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Title: Nontuberculous mycobacteria and allergic bronchopulmonary aspergillosis in lung transplant candidate

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**Nontuberculous mycobacteria and allergic bronchopulmonary aspergillosis
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Abstract

Airway infections are a key component of cystic fibrosis (CF) lung disease. The approach to common pathogens such as *Pseudomonas aeruginosa* or *Staphylococcus aureus* is guided by a significant evidence base, but the treatment of other infections is significant challenge to pharmacotherapy teams. Here we present a specific approach to treatment of chronic infections with non-tuberculous mycobacteria (NTM) anaerobic bacteria and fungi in a 25 year old patient with CF and severely decreased lung function. Also, allergic bronchopulmonary aspergillosis (ABPA) was diagnosed in the patient.

Key words: cystic fibrosis, non-tuberculous mycobacteria, allergic bronchopulmonary aspergillosis, antibiotics, systemic steroids

Introduction

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CF airway disease is characterized by a continuous cycle of persistent infection and inflammation contributing to morbidity and mortality in CF. One of the major lower airway pathogen is *P. aeruginosa*, which remains as the main cause of lung infections in last decades (Smith et al., 2017). Once established, *P. aeruginosa* chronic infection becomes almost impossible to eradicate. Chronic phenotypes and genotypes emerge as a result of adaptation to the lung environment as well as interspecies competition between *P. aeruginosa* strains. Literature on antibiotic prophylaxis and treatment of *P. aeruginosa* infections has remained scarce so far and there is insufficient evidence whether existing strategies decrease morbidity or mortality or improve quality of life. Conventional strategies that include antibiotic treatment are only partially effective and contribute to antibiotic resistance.

It was also demonstrated that *P. aeruginosa* interacts with fungi, but the potential consequences of co-colonization with most of them are poorly understood. Briard et al. (2016) showed that *P. aeruginosa* stimulates *Aspergillus fumigatus* growth via volatile communication mediators, while Reece et al. (2018) that both pathogens had mutually antagonistic effect at the biofilm formation stage. These co-infecting microbes contribute to altered inflammatory response, evasion of the immune system and to the establishment chronic colonization, which could have a significant impact on their treatment in patients with CF.

With increase in the patients' life span, other pathogens such as environmental NTM become clinically more relevant. During the last two decades, an increasing prevalence of *M. abscessus* in sputum samples from CF patients has been noticed, causing up to 95% of NTM infections. Many risk-factors may contribute to CF-associated *M. abscessus* disease such as gender, advanced age, lower BMI, worse FEV1, infection by *P. aeruginosa*, *S. maltophilia* and *A. fumigates*, pneumothorax requiring chest drain, haemoptysis, liver disease, CF related diabetes and ABPA with steroid treatment, as well as use of inhaled hypertonic saline, inhaled antibiotics, inhaled bronchodilators, oxygen therapy, inhaled rhDNase, macrolides, ursodeoxycholic acid and pancreatic enzymes (Viviani et al., 2016). *M. abscessus* grows rapidly, it is inherently multidrug resistant and therefore, difficult to treat (Verregghen et al., 2012).

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Difficulties in the treatment are presented in the actual report of CF patient, with positive *P. aeruginosa*, *M. abscessus* ssp. *abscessus* and *A. fumigates* isolates and ABPA, for whom in the end-stage lung transplantation emerged as a life-saving therapy.

Case presentation

A 25-year-old male (born on March 8, 1994), with CF and BMI 25.2 kg/m² was regularly followed at our Centre since 2016. The diagnosis of CF was established at the age of 5 years and confirmed genetically: patient is double heterozygote one copy of F508del and one copy of 3839G>A in the CFTR gene. His lung function was relatively stable until age of 21 yrs (end of 2015), when alongside with multiple admissions for pulmonary exacerbations/massive pneumonia and episodes of haemoptysis, he began to experience a serious decline in pulmonary function demonstrated by a fall in FEV1 from 46% predicted (FEV1/FVC 55%) at the age of 22 yrs (in 2016) to less than 26% predicted (FEV1/FVC less than 40%) by the age of 24 yrs (end of 2018).

At the beginning of 2019, he was hospitalized with severe tachydyspnea and airflow obstruction (FEV1 23%, FVC 48%), hyposaturation 86%, haemoptysis, tachycardia and need for continuing oxygen therapy. He was aware, non-febrile, pale and chalonated, his lung auscultation revealed bronho-vesicular breathing, with prolonged expirium and small wet crackles bilaterally, especially in the apical and medial portions. Chest radiograph indicated obstructed and bronchiectatic segmental branches (Fig. 1).

Fig. 1

In laboratory biochemical evaluation, the values for albumin, total protein, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatine kinase, acidum uricum, lactate dehydrogense, gamma-glutamyltranspeptidase and rheumatoid factor were within the normal range (NR), while for C-reactive protein, the value was increased to 16.1 mg/L (NR < 3.0 mg/L). The hematological parameters were normal, except the values for white blood cells ($13.3 \times 10^9/L$, NR $4.5-11.0 \times 10^9/L$), polymorphonuclear leukocytes (PMN, 79%, NR 25-70%)

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and platelets ($459 \times 10^9/L$, NR 150- $400 \times 10^9/L$), which were slightly elevated and the level for lymphocytes (15.2%, NR 28-55%), which was slightly decreased. Tests for hepatic function and renal function were normal.

He was known to be suffering from a chronic colonization with *P. aeruginosa* and *M. abscessus* ssp. *abscessus*, for which he has been permanently treated with oral antibiotics: clarithromycin (2×500 mg), moxifloxacin (1×800 mg) and inhalatory antibiotic amikacyn (500 mg/2 mL+2 mL saline) in addition to the eradication therapy, repeatedly applied during his frequent hospitalizations, consisted of three of the following intravenous antibiotics: ceftazidim, amikacyn, imipenem, meropenem, colistimethate, tygecyclin, teicoplanin. *A. fumigatum* infection was also present for several years. Three years ago, ABPA was diagnosed, for which he was treated by oral corticosteroid (prednisone at 40 mg once daily for 2 weeks with taper over 3 months) and itraconazole (200 mg twice daily for 2-5 months). In that period he was receiving regularly oral azithromycin as immunomodulatory therapy (1×500 mg three times a week). Periodically, colonies of *Enterococcus casseliflavus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus haemolyticus* (MRSH), *Staphylococcus sciuri* were isolated, also, atypical microorganisms such as *M. pneumonia*, *C. burneti*, *Influnza B* and *L. pneumophila* and *C. albicans* as well, for which oral rifampicin (2×300 mg), trimethoprim+sulfamethoxazol (2×480 mg), ciprofloxacin (2×750 mg) and nystatin 100,000/30 mL (3×1.5 mL) were introduced at times. During some pulmonary exacerbations, there was a need for extra short-term oral steroid therapy (prednisolone) due to severe obstruction.

Within this period (2016-2019), the patient was also permanently treated with dornase alfa (rhDNasa), oral and inhalatory β_2 -adrenergic agonist (salbutamol), oral calcium channel blocker (verapamil), oral pancreatic enzyme substitutes (due to pancreatic insufficiency), proton-pump inhibitor (PPI)- omeprazole or H2-blocker- ranitidine (during the steroid therapy), various multivitamin and multimineral preparations, hepatoprotective supplements (e.g. omega 3, silymarin). Depending on the needs, he additionally received oral desloratadin and nasal ectoine and xylometazoline for pollen allergy, inhalatory tiotropium bromide, N-acetylcysteine as a mucolytic, and tranexamic acid for treatment of haemoptysis. However, despite the regular antibiotic and above-mentioned supplemental therapy, his lung function was rapidly declining

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(FEV1 being constantly below 25% predicted), the frequency of exacerbations requiring hospitalization was increasing and the recurrent episodes of pneumonia and haemoptysis could not be controlled. Therefore, the patient was listed for lung transplantation, which was performed at his age of 25 yrs (April, 2019).

Discussion

In CF, *P. aeruginosa* airways infection may occur early in life. Initially, dominantly non-mucoid species of *P. aeruginosa* are present, with isolates susceptible to a range of antibiotics. With advancing age, *P. aeruginosa* generates tools to resist antibiotics (e.g. efflux pumps, β -lactamases, reduced porins, switching to a biofilm lifestyle) and smartly escapes the immune clearance, leading to chronic infection (Faure et al., 2018). Current strategies used to prevent acquisition of infection, eradicate early infection, control chronic infection and treat pulmonary exacerbation include antibiotic treatment delivered by oral, intravenous or inhalatory route. In choice of suitable antibiotic, various factors are considered among which are co-infecting microorganisms (Smith et al., 2017).

Current Macedonian Guideline (Naceva Fushtikj & Jakjovska, 2018) follows the recommendations given by the European Cystic Fibrosis Society (ECFS), suggesting life-lasting month on/month off or continual use of inhalatory antibiotics (tobramycin, colistimethate /colistin or aztreonam) in chronic infection with *P. aeruginosa* for children ≥ 6 yrs. In acute exacerbations, i.v. antibiotic treatment is recommended, with ceftazidime plus amikacyn being the first-line, while meropenem plus amikacyn, second-line treatment (or first, if *S. aureus* is increased). As alternative to aminoglycoside in patients with impaired renal function or resistance to aminoglycosides, colistimethate is recommended. In patients, with evident decline of lung function despite the regular treatment (incl. inhalatory antibiotic), elective i.v. antibiotic treatment is suggested every 3 months, while for those with stable lung function i.v. antibiotics on demand. Impaired mucus clearance, local immunogenic dysfunction and antibiotic use, at one side, and exposure to airborne fungal spores, at the other side, increase the risk for fungal colonization in the CF patients, with *A. fumigates* and *C. albicans* being the major clinical challenges. The frequent

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co-colonization with *P. aeruginosa* and *A. fumigatus* in CF patients and decreased lung function compared to patients clear of both pathogens (Amin et al., 2010) emphasize the importance of their interaction in the CF airways. It has been well established that *P. aeruginosa* inhibits and damages *A. fumigatus* by direct cell contact and *via* volatile communication mediators (Anand et al., 2017; Briard et al., 2016), while recent study (Reece et al., 2018) reported that *A. fumigatus* have also inhibited *P. aeruginosa* biofilm formation producing a number of toxins, incl. gliotoxin (Gt). *A. fumigatus* colonization and Gt production may disrupt airway microbiome, but the clinical implications of this impact have not been explored yet. What has been confirmed was that the interaction between *P. aeruginosa* and *A. fumigatus* could cause a more virulent infection. Enhanced production of *P. aeruginosa* elastase in the presence of *A. fumigatus* and its damaging effect in CF patients is documented (Smith et al., 2015), however, a key consequence of invasive infection with *A. fumigatus* remains ABPA.

In acute ABPA, corticosteroids suppress the inflammatory response. The Macedonian treatment protocol (Naceva Fushtikj & Jakjovska, 2018) includes prednisolone at 2 mg/kg once daily for 2 weeks, 1 mg/kg once daily for additional 25 weeks, with subsequent tapering over 1-3 months tailored to clinical symptoms, lung function and total serum IgE concentration. When there is a concern for side effects of long-term steroid treatment, alternative regimens such as high dose i.v. methylprednisolone 10 mg/kg daily (1 g maximum) for 3 days monthly for up to 10 months is recommended. Concurrent administration of antifungal therapy is also suggested, with preference to itraconazole (due to the favorable side effect profile). Having in regard its interaction with the H2 blockers and PPI and their significance when systemic steroid therapy is indicated, alternatives are offered and they include posaconazole, and in case of azole resistance or refractory response (steroid-resistant) cases, nebulized (liposomal) amphotericine, i.v. caspofungin or s.c. omalizumab (anti-IgE monoclonal antibody).

Literature data point that ABPA and systemic steroid therapy were associated with NTM pulmonary infections (Liu et al., 2018), increasingly observed in patients with CF. In particular, *M. abscessus* is associated with worse outcome (rapid decline of lung function) and need for post-transplantation treatment (present in up to 20% of lung transplant candidates). Some paper report that *M. abscessus* infection is impossible to eradicate and the disease is diffuse and because of that

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not manageable for surgery (Mussafi et al., 2005). For these reasons, many of the transplant centers consider the presence of NTM lung disease a relative contraindication for transplantation (Esther et al., 2010; Lynch et al., 2015). The complexity and intensity of NTM treatment depends largely on disease severity, individual variables and overall goals of therapy. Inhaled amikacyn has been increasingly used for the treatment of *M. abscessus*, with variable doses ranging between 250 mg and 500 mg once or twice daily. The treatment of *M. abscessus* ssp. *abscessus* lung disease most often include a macrolide- clarithromycin or azithromycin (depending on the presence/absence of an active erythromycin ribosomal methylation (*erm*) gene) or non-macrolide agents such as cefoxitin or imipenem/meropenem or tigecycline or linezolid in addition to amikacyn (Chmiel et al., 2014; Naceva Fushtikj & Jakjovska, 2018; Skolnik et al., 2016). Typically, with an intensive regimen is started, consisted of parenteral and oral regimens followed by de-escalation to an inhaled and oral regimen after a period of weeks and months. In the period of transition, there is essential need to avoid monotherapy and to maintain a multidrug regimen with effective non-parenteral agents, by balancing the efficacy against the risk of toxicity.

The association of NTM/*M. abscessus* with ABPA is explained by altered immune balance i.e. increased T-helper (Th)2 CD4+ T-cell response to *Aspergillus* and high levels of interleukins (IL) 4, 5 and 10 secreted by peripheral blood mononuclear cells. IL-10 down-regulates Th1 CD4+ T-cells and related cytokines, such as interferon (IFN)- γ , IL-2 and tumor necrosis factor (Skov et al., 1999). Steroids have additional role in CF patients by further suppressing innate lung defense, including IFN- γ signaling and nitric oxide production, which is already deteriorated (Liu et al., 2018). These and other predisposing factors to NTM lung disease impose perplexing dilemma of NTM/*M. abscessus* treatment.

The main dilemma considering the treatment of actual patient was to use or not systemic steroids. The second one was to perform or not lung transplantation despite the presence of NTM/*M. abscessus* lung disease.

Considering the first one, since establishing the diagnosis of *M. abscessus* lung disease for the first time at his age of 22 yrs (first half of 2016) until his age of 23 yrs (last trimester of 2017), no systemic steroids were administered. Within this period, he was hospitalized several times due to the worsening of his lung function (FEV1 32-40%) and occurrence of haemoptyses before each

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hospitalization. After antibiotic and adjuvant treatment in accordance with the protocol (Naceva Fushtikj & Jakjovska, 2018) and recommendations by the ECFS, he was released from the hospital in good general condition and improved lung function (FEV1 39-44%). However, despite the regular triple parenteral antibiotic and adjuvant treatment for 2 weeks during each hospitalization, at the end of 2017 his lung function significantly declined (FEV1 23%, FEV1/FVC 35.5%), bronchial obstruction was potentiated (saturation 86-87%) and massive pneumonia was evidenced bilaterally at his chest X-ray. Considering that, the decision was made oral prednisolone to be included, with dosage regimen tailored to the clinical symptoms. By the beginning of 2019, he had been admitted to hospital four times, always with the same clinical presentation (FEV1 20-23%; saturation 83-85%) and each time prednisolone with the same dosage schedule was administered in addition to the standard antibiotic and adjuvant treatment. After 2 weeks hospital treatment, the patient was discharged with slightly improved general condition and lung function (25-27%), increased saturation without oxygen support (95%) and discrete improvement in lung auscultatory finding.

Considering the second dilemma, the lung transplantation has been successfully performed two months ago (April 2019) and no complication related to NTM and *Aspergillus* spp. are observed so far (June 2019).

Conclusion

Infections with NTM and *Aspergillus* spp. and ABPA are associated with accelerated loss of lung function, worse outcome and often need for lung transplantation and post-transplantation treatment. The decision regarding how to treat them must balance the risks and benefits of treatment vs. observations. However, for successful management, deeper understanding of the impact of these polymicrobial infections on disease progression i.e. of their dynamics, inter-microbial and host-microbe interactions and diverse host factors is needed. In addition, novel treatments which interfere with elements that enable persistence of these microbes are required as an alternative to antibiotic treatment or add-on therapy.

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Резиме

Нетуберкулозни микобактерии и алергична бронхопулмонарна аспергилоза кај кандидат за трансплантација на бели дробови

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Клучни зборови: цистична фиброза, нетуберкулозни микобактерии, алергиска пулмонарна аспергилоза, антибиотици, системски кортикостероиди

Инфекциите на дишните патишта се клучна компонента на белодробното заболување цистична фиброза (ЦФ). Пристапот во третманот на вообичаените патогени како *P. aeruginosa* или *Staphylococcus aureus* е управуван од значајна збирка на докази, но третманот на другите инфекции претставува голем предизвик за фармакотерапевтските тимови. Во трудот е прикажан специфичен пристап во третманот на хронични инфекции со нетуберкулозни микобактерии (НТМ), анаеробни бактерии и габи кај пациент со ЦФ на возраст од 25 години и сериозно намалена белодробна функција, кај кој е дијагностицирана и алергиска бронхопулмонарна аспергилоза (АБПА).

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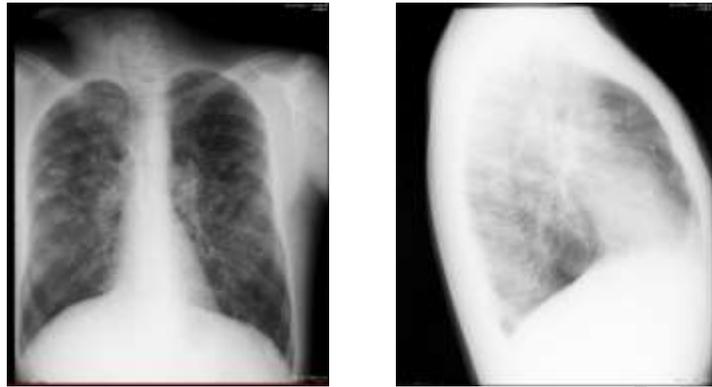


Fig. 1. Posteroanterior and lateral chest X-ray showing bilateral lungs hyperinflation, reticulonodular pattern peripherally, interstitially, with presence of bronchiectasis in the basal bilateral lung fields and centrally. Numerous subpleural fingerlike shadows (densities) and small nodular changes in the upper lung fields that reflect the obstructed and nonobstructed bronchiectatic segmental branches.

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