and sputum conversion, but a long term sputum conversion could not be achieved, and there was continuously slow progression of the disease, documented by chest X-rays.

After 16 months a further aggravation of the patient’s condition, led to hospitalisation on our unit. The isolate of M. abscessus from expectorated sputum samples revealed the same susceptibility pattern. We restarted immediately imipenem/cilastatin. New Chest CT scan revealed extensive disease with involvement of every lobe of the patients’ lungs with cavitary and interstitial lesions, leading to the total parenchymal destruction (Figure 6).

Figure 5: Chest CT scan showing progression of the cavities in the upper left lobe.

Figure 6: Chest CT scan showing extended lesions bilateral, both cavitary and interstitial.

So in spite of the continuous treatment, further deterioration could not be prevented and the patient has to face an extremely poor prognosis.

Discussion

Lung infections due to M. abscessus are extremely difficult to treat. M. abscessus isolates are uniformly resistant to the standard antituberculous agents. Because of varying in vitro drug susceptibilities, antibiotic susceptibility testing of all clinically significant isolates is recommended. There are no drug regimens of proven efficacy. Multidrug therapy that includes a macrolide may cause symptomatic improvement and disease regression. Surgical resection of localized disease combined with multidrug therapy offers the best chance for cure [7].

The 2007 ATS/IDSA guidelines recommended 2-4 months of intravenous therapy with amikacin plus cefoxitin or imipenem combined with clarithromycin or azithromycin [7], but there was little evidence supporting this recommendation, which means that a reliable therapy concept that could cure M. abscessus still has to be developed. Amikacin showed almost uniform activity, the activity of cefoxitin and imipenem can vary [7]. Yet the relation between in vitro and in vivo susceptibility is not really clear [8]. Treatment recommendations rely
clarithromycin (minimal inhibitory concentrations ≥ 32 μg/ml) was higher in patients with M. massiliense infection (88%) than in (88.5%) of the subjects received antibiotic therapy prior to treatment.

M. abscessus pulmonary infection [10]. 17 were treated with a macrolide and one parenteral antibiotic (amikacin) and 24 with macrolide and two parenteral antibiotics (amikacin and cefoxitin or imipenem); 80% showed sputum conversion and the results were similar in the patients with one and two parenteral antibiotics.

Wallace et al. reported about the clinical experience collected between 2002-2006 using tigecycline-containing regimens for salvage treatment of patients with Mycobacterium abscessus and Mycobacterium chelonae. Data were collected from 52 patients, 46 (88.5%) of the subjects received antibiotic therapy prior to treatment with tigecycline. Treatment groups were evaluated based on length of tigecycline therapy (<1 and ≥1 month). The most commonly used concomitant antimicrobials were macrolides, amikacin and linezolid. Pulmonary disease was the most common presentation (69.2%), and 58.3% of these patients had underlying cystic fibrosis. The majority were M. abscessus [11,12] or M. chelonae/abscessus [4]. The tigecycline therapy ≥1 month (88.1 ± 249.8 days) as part of a multidrug regimen resulted in improvement in >60% of patients with M. abscessus infections, including those with underlying cystic fibrosis, despite failure of prior antibiotic therapy.

Recently new nomenclature, which differentiates three major subspecies within M. abscessus: M. abscessus subsp. abscessus, M. abscessus subsp. massiliense and M. abscessus subsp. bolletii, was worked out [12]. Species- and subspecies-level identifications are important because antibiotic susceptibility and outcomes of therapy can differ significantly depending on the isolated subspecies.

Koh et al. reported about 57 patients with pulmonary M. abscessus infection (24 with M. abscessus complex and 33 with M. massiliense) [13]. They received standardized combination of antibiotic therapy, including a clarithromycin-containing regimen in combination with an initial 4-weeks course of cefoxitin and amikacin for more than 12 months. The proportion of patients with long-term sputum conversion was higher in patients with M. massiliense infection (88%) than in those with M. abscessus infection (25%). Inducible resistance to clarithromycin (minimal inhibitory concentrations ≥ 32 μg/ml) was found in all tested M. abscessus isolates, but in none of the M. massiliense isolates. That reflects the treatment outcome, which is much better in case of M. massiliense as in case of M. abscessus [13].

The proportions of M. massiliense and M. bolletii among M. abscessus complex are variable, according to geographical distribution. For example, among 40 patients monitored at the National Institutes of Health (USA), the prevalence of M. massiliense and M. bolletii was 28% and 5%, respectively [14].

At our hospital we are unfortunately not yet able to differentiate between subspecies of M. abscessus, but according to the dramatic clinical presentation, we assume that in our case it is most likely we were faced M. abscessus infection.

As the last therapy option, the possibility of lung transplantation should also be mentioned. M. abscessus lung infection has been considered a strong relative contraindication to lung transplantation. But recently singular cases of double lung transplantation in patients with cystic fibrosis and M. abscessus infection have been reported. Gilljam et al. reported double lung transplantation in three cystic fibrosis patients with ongoing, and a fourth with recent treatment for Mycobacterium abscessus lung infection [15]. Despite prolonged antibiotic courses and adjustment of immunosuppressive therapy the first three patients developed skin infection and abscesses. But at follow-up after 1, 3, 5 and 7 years respectively none of the patients had evidence of M. abscessus infection and all had stable lung function. So nowadays, some transplantation centres consider lung transplantation in patients with M abscessus lung infection feasible but challenging because it may involve severe complications.

In conclusion, we want to emphasise that it is important to consider NTM as a differential diagnosis of pulmonary infection, especially in patients with COPD and other chronic respiratory diseases. The risk of NTM infection is clearly associated with use and dose of ICS. The precise differentiation between types and subtypes of NTM is necessary because of different therapy recommendations and prognosis. There is still a need to develop more reliable therapy strategies according to precise microbiological differentiating of NTM types and subtypes.
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