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Review Article

Review Article

Challenges in the management of chronic pulmonary aspergillosis

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Abstract

The management of chronic pulmonary aspergillosis (CPA) presents multiple challenges. We present three cases that illustrate some of the most challenging aspects of caring for patients with CPA: specifically, antifungal drug resistance, drug interactions, coinfection with nontuberculous mycobacteria, and large-volume hemoptysis.

Key words: chronic pulmonary aspergillosis, case series, haemoptysis, non-tuberculous mycobacteria, resistance.

Introduction

Chronic pulmonary aspergillosis (CPA) is a progressive, debilitating infection associated with significant morbidity and several difficulties in diagnosis and management. Symptoms are nonspecific, mimicking other chronic respiratory disease, and the diagnosis may be challenging as fungal cultures lack sensitivity. Treatment with oral antifungals is the mainstay, but is often prolonged, resulting in significant side effects, cost and development of resistance. Guidelines for the treatment of CPA have only recently been published.[1,2] As tri-azole antifungal agents are the only class of oral antifungals active against *Aspergillus spp.*, loss of activity of this drug class is problematic. The most important challenges encountered by clinicians caring for patients with CPA are illustrated in the following brief case presentations.

Case 1

A 65-year-old female was referred with productive cough, fatigue, and weight loss for 3 months. She had a past medical history of chronic obstructive pulmonary disease requiring frequent steroid courses because of exacerbations. Her medications included inhaled salbutamol, inhaled formoterol/beclomethasone, inhaled tiotropium and oral prednisolone, currently 30 mg/day. She had a 60 pack/year history of smoking, occasional alcohol use, no recent travel and no known tuberculosis contacts. She had never lived abroad and had an office-based job.

Six weeks before presentation, a chest X-Ray showed a large cavity in the right upper lobe. On CT scan, a thick-walled cavity in the right upper lobe with intra-cavitary material was seen, on a background of emphysema (Fig. 1). She had a bronchoscopy with bronchoalveolar lavage (BAL)

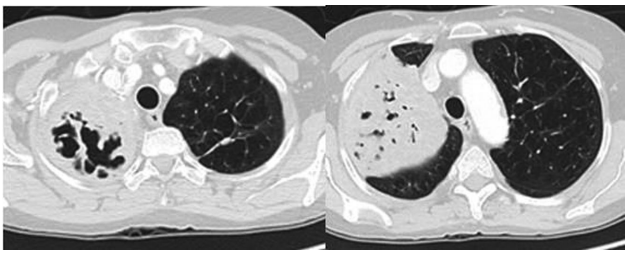

Figure 1. Chest CT scan of patient 1 on presentation, before initiation of antifungal therapy.

that grew *Mycobacterium avium* sensitive to macrolides. BAL culture was negative for fungi, but BAL galactomannan (GM) index (Platelia *Aspergillus* ELISA, Bio-Rad) was 9.6. Cytology was negative for malignancy. Aspergillus IgG was 11 mg/l (<40 mg/l) using ThermoFisher Scientific ImmunoCAP assay. She was started on rifampicin, ethambutol and azithromycin and referred to the National Aspergillosis Centre. A few days later, she developed visual blurring, and ethambutol was switched to moxifloxacin. Six weeks later, her symptoms had not improved and continued to experience weight loss and productive cough.

A repeat sputum culture was positive for *Aspergillus fumigatus*, fully sensitive to azoles, and repeat Aspergillus IgG at that time was positive at 66 mg/l. Mycobacterial sputum culture remained positive for *M. avium*. She was started on itraconazole; rifampicin was stopped due to interaction with itraconazole, and intravenous amikacin commenced. Four weeks later, she developed peripheral oedema and breathlessness, and itraconazole was changed to voriconazole. Within a few weeks, she reported significant improvement in productive cough and her weight stabilised. She was able to reduce her prednisolone from 30 mg to 15 mg daily.

Two months later, she developed further weight loss and worsening productive cough. *Aspergillus* immunoglobulin G (IgG) was 165 mg/l, and voriconazole level was low (trough level 0.26 mg/l). A repeat CT scan showed progressive disease, with extension of cavitary change in the right lung (Fig. 2). Mycobacterial culture was positive for M. avium and fungal culture was negative. Voriconazole dose was increased. Four months later, she reported subjective improvement. *Aspergillus* IgG decreased to 87 mg/l. Sputum cultures were positive for *M. avium*. Her prednisolone dose was reduced to 10 mg daily.

Case discussion

This patient was initially diagnosed with nontuberculous mycobacterial (NTM) pulmonary disease, although CPA developed concomitantly or shortly afterward. Initial sputum and BAL fungal cultures were negative. The sensitivity of routine sputum or BAL culture for fungi is poor, and culture onto fungal media is recommended to increase the yield; multiple cultures rather than a single culture are likely to increase sensitivity.[3] False-positive results are also common, as *Aspergillus* can represent airway colonisation. Use of BAL GM in this case alerted to the possibility of concomitant CPA; BAL GM has reasonable sensitivity and specificity for the diagnosis of CPA, although serum GM has poor sensitivity.[4,5] GM testing in sputum has not been validated and is not recommended at present.[1] Serology (precipitins or specific *Aspergillus* IgG) has been used as a biomarker of disease, although there is limited evidence to support this. In a study of posaconazole in CPA, reducing precipitin titres were associated with clinical improvement.[6]

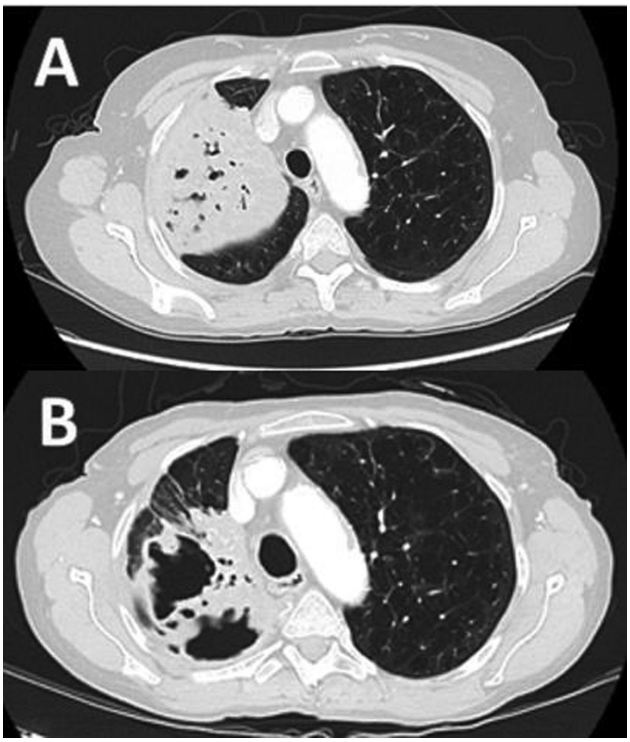

Figure 2. Patient 1: A) Chest CT scan before treatment initiation; B) 4 months after initiation of antifungal treatment.

Drug interactions between antifungal azoles and other medications are very common and often overlooked. As in this patient, an azole often needs to be co-administered with antimycobacterial treatment in NTM/CPA coinfected patients. Rifampicin cannot be administered with itraconazole, as CYP enzyme induction results in undetectable itraconazole levels. Other frequently missed interactions are co-administration of itraconazole with simvastatin, resulting in rhabdomyolysis, and of itraconazole with omeprazole or other proton-pump inhibitor, resulting in poor itraconazole absorption and subtherapeutic levels. Before prescribing, interactions affecting antifungal agents can be reviewed using online tools.[7,8]

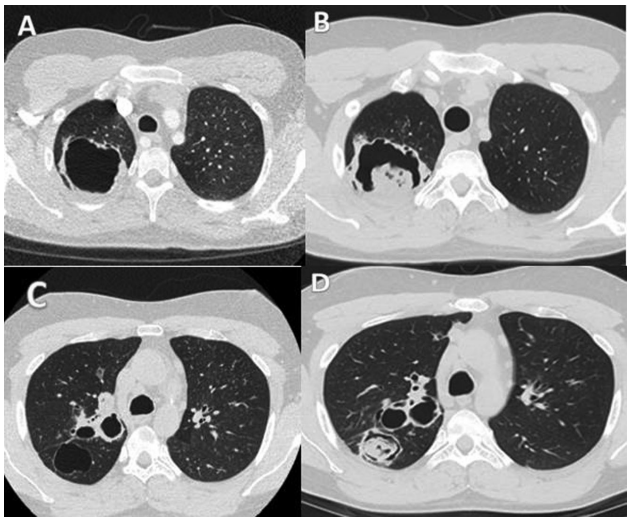

Figure 3. Patient 2: Panels A and C) Chest CT scan before referral (on itraconazole); panels B and D) 8 months after voriconazole started.

Emergence of CPA can occur several years after NTM infection;[9] the average time was 7 years in a series from Japan.[10] It can also present concurrently or even before diagnosis of NTM infection. A high index of suspicion for CPA should be present in patients with NTM who deteriorate on treatment or who present with worsening radiological findings, such as thickening of a pre-existing cavity or intracavitary material.[11] The risk factors for developing CPA following NTM infection were steroid use and cavity formation in a retrospective study.[12] Outcomes in these patients are generally poor.

Case 2

A 32-year-old male with CPA, on itraconazole for 2 years, was referred due to clinical deterioration. He presented with symptoms of several months' duration, including fatigue, a cough productive of purulent sputum, occasional hemoptysis, and frequent chest infections requiring antibiotics.

He had a past medical history of hyper-immunoglobulin E (IgE) syndrome, multiple pneumatocoeles, previous pyopneumothorax, CPA and previous requirement for bronchial artery embolization (BAE) due to large volume haemoptysis. His medications included inhaled salbutamol and flixotide, and oral itraconazole. He worked as an engineer, never smoked, had no known tuberculosis contacts, and no travel history.

A recent chest CT scan showed multiple cavities in the right upper lobe (Fig. 3). Initial investigations included a sputum culture positive for *Aspergillus fumigatus*, resistant to itraconazole (Table 1), and a very high *Aspergillus* IgG at 656 mg/lL. Random itraconazole levels were high at 22.4 mg/l. He was switched to voriconazole. Four weeks later, trough voriconazole levels were low (0.45 mg/l) and the dose was increased to 250 mg twice daily. In the subsequent weeks, he was taking voriconazole intermittently because of the development of photosensitivity. Three months after starting voriconazole, resistant *A. fumigatus* was isolated from sputum (Table 1).

Based on the resistant isolate, he was switched to oral posaconazole tablets 300 mg once daily. On follow up 4 weeks later, a pan-azole resistant isolate was identified on sputum culture. His *Aspergillus* IgG was now lower at 192 mg/l. Two months later, presented with large volume haemoptysis and underwent emergency bronchial artery embolization. Posaconazole was stopped, and he was given a 3-week course of intravenous liposomal amphotericin B. A repeat CT scan showed development of new aspergillomas within pre-existing cavities. (Fig. 3) He was started on gamma-interferon replacement therapy.

Discussion

This patient developed CPA on a background of hyper-IgE syndrome. Patients with hyper-IgE syndrome are susceptible to pulmonary Aspergillosis due to defective production of interleukin 17 (IL-17)-producing Th17 cells and associated neutrophil chemotaxis defects.[13] *Aspergillus* infection is a leading cause of death in patients with hyper-IgE syndrome.[14] Active cytokine profiling in patients with CPA showed significant impairment of IL-17 and IFN-gamma production compared to healthy controls, whereas the

Table 1. Consecutive *Aspergillus fumigatus* sputum isolates from patient 2.

	MIC (mg/l)				
Drug	On presentation	2 months	3 months	4 months	6 months
Itraconazole	>8	>8	>8	>8	>8
Voriconazole	2	4	8	4	4
Posaconazole	1	0.25	0.5	1	0.5
Isavuconazole			8	8	4
Amphotericin B	0.5	0.25	0.5	0.25	0.25

Note, EUCAST clinical breakpoints (in mg/l): itraconazole > 2; voriconazole > 2; posaconazole > 0.25; isavuconazole >1; amphotericin B > 2.

inflammatory cytokines TNF and IL-6 were increased, likely mediated by increased monocyte activity.[15] Therefore, the potential may exist for immunomodulatory therapy in patients with CPA and defects in the IFN-gamma production, although no controlled series exist, and this approach should only be considered as salvage therapy.[16]

In this patient, prolonged itraconazole therapy is likely the cause of the development of *Aspergillus* resistance. A switch to voriconazole was based on the sensitivity profile of an *Aspergillus* strain isolated on itraconazole therapy, but subsequent voriconazole resistant strains emerged rapidly. Emergence of resistance during therapy in CPA is a common and feared occurrence due to the lack of alternative oral antifungal agents. Risk factors for resistance development include poor drug levels, noncompliance with therapy, and high burden of disease, for example, extensive cavitary disease, or multiple aspergillomas.[17] *Aspergillus* has been shown to develop resistance readily, and several different resistant genotypes can arise simultaneously in patients challenged with azoles.[18] Single nucleotide substitutions in the *cyp51A* gene (such as G54) have been shown to arise on itraconazole treatment in CPA patients; these isolates typically retain voriconazole sensitivity.[19] In addition, strains with tandem repeat mutations (TR_{34}/L98H and TR_{46}/Y121F/T289A), originally described in environmental isolates, are being increasingly isolated from clinical samples. Both mechanisms are typically associated with pan-azole resistance, although voriconazole activity may be retained in the former, while voriconazole resistance is more common in the latter mechanism.[20,21] Finally, a few patients with pan-azole high level resistance (MIC > 8 mg/l for all azoles) have been described, likely carrying a combination of resistance mechanisms, yet to be elucidated.[22]

Case 3

A 52-year-old male, with a known diagnosis of CPA for 10 years, on a background history of pulmonary sarcoid, maintained on 10 mg of prednisone for more than 20 years, was referred for further management due to hemoptysis and the inability to tolerate itraconazole therapy due to severe gastro-intestinal side effects. He had previously undergone BAE following a prior episode of hemoptysis (details of BAE procedure not available). On initial assessment he described multiple episodes of haemoptysis in the preceding 2 months, totalling more than 2 l of blood. He underwent a further BAE bilaterally and was commenced on voriconazole therapy. He was diagnosed with gamma-interferon deficiency, interleukin 17 deficiency, and vitamin D deficiency. His voriconazole was discontinued 3 weeks into therapy due to significant hepatic derangement.

He continued to complain of hemoptysis off antifungal therapy, describing blood loss of approximately 10–20 ml every 2 weeks. He was commenced on posaconazole (liquid formulation); however, despite some improvement in symptoms he failed to achieve therapeutic levels, and required a further BAE, again bilateral, 2 months later, using 350–550 micron Poly Vinyl Alcohol embolization particles. Given this, and the failure to achieve therapeutic posaconazole levels, the decision was taken to discontinue posaconazole. His symptoms progressed, with further hemoptysis, and posaconazole was restarted. Six months later, he required emergency admission for hemoptysis of 500 ml at a time. He underwent further BAE; on this occasion the vascular radiologist was unable to catheterize a small branch of the left internal mammary artery. His condition stabilized, and he was discharged home, only to require readmission 2 months later for a further BAE; this admission was complicated by a health care associated pneumonia. One month later, he experienced further significant hemoptysis of >1.5 l and was readmitted. Despite right intercostal artery embolization, he had ongoing hemoptysis of >600 ml. To investigate this further, he had repeat CT pulmonary angiogram, which demonstrated a 2.5 cm pseudoaneurysm surrounded by thrombus and inflammatory tissue adjacent to the aspergilloma. A further attempted BAE was abandoned due to severe chest pain, and the decision made to intubate the patient to re-attempt embolization to stop the bleeding. Unfortunately, despite these efforts and successful embolization of the pseudoanerysm, he had ongoing hemoptysis and increasing oxygen and ventilatory requirements. A further CT pulmonary angiogram did not demonstrate any further sources of bleeding, and the patient passed away.

Discussion

Hemoptysis is a relatively common symptom in CPA and simple aspergillomas; it may be mild, but in some cases can be significant and of large volume, such as in our patient. The bleeding generally arises from abnormal or novel vascular nexus of small vessels derived from the systemic circulation. Large volume haemoptysis is potentially life threatening, and untreated carries a reported mortality of between 50 and 100%.[23] BAE is the preferred treatment for large volume hemoptysis, given the often poor surgical outcomes, and frequent contra-indications to thoracic surgery in patients presenting with haemoptysis of all causes.[23] Similarly in chronic pulmonary aspergillosis, BAE is the recommended therapy for moderate to severe haemoptysis.[1] BAE has a reported success rate of 50–90%; however, this will be operator dependent. Recurrent hemoptysis occurs in up to 50% of patients.[24] Refractory hemoptysis is an

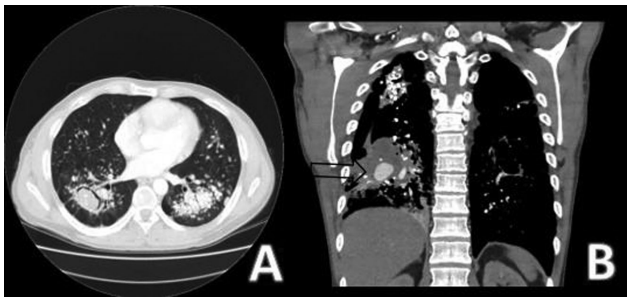

Figure 4. Patient 3: A) Chest CT scan on initial assessment; and B) pseudoaneurysm (arrow).

indication for considering surgery; however, this was unlikely to be an option in our patient, given his significant underlying lung disease and bilateral CPA (Fig. 4).[1] Adverse events associated with BAE include chest wall pain, embolic phenomena including stroke, renal impairment, or reactions secondary to intravenous contrast, and rarer sequelae such as dissemination of infection.[1,25] Bronchial artery aneurysms and pseudoaneurysms have been previously described in tuberculosis and other infections of the lung, including aspergillosis, and may occur in up to 11% of patients presenting with large volume hemoptysis associated with pulmonary infection.[26,27] Embolization is the recommended treatment of such aneurysms to control bleeding.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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