Long-term follow-up: tuberculosis, bronchiectasis and chronic pulmonary aspergillosis

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Abstract

English:
Pulmonary sequelae related to tuberculosis (TB) are among the major causes of bronchiectasis in Eastern Europe. The role of bacterial colonisation in the pathogenesis of bronchiectasis has been continuously studied over the last decades, less understood remains the impact of fungal infection, alone or in association with bacterial. Although the data on the development of chronic pulmonary aspergillosis (CPA) secondary to TB are scarce, recent evidence suggests a higher prevalence of CPA in patients with a past history of pulmonary TB than it was previously estimated. We present a case of natural evolution of CPA, with a radiological follow-up, in a patient with post-tuberculous bronchiectasis.

Keywords
tuberculosis • bronchiectasis • imaging • chronic pulmonary aspergillosis

Monitorizare pe termen lung: tuberculoză, bronșiectazii, aspergiloză pulmonară cronică

Romanian:
Sechelele pulmonare posttuberculoase sunt o cauză frecventă de bronșiectazii în țările din Europa de Est. Rolul colonizării bacteriene în patogenia și evoluția bronșiectaziilor de diferită etiologie este un subiect intens studiat pe parcursul ultimelor decenii, mai puțin înțeles fiind impactul infecției fungice, izolate sau în asociere cu cea bacteriană. Deși datele privind dezvoltarea aspergilozei pulmonare cronice (APC) secundare tuberculozei sunt moderate, publicațiile recente sugerează o prevalență mai mare a APC, decât cea estimată anterior, printre pacienții cu istoric de tuberculoză pulmonară. Prezentăm evoluția naturală într-un caz de APC, monitorizat imagistic pe parcursul mai multor ani, la o paciență cu bronșiectazii posttuberculoase.

Cuvinte-cheie
tuberculoză • bronșiectazii • imagistica • aspergiloză pulmonară cronică

Introduction

Chronic pulmonary aspergillosis (CPA) is an uncommon destructive pulmonary syndrome, caused by fungi belonging to Aspergillus genus, and it is characterised by slowly progressive cavitation (except Aspergillus nodules), fibrosis and pleural thickening. It usually affects persons without an evident immune suppression but frequently with an underlying pulmonary condition such as chronic obstructive pulmonary disease (COPD), sarcoidosis, non-tuberculous mycobacterial pulmonary disease (NTM-PD) or pulmonary tuberculosis (PTB), prior or concurrent. CPA is an overlooked potentially...
A 60-year-old woman presented, in August 2016, with progressively increasing dyspnoea for the past 4 years (modified Medical Research Council – 4), productive cough (greenish purulent sputum 50 ml/day – Figure 1B), two episodes of haemoptysis in the past 2 weeks, 10 kg weight loss, night sweats and anorexia during the past 6 months. On admission, she was ill-looking, pale, cachectic (Figure 1A) and without oedemas and had blood pressure 100/60 mm Hg, pulse 96 b/m, respiratory rate 26 b/m, BMI 15 kg/m², SaO₂ 92% at room air and a high body temperature of 39.2°C. Chest auscultation revealed wheezing and scattered crackles. She had no evidence of any immunosuppression, comorbidities, alcohol abuse or smoking. She was cured of smear-positive PTB at the age of 42 years and experienced a relapse episode of smear-negative PTB at the age of 46 years.

Chest radiography during the episode of TB relapse (22 August 2002; Figure 2A) showed a cavitary lesion in the upper right lobe and multiple nodular circular opacities on both inferior lung areas. These abnormalities persisted after 1 year of TB treatment (Figure 2B), and the patient was discharged with diagnosis of post-tuberculous bronchiectasis. From 2012 to 2016, she reported three to four acute exacerbations per year treated empirically with antibiotics, usually 7 days without any bacteriological tests.

Nine years later, chest radiography (26 January 2012 – Figure 2C) revealed extensive fibrosis, right lung volume reduction and progression of the lesions suggestive of bronchiectasis. At that time, a fungus ball could be suspected in the right upper lobe cavitary lesions (Figure 2C).

On hospital admission in August 2016, chest radiography (Figure 2D, E) showed an important thickening of the right apical pleura, a completely destroyed right upper lobe, bilateral progression of varicose and cystic bronchiectasis (some with air-fluid level), right-side traction and dilatation of the trachea. Fungus ball was not suspected at that time. Pulmonary function tests revealed a severe obstructive defect: forced expiratory volume in 1 second (FEV₁) – 0.91 L (43%), forced vital capacity (FVC) – 1.27 L (50%)
and FEV₁/FVC – 72%. Blood tests proved a mild anaemia (haemoglobin – 111 g/L), leucocytosis (white blood cells – \(21.7 \times 10^9/L\), neutrophils – 94%) and increased C-reactive protein level – 42 mg/L.

Sputum culture was positive for *Pseudomonas aeruginosa* (Figure 1C) susceptible to fluoroquinolones and ceftazidime. No growth of *Aspergillus* on the Sabouraud Dextrose Agar medium was attested. Sputum microscopy for acid-fast bacilli, real-time polymerase chain reaction based test Xpert MTB/RIF and culture on the Löwenstein–Jensen medium were negative on three sputum samples.

The patient was discharged with the diagnosis of bronchiectasis colonised by *P. aeruginosa*. An eradication treatment with ciprofloxacin was prescribed. Chest computed tomography (CT) scan and measurement of serum *Aspergillus* IgG have been recommended. High-resolution CT (HRCT) scan performed in October 2016 (Figure 3A, C) revealed extended cystic bronchiectasis in both lungs and multiple cavitary lesions with intracavitary masses in the right upper lobe, probably of fungal origin, but considered as post-tuberculous sequelae by the radiologist.
She was readmitted after 2 years (April 2018); during this period, she had four episodes of infectious exacerbations (increase of sputum purulence and volume, haemoptysis and fever), treated with ciprofloxacin. Sputum culture in March 2017 identified *Staphylococcus aureus*, *Escherichia coli* and no *P. aeruginosa*. In April 2018, sputum culture was again positive for *P. aeruginosa* and *S. aureus*.

A second HRCT scan (Figure 3B, D), obtained 18 months later (6 April 2018, patient being without any antifungal treatment), showed a completely destroyed right upper lobe, an increase in size of the cavities and pleural thickness. New areas of consolidation close to cavitary lesions were observed and no intracavitary masses. Both lungs show distortion features, severe cystic bronchiectasis and progression of the disease.

**Discussion**

Tuberculosis is among the most impactful infectious causes of morbidity and mortality worldwide (6). Even though the majority of the TB cases could be efficiently treated, patients with cured respiratory TB may suffer from lifelong disabling pulmonary sequelae, which was shown in the presented case as well. Lung damage related to TB is one of the major contributors in the aetiology of bronchiectasis in South Asia and Eastern Europe (7). In time, bronchiectasis tends to be colonized by a variety of potentially pathogenic microorganisms. The most commonly isolated microorganisms are *Haemophilus influenzae*, *P. aeruginosa*, *Streptococcus pneumoniae*, *S. aureus* and *Moraxella catarrhalis* (8). Other germs, also often detected, are non-tuberculous mycobacteria (9), yeasts and filamentous fungi (10). Apart from *P. aeruginosa*, it is little known about the role of other bacteria in bronchiectasis
Alcohol, the impact of fungal infection being even less understood (11).

The inhalation of fungal spores by healthy adults usually does not lead to an active pulmonary disease. Proliferation of spores could be enhanced by impaired mucociliary clearance, thickening of airways mucus and the fungi capacity to escape the host's immune defence mechanisms. In chronic pulmonary diseases (such as bronchiectasis, COPD, post-TB pulmonary sequelae, NTM-PD, CF and allergic bronchopulmonary aspergillosis), saprophytic Aspergillus colonisation or infection could cause CPA.

Multiple aspects of pulmonary Aspergillus infection have been extensively studied in immunocompromised persons and patients with CF or COPD. It is little known about the epidemiology, risk factors and management of Aspergillus infection in bronchiectasis patients (12). However, Aspergillus spp. are among the most frequently isolated fungi in the respiratory specimens of patients with both CF and non-CF bronchiectasis (13,14). A variety of Aspergillus species have been reported in bronchiectasis patients, A. fumigatus being the most common, followed by Aspergillus niger, Aspergillus terreus and Aspergillus flavus. However, there is a huge variation in their prevalence among studies. For instance, the prevalence of Aspergillus spp. ranges from 7% to 24% (10,14). The prevalence of Aspergillus infection in Eastern European countries is not known exactly. Some estimates suggest a prevalence of 8.98/100,000 of CPA in former TB patients from this region (15).

The incidence of Aspergillus spp. in the respiratory specimens increases with age, severity of lung disease and chronic antibiotic treatment (16). However, these data have been derived from studies on CF patients and still should be proven in case of non-CF bronchiectasis. Some of currently existing data do not confirm the association between Aspergillus spp. and chronic antibiotic treatment in bronchiectasis patients. At the same time, a couple of unexpected association, such as sputum purulence, have been reported (10).

Clinical significance of positive fungal cultures from respiratory samples obtained in bronchiectasis patients has not been clearly established. That is due to lack of clear criteria for Aspergillus colonisation and frequent contamination of Aspergillus culture plates by other fungi (e.g. Candida albicans) or bacteria (14,17). Even more a negative sputum culture for Aspergillus could not exclude aspergillosis and can delay the diagnosis, as it was in our case. It could be that sputum culture and other techniques such as microscopy and serology (this was decisive in the present case) are not the most appropriate methods to check for Aspergillus infection of lower respiratory tract in case of bronchiectasis. The use of other microbiological techniques instead of sputum cultures is intensively debated (14). Currently, studies of great interest are on metagenomic analysis and other omics using molecular or mass spectrometry-based techniques. Utility of these technologies for clinical purposes in the upcoming future is still uncertain.

There are still many tasks pending to be solved concerning fungal infection in bronchiectasis such as: establishing the real prevalence of the fungal infection in this population group, evaluating the limitations associated with currently available diagnostic methods, assessing the clinical significance of individual species, verifying whether fungi are a cause or a consequence of bronchiectasis and defining the risk factors for fungal infection and the importance of fungal sensitization (14).

The presented case illustrates several missed opportunities for a timely diagnosis of CPA in a patient with post-TB sequelae. This was due to an overlooked diagnostic alternative, such as CPA, in a former TB patient in whom reactivation was less possible due to negative tests for TB. On top of this, initial access only to low sensitivity culture for Aspergillus and postponed testing by highly sensitive and specific serological assays led to delayed diagnosis. Unfortunately, this is a common reality in low-income countries where proper diagnosis and treatment of fungal infection implies out-of-pocket expenditures from the patient side.

Conclusions

Aspergillus-related diseases can overlap bronchiectasis or other pulmonary sequelae. CPA can mimic smear-negative PTB that could lead to its misdiagnosis. Clinicians need to consider various clinical information such as patients' background, radiological images, clinical course of the disease, microbiological tests and other supportive diagnostic methods to diagnose CPA.

Ethics approval and consent to participate

Inform consent was obtained from the patients in order to write the article.

References

1. Barac A, Kosmidis C, Alastruey-Izquierdo A, Salzer HJF. Chronic pulmonary aspergillosis update: A year in review. Medical Mycology. 2019;57(Supplement_2): S104–S109.
2. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: Rationale and clinical guidelines for diagnosis and management. European Respiratory Journal. 2016;47(1): 45–68.
3. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. *Bulletin of the World Health Organization.* 2011;89(12):864–872.

4. Alastruey-Izquierdo A, Cadranel J, Flick H, Godet C, Hennequin C, Hoenigl M, et al. Treatment of chronic pulmonary aspergillosis: Current standards and future perspectives. *Respiration.* 2018;96(2):159–170.

5. The Lancet Respiratory Medicine. Chronic pulmonary aspergillosis: Help is on the way. *The Lancet Respiratory Medicine.* 2016;4(2):83.

6. Jaramillo J, Yadav R, Herrera R. Why every word counts: Towards patient- and people-centered tuberculosis care. *International Journal of Tuberculosis and Lung Disease.* 2019;23(5):547–551.

7. Redondo M, Keyt H, Dhar R, Chalmers JD. Global impact of bronchiectasis and cystic fibrosis. *Breathe (Sheff).* 2016;12(3):222–235.

8. McDonnell MJ, Jary HR, Perry A, MacFarlane JG, Hester KL, Small T, et al. Non cystic fibrosis bronchiectasis: A longitudinal retrospective observational cohort study of Pseudomonas persistence and resistance. *Respiratory Medicine.* 2015;109(6):716–726.

9. Maiz L, Giron R, Olveira C, Vendrell M, Nieto R, Martinez-Garcia MA. Prevalence and factors associated with non-tuberculous mycobacteria in non-cystic fibrosis bronchiectasis: A multicenter observational study. *BMC Infectious Disease.* 2016;16(1):437.

10. Maiz L, Vendrell M, Olveira C, Girón R, Nieto R, Martínez-García MÁ. Prevalence and factors associated with isolation of Aspergillus and Candida from sputum in patients with non-cystic fibrosis bronchiectasis. *Respiration.* 2015;89(5):396–403.

11. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. *Annals of the American Thoracic Society.* 2015;12(11):1602–1611.

12. Denning DW, Pashley C, Hartl D, Wardlaw A, Godet C, Del Giacco S, et al. Fungal allergy in asthma-state of the art and research needs. *Clinical and Translational Allergy.* 2014;4:14.

13. Angrill J, Agustí C, de Celis R, Rañó A, Gonzalez J, Solé T, et al. Bacterial colonisation in patients with bronchiectasis: Microbiological pattern and risk factors. *Thorax.* 2002;57(1):15–19.

14. Maiz L, Nieto R, Canton R, Gómez G de la Pedrosa E, Martínez-García MÁ. Fungi in bronchiectasis: A concise review. *International Journal of Molecular Sciences.* 2018;19(1):pii:E142.

15. Mares M, Moroti-Constantinescu VR, Denning DW. The burden of fungal diseases in Romania. *Journal of Fungi (Basel).* 2018;4(1):31.

16. Milla CE, Wielinski CL, Regelmann WE. Clinical significance of the recovery of *Aspergillus* species from the respiratory secretions of cystic fibrosis patients. *Pediatric Pulmonology.* 1996;21(1):6–10.

17. Moss RB. Fungi in cystic fibrosis and non-cystic fibrosis bronchiectasis. *Seminars in Respiratory and Critical Care Medicine.* 2015;36(2):207–216.