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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

Rezumat

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 modeste, 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 pacientă 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

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life-threatening disease that includes several clinical and imaging presentations such as *Aspergillus* nodules, simple aspergilloma (presence of a fungus ball in a single lung cavity), chronic cavitary pulmonary aspergillosis (the most common form characterized by lung cavities with or without aspergilloma or nodules) and subacute invasive aspergillosis and chronic fibrosing pulmonary aspergillosis (the advanced stage implying extensive lung scarring) (1,2).

Although the data on the development of CPA secondary to PTB are scarce, recent evidence suggests a higher prevalence of CPA in patients with cured PTB than previously estimated (3,4). While tuberculosis-related CPA is rare in high-income countries, it is relatively common in Eastern Europe (3,5). CPA can mimic smear-negative or recurrent PTB and should be suspected in TB patients with progressive cavitating disease and persistent symptoms despite an adequate anti-tuberculous treatment.

Case report

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/m^2, SaO_2 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 (FEV_1) – 0.91 L (43%), forced vital capacity (FVC) – 1.27 L (50%)

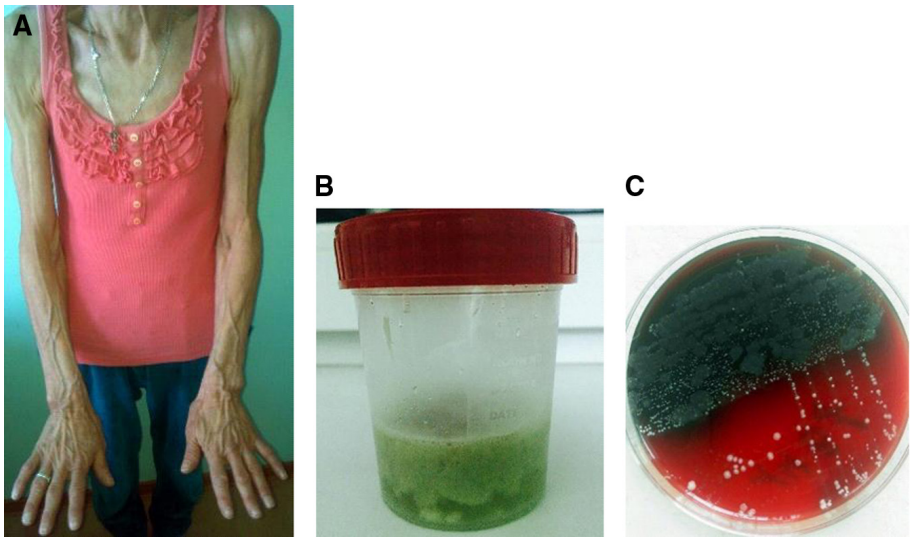

Figure 1. (A) Cachectic aspect of the patient. **(B)** Greenish colour of sputum suggestive of *Pseudomonas aeruginosa* infection. **(C)** *P. aeruginosa* colonies growing on blood agar. The colonies are spreading and flat with serrated edges and metallic sheen; in areas of confluent growth, the colonies and agar are dark due to production of the pigments pyoverdine and pyocyanin.

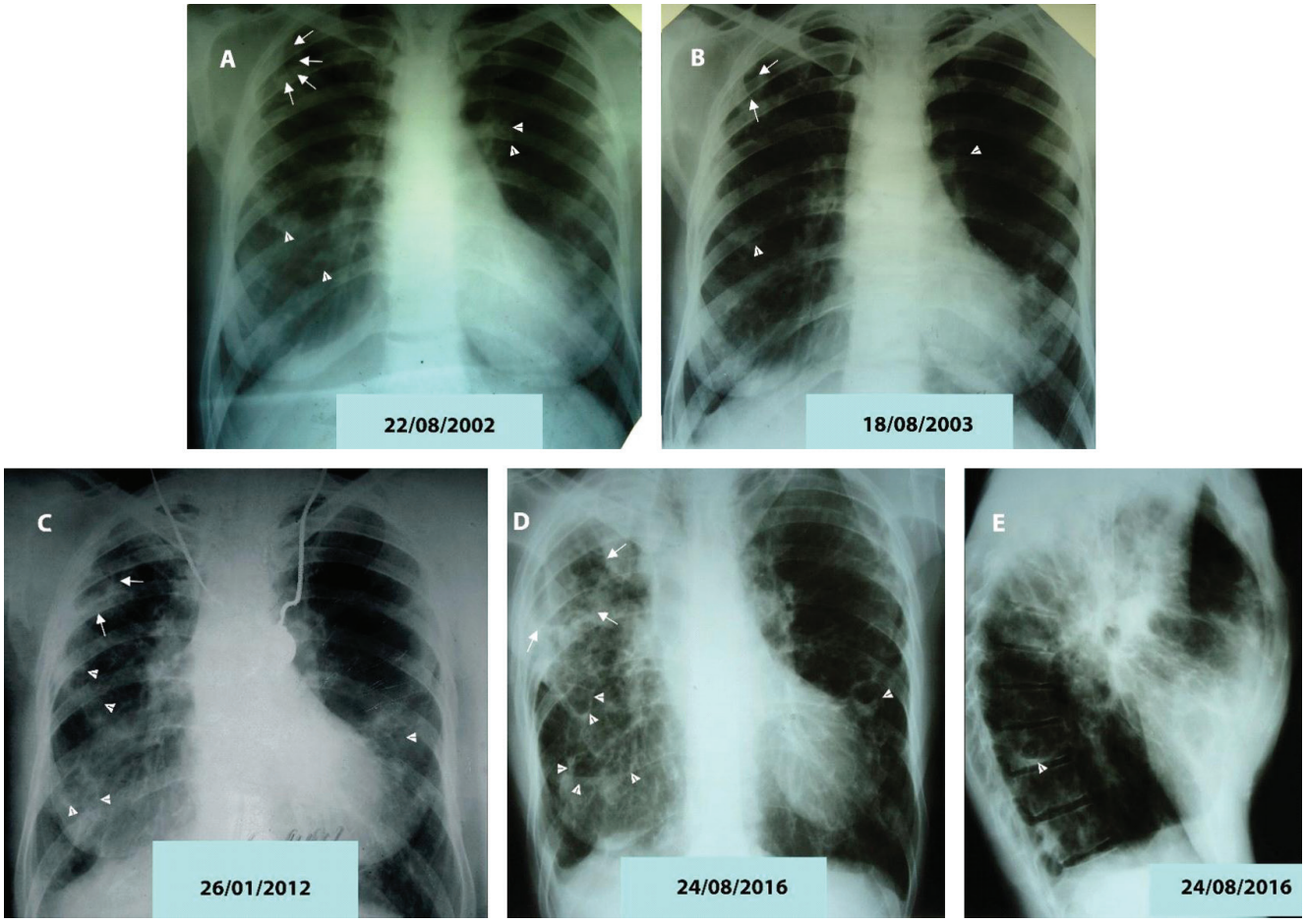

Figure 2. (A) Chest radiograph during the episode of TB relapse (22 August 2002) showing a cavitary lesion in the upper right lobe (arrows) and multiple nodular opacities (suggestive of mucoid bronchial impaction), circular opacities (arrowheads) and the tram-track appearance of bronchial walls, with paired parallel linear opacities radiating from the hilum of both lungs, more prominent in the right inferior area. Note "*rosette*" images in the left perihilar area (arrowheads). The right hemidiaphragm, costophrenic angle and cardiac silhouette are obscured due to fibrotic lesions. **(B)** Chest radiograph after 1 year of treatment for PTB showing persistence of previous pulmonary lesions and a small improvement of peribronchial cuffing. **(C)** A 9 years later chest radiograph (26 January 2012) reveals extensive fibrosis, reduced size of the right lung and progression of the bronchiectasis (arrowheads) with upward hilar traction. A possible fungus ball with the air-crescent sign could be supposed inside the cavitary lesion (arrows). **(D, E)** 12 years later (24 August 2016), frontal and lateral view of chest radiography showing reduced upper lobe volume with an important thickening of the pleura and a single lung cavity with thick walls and completely destroyed right upper lobe. Progression of varicose and cystic bronchiectasis (some of them with air-fluid level – arrowheads) in both lungs; right sight traction and dilatation of the trachea were identified. Associated signs of hyperinflation could be seen; there are marked flattening of the hemidiaphragms (more evident on the lateral view) and widening of the retrosternal clear space.

and FEV_1/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 MBT/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.

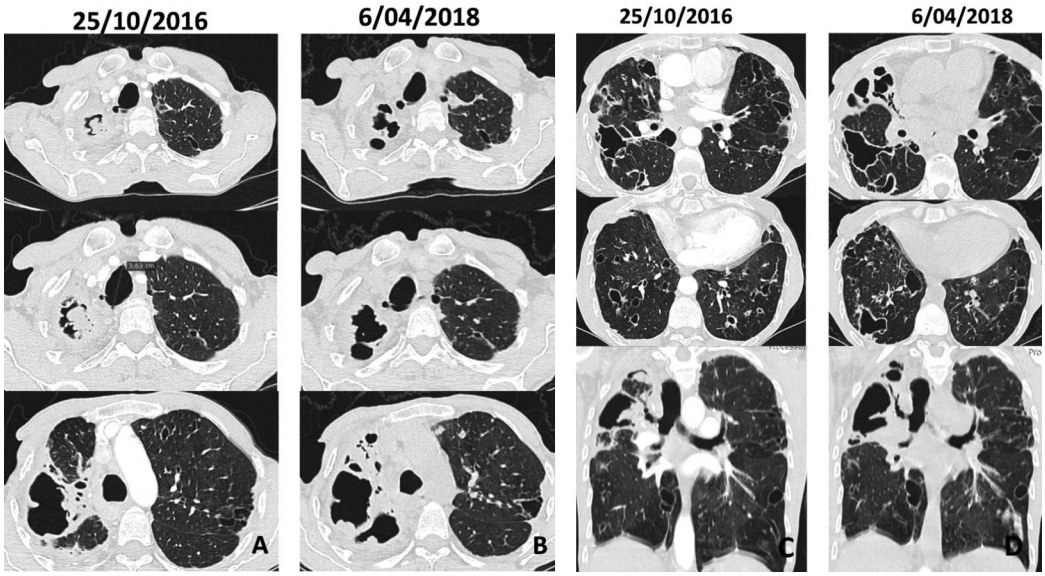

Figure 3. HRCT, lung window, prone position, five transversal images at different anatomical levels and coronal reconstruction (October 2016) demonstrating the spread of bronchiectasis (tubular, varicose and cystic) in all lobes and multiple large, irregular, thick-walled cavities with intracavitary masses (*fungus ball*) and pleural thickening. The mass is with air-crescent sign but no fluid level. Note tracheal enlargement and a tracheal diverticulum. **(B, D)** HRCT images taken 18 months later, patient being without any antifungal treatment. Transversal sections and coronal reconstruction at the same anatomical levels as in 2016 showing 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.

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 cavities and extension of pleural thickness and no intracavitary masses.

Increased *Aspergillus fumigatus*-specific IgG (140 mg/L, normal range ≤14 mg/L) was found in April 2018. Considering imaging lesions, positive IgG and negative sputum culture for *Mycobacterium tuberculosis*, the patient was diagnosed with chronic fibrosing pulmonary aspergillosis; itraconazole was started. After 2 months of treatment, an improvement in self-reported clinical status, weight gain (5 kg), no recurrence of haemoptysis and a decrease in the IgG level (102 mg/L) have been achieved. The patient discontinued the treatment and was hospitalized after 2 months with worsening of general and respiratory symptoms and with recurrent haemoptysis. Lateral flow assay (LDBio Diagnostic, France) for *A. fumigatus* was positive (Figure 4). Antifungal therapy was restarted.

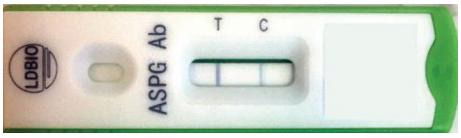

Figure 4. Positive lateral flow assay for *A. fumigatus* (LDBio Diagnostic, France).

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

pathogenesis, 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 sequalae, 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.

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