

Treatment of chronic pulmonary aspergillosis with voriconazole: review of a case series

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Abstract

Purpose Chronic pulmonary aspergillosis (CPA) is a rare disease that primarily affects subjects with moderate immunodepression and/or structural alterations in the lung.

Methods Data for patients with probable CPA were collected over 24 months. Patients with probable CPA received oral voriconazole, and clinical, laboratory and radiological follow-up was performed at 3, 6 and 12 months.

Results 21 patients (mean age 52.4 years) were evaluated. Factors predisposing to CPA were tuberculosis ($n = 8$), chronic obstructive pulmonary disease ($n = 7$), corticosteroids ($n = 14$), chemo- or radio-therapy ($n = 6$), tracheostomy or endotracheal prosthesis ($n = 5$), smoking ($n = 4$), asthma ($n = 3$), and chronic liver disease ($n = 3$). Sputum or bronchial aspirate cultures were positive for *Aspergillus* spp. in 14 cases (66.6 %). (1,3)- β -D-glucan on serum was positive in 16 cases (76.2 %). Excavated pulmonary thickening was evident in 14 patients (66.6 %) and in 9 of these cases (64.2 %) aspergilloma was present. [^{18}F]2-fluoro-2-deoxy-D-glucose-PET-CT was positive in 13/15 patients, and simple aspergilloma was diagnosed after surgical excision in one of the negative cases. All patients were treated with oral voriconazole. Therapy was discontinued due to skin toxicity ($n = 3$), liver toxicity ($n = 2$) and severe mental disorder ($n = 1$). At 12 months' follow-up, nine patients (42.9 %) were considered cured or improved.

Seven patients (33.3 %) died during follow-up, mainly due to underlying disease.

Conclusions A reasonable proportion of patients achieved cure or improvement with voriconazole, but 28.5 % of treated patients had to discontinue therapy because of toxicity. The high mortality makes it difficult to fully assess the real efficacy of voriconazole and to establish the correct duration of therapy.

Keywords Aspergillosis · *Aspergillus fumigatus* · Lung disease · Voriconazole · Triazole

Introduction

Aspergilli are filamentous fungi (molds) that grow on soil and decaying vegetation [1]. They are widespread in the environment as spores that regularly reach the lower respiratory tract through inhalation [2]. While spore inhalation is usually harmless in healthy individuals with intact host defence mechanisms, in those with predisposing risk factors exposure to *Aspergillus* may cause a spectrum of illnesses, with the lung being the most frequent site of disease [1, 2]. The most common *Aspergillus* species infecting humans is *A. fumigatus* [2]. The spectrum of *Aspergillus*-related diseases encompasses invasive aspergillosis, chronic pulmonary aspergillosis (CPA), aspergilloma, and allergic bronchopulmonary aspergillosis [1, 3, 4]. Invasive aspergillosis is a rapidly progressive disease that occurs in severely immunocompromised persons (i.e. patients with prolonged neutropenia, recipients of haematopoietic stem cell or solid organ transplant, patients with AIDS, and patients with chronic granulomatous disease) and is frequently fatal [1]. Aspergilloma is a fungal mass (fungus ball) that develops in a pre-existing cavity in the lung parenchyma without

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invasion of hyphae into the lung tissue [3]. It is usually asymptomatic and the most frequently experienced symptom is haemoptysis [3]. Allergic bronchopulmonary aspergillosis, which commonly affects patients with asthma or cystic fibrosis, is caused by a hypersensitivity reaction to *Aspergillus* antigens [1, 3]. CPA is a rare syndrome [3] which occurs in mildly immunocompromised patients with underlying lung disease, and slowly progresses to gradual lung tissue destruction [1].

Due to the rarity of CPA, the non-specificity of its symptoms, and the complex clinical background of patients chronically affected, this form of pulmonary aspergillosis has proven difficult to define as a disease entity and to sub-categorise [4–8]. The nomenclature describing this form of aspergillosis is also poorly standardised. Guidelines issued by the Infectious Diseases Society of America (IDSA) in 2008 recognised three major subtypes of CPA, namely chronic necrotising pulmonary aspergillosis, chronic cavitary pulmonary aspergillosis and aspergilloma [9]. In the present article, the general term CPA will be used to include all these subtypes.

Chronic pulmonary aspergillosis usually affects middle-aged and elderly people with underlying structural lung conditions including chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis sequelae, and thoracic surgery [3]. Other host factors predisposing to the development of CPA are concomitant diseases leading to mild immunodepression, such as diabetes mellitus, chronic liver disease, alcoholism, malnutrition, rheumatoid arthritis, and ankylosing spondylitis [3]. CPA patients usually experience constitutional symptoms such as fever, fatigue, and weight loss, as well as respiratory symptoms such as breathlessness, cough, and haemoptysis. The diagnosis of CPA is complex and should take into account host predisposing factors, clinical manifestations (symptoms and radiological features), and microbiological evidence [4, 9]. Differential diagnosis should also be performed to exclude diseases with similar clinical manifestations. Diagnosis confirmation requires the histological demonstration of lung tissue invasion by *Aspergillus* species and growth of the fungus in cultures. However, invasive biopsy procedures are rarely performed in CPA patients due to their comorbidities and reduced respiratory function, while transbronchial biopsy specimens or percutaneous aspirates yield poor results. As a consequence, diagnosis confirmation is usually delayed in these patients [3].

Untreated CPA patients have a ≥ 50 % 5-year mortality, according to recent estimates [10–12]. Current guidelines recommend therapy with antifungal agents for the treatment of CPA [9, 13]. Voriconazole, a broad spectrum triazole antifungal agent, has recently emerged as a primary option for CPA treatment [9, 13–18]. The literature regarding the use of voriconazole in CPA is quite limited,

however, and many aspects of voriconazole therapy, such as effectiveness and treatment duration, need to be better documented and defined.

To provide information on the management of patients with CPA in clinical practice, we retrospectively analysed the medical records of patients referring to our centre with probable CPA. Before initiating voriconazole, a diagnosis of CPA was confirmed. Patients received voriconazole for up to 6 months and were followed for 12 months.

Methods

Patients and data collection

This study analysed the medical records of non-consecutive, selected patients who were referred to the Institute of Infective Diseases of the University of Verona, Italy, with probable CPA between 1 August 2010 and 31 July 2012. Patients were treated with voriconazole after diagnosis confirmation. The following data were collected and analysed: demographic characteristics, clinical characteristics on presentation, medical history, diagnostic procedures, voriconazole regimen, and outcomes at 3, 6, and 12 months from treatment initiation. The study was notified to the Institutional Review Board, Azienda Ospedaliera Universitaria Integrata di Verona, Italy. Because of the retrospective observational design of the study, no signed informed consent was required from the patients.

Diagnosis of CPA

The diagnosis of CPA was considered confirmed if all the following criteria were fulfilled: (a) constitutional symptoms (fever, weight loss) and/or respiratory symptoms (cough, dyspnoea, haemoptysis) for >3 months; (b) presence of lung infiltrates with or without cavities on chest computed tomography (CT); (c) exclusion by means of bronchoscopy or CT-guided biopsy of diseases resulting in similar signs and symptoms (e.g. tuberculosis, lung cancer); (d) histological identification of *Aspergillus* spp. in biopsies, or sputum cultures positive for *Aspergillus* spp., or positive galactomannan assay of bronchoalveolar lavage (BAL) specimens; (e) presence of precipitating (IgG) antibodies to *Aspergillus* in serum; (f) exclusion of neutropenia or severe immunosuppression during the past 6 months (haematological malignancies, AIDS, haematopoietic stem cell or solid organ transplantation, prolonged treatment with steroids at doses >0.2 mg/kg/day prednisolone). Cultures were tested for the presence of *Aspergillus* spp. using blood agar and Sabouraud's dextrose agar (SDA) (Oxoid, Basingstoke, England) and incubated at 25, 30, and 37 °C for 21 days. Serum *Aspergillus* precipitating

IgG (precipitins) was assayed using a double immunodiffusion test, according to Ouchterlony (positivity indicated by detectable precipitin arcs). The presence of the *Aspergillus* marker galactomannan in BAL specimens was tested by means of a Platelia® *Aspergillus* enzyme immunoassay EIA (Bio-Rad, Marne La Coquette, France) with positivity defined by an optical density (OD) index >0.5. The galactomannan assay was also performed on serum samples. Serum samples were also tested for the presence of (1,3)- β -D-glucan (BG), another diagnostic marker for aspergillosis, using a Fungitell assay (Associated with Cape Cod, Falmouth, MA, USA) with positivity defined by levels ≥ 80 pg/ml. Biopsy specimens were stained with Haematoxylin–Eosin, Grocott's methenamine silver stain, periodic acid schiff stain and acid fast stain to exclude other co-infections. Besides CT, other radiological pulmonary examinations on presentation included chest radiography performed on all patients and [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)/CT performed on selected patients only.

Treatment and follow-up

After confirmation of a diagnosis of CPA, patients initiated therapy with oral voriconazole, according to the centre protocol. On the first day of treatment, patients received 800 mg oral voriconazole, decreasing to 400 mg/day (in two doses), according to the manufacturer's instructions [19]. During the first weeks of treatment, biochemical parameters (haemochromocytometric, hepatic, and renal function tests) and inflammatory markers were evaluated weekly. 15 and 30 days after treatment initiation, chest radiographs were performed. In the following weeks, these were repeated if necessary. The response to treatment was assessed at 3, 6 and 12 months from treatment initiation, as previously described. After 3 months of treatment, the disease was considered resolved if patients were free of CPA-related symptoms and their CT scans showed complete disappearance of CPA-related features seen at presentation. Patients who achieved disease resolution interrupted voriconazole treatment after 3 months and were followed up at 6 and 12 months. Patients with complete resolution of clinical symptoms but still showing CPA-related lung abnormalities on CT scans were considered improved and continued treatment with voriconazole for 3 additional months. Patients with unchanged clinical symptoms and radiological features also continued treatment with voriconazole for 3 additional months. The response to treatment was assessed again at 6 months. At 6 months, voriconazole treatment was discontinued in all patients, regardless of outcome. All patients were followed for 6 additional months and evaluated again at 12 months.

Data analysis

Selected data were expressed as mean value [$\pm$ standard deviation (SD)]. Treatment outcomes were expressed as percentages.

Results

Patient characteristics

Retrospective analysis of medical records identified 21 patients who received voriconazole therapy for CPA and were followed for 1 year at the study centre. Patients' demographic and clinical characteristics are shown in Table 1. Their mean age was 52.4 (± 17.3) years and the majority were men (15/21, 71.4 %). Fever was the most frequently reported symptom on presentation (16/21, 76.2 %), followed by cough (13/21, 61.9 %), haemoptysis (11/21, 52.4 %), weight loss (8/21, 38.0 %), and acute respiratory insufficiency (2/21, 9.5 %). Most patients (15/21, 71.4 %) had one or more underlying pulmonary diseases predisposing to the development of CPA. In 38.0 % of patients (8/21), the underlying predisposing condition was previous tuberculosis, while 33.3 % of patients (7/21) had COPD and 14.3 % (3/21) had bronchial asthma. One patient had cystic pulmonary dysplasia and 1 patient had treated lung carcinoma. Factors predisposing to mild immunodepression were also present: two-thirds of the patients had taken corticosteroids (14/21, 66.7 %) and 28.6 % (6/21) had received chemo- or radiotherapy for malignancies including intestinal, laryngeal, pharyngeal, or lung carcinoma. None of the patients were still receiving corticosteroids, chemo- or radiotherapy. Other concomitant diseases associated with mild immunodepression and thus predisposing to CPA were chronic liver disease ($n = 3$), type 2 diabetes mellitus ($n = 2$), chronic pancreatitis ($n = 1$), anorexia ($n = 1$) and alcoholism ($n = 1$). Several patients presented with more than one of these conditions. Other conditions potentially contributing to CPA were tracheostomy ($n = 4$), cigar smoking ($n = 2$), marijuana use ($n = 2$) and endotracheal prosthesis ($n = 1$). Four of the 21 patients were current smokers (19 %), 6 were non-smokers (28.6 %), and 11 were former smokers (52.4 %).

Diagnosis of CPA

Chest radiography and CT confirmed the presence of thickening and cavities, especially in the upper and middle lobes of the lung in 66.6 % of patients (14/21) on presentation (Table 2). In most patients with cavities (9/14, 64.3 %), an aspergilloma (fungus ball) was present in the cavity. Other lung abnormalities included bronchiectasis in 5 patients

Table 1 Summary of patient demographic and clinical characteristics

Patient	Sex/age (years)	Symptoms	Predisposing factors	Additional predisposing factors
1	M/49	Fever, cough, weight loss	Systemic corticosteroids, chronic hepatitis	Autoimmune nephropathy
2	M/70	Fever, cough, weight loss	TBC sequelae, COPD, inhaled corticosteroids	Smoke (Italian cigars)
3	M/70	Cough, fever	COPD, diabetes, inhaled corticosteroids	Smoke (Italian cigars)
4	F/40	Cough, haemoptysis	TBC sequelae, COPD, inhaled corticosteroids	Chronic pancreatitis
5	F/42	Acute respiratory insufficiency	Anorexia, cystic pulmonary dysplasia	Bilateral pneumothorax, empyema
6	M/60	Fever, cough	Previous chemotherapy for intestinal cancer	None
7	F/66	Fever, cough, haemoptysis, weight loss	TBC sequelae	Previous left upper lobectomy for CPA
8	M/44	Acute respiratory insufficiency	TBC sequelae, COPD, liver cirrhosis, inhaled corticosteroids	None
9	F/29	Fever, cough, haemoptysis	TBC sequelae	None
10	M/73	Fever, cough, dyspnoea	TBC sequelae, COPD, inhaled corticosteroids	None
11	M/69	Fever, cough, weight loss	Previous chemo- and radiotherapy for pharyngeal cancer, COPD, systemic corticosteroids	Tracheostomy
12	M/43	Fever, cough, haemoptysis	Previous chemo- and radiotherapy for pharyngeal cancer, TBC sequelae	Tracheostomy
13	M/38	Fever, weight loss, haemoptysis	Previous chemo- and radiotherapy for pharyngeal cancer	Tracheostomy
14	F/34	Fever, haemoptysis	Systemic corticosteroids for asthma	None
15	M/40	Fever, cough	TBC sequelae, COPD, alcoholism, inhaled corticosteroids	Smoke (marijuana)
16	M/54	Chest pain, haemoptysis	Chronic hepatitis, diabetes, systemic corticosteroids for atopic dermatitis	Smoke (marijuana)
17	M/87	Fever, weight loss, haemoptysis	Systemic corticosteroids for rheumatoid arthritis	None
18	M/37	Fever, cough, dyspnoea	Systemic corticosteroids for asthma	Empyema
19	M/65	Fever, cough, weight loss, haemoptysis	Previous chemo- and radiotherapy for lung cancer, systemic corticosteroids	Endotracheal prosthesis
20	F/22	Haemoptysis	Asthma, inhaled corticosteroids	None
21	M/68	Fever, weight loss, haemoptysis	Previous surgery and radiotherapy for laryngeal cancer	Tracheostomy

COPD chronic obstructive pulmonary disease, *CPA* chronic pulmonary aspergillosis, *TBC* tuberculosis

(23.8 %), fibrosis in 3 patients (14.3 %), peripheral thickening with patent bronchi in 2 patients (9.5 %) and pleuritis in 2 patients (9.5 %).

Cultures of sputum or bronchial aspirate were positive for *Aspergillus* spp. in 66.6 % of patients (14/21), with *A. fumigatus* being the predominant species (12/14, 85.7 %). The cultures of two patients were positive on blood agar and SDA for *A. niger* (14.3 %). The presence of *Aspergillus* hyphae was demonstrated by histological assessment in six patients. The identification of the *Aspergillus* markers galactomannan and BG failed to provide clear-cut results.

All 21 patients were tested for the presence of galactomannan in serum samples, with only 2 (9.5 %) patients proving positive. By contrast, the BG assay, performed on serum samples of all patients, yielded 16 (76.2 %) positive results and 5 (23.8 %) negative results [mean level of BG 255 (± 109.39) pg/ml]. The galactomannan assay was also performed in BAL samples of nine patients, yielding positive results in all nine cases [mean OD index 4.95 (± 2.63)].

To get further insight into the structural abnormalities detected by CT, [^{18}F]FDG-PET/CT was performed in 15/21 patients. We planned [^{18}F]FDG-PET/CT in all patients but

Table 2 Summary of diagnostic procedures

Patient	Histology (<i>Aspergillus</i> hyphae)	Culture (<i>Aspergillus</i> spp)	GM BAL	GM serum	BG serum	Rx/CT	PET/CT
1	Positive	Negative	NA	Negative	Negative	Thickening with cavity in upper lobe	Positive (SUV max 6.1)
2	NA	Positive (<i>A. niger</i>)	NA	Negative	Negative	Multiple peripheral opacities in right lower lobe, some of them with cavities	Positive (SUV max 5.1)
3	NA	Negative	Positive (OD 4.2)	Negative	Positive (186 pg/mL)	Peripheral thickening with patent bronchi	NA
4	NA	Positive	NA	Negative	Positive (116 pg/mL)	Fibrosis and bronchiectasis in left upper lobe	Positive (SUV max 6.1)
5	NA	Positive	NA	Negative	Negative	Thickening in right upper lobe, pleural effusion	NA
6	NA	Positive	NA	Negative	Positive (226 pg/mL)	Thickening with cavity containing fungus ball	Positive (SUV max 6.0)
7	Positive	Negative	Positive (OD 5.0)	Negative	Positive (196 pg/mL)	Left apical infiltration with cavity and fungus ball	Positive (SUV max 5.0)
8	NA	Positive	NA	Negative	Positive (230 pg/mL)	Bilateral apical thickenings with cavities, bronchiectasis	NA
9	Positive	Negative	NA	Negative	Positive (125 pg/mL)	Cystic bronchiectasis, lung fibrosis	NA
10	NA	Negative	Positive (OD 3.2)	Negative	Positive (426 pg/mL)	Lung fibrosis, bronchiectasis in left lower lobe	NA
11	NA	Positive	Positive (OD 1.4)	negative	Positive (240 pg/mL)	Lesion with cavity containing fungus ball, in right mid zone	Positive (SUV max 6.0)
12	NA	Positive	NA	Positive (OD 4.4)	Negative	thickenings with cavities containing fungus ball	Positive (SUV max 5.7)
13	NA	Positive	NA	Negative	Positive (114 pg/mL)	Thickening with cavity in middle lobe	Positive (SUV max 6.5)
14	Positive	Negative	Positive (OD 4.2)	Negative	Positive (187 pg/mL)	Right apical thickening with cavity	Positive (SUV max 6.4)
15	NA	Positive	NA	Negative	Positive (286 pg/mL)	Right apical thickening with cavity	Positive (SUV max 7.2)

Table 2 continued

Patient	Histology (<i>Aspergillus</i> hyphae)	Culture (<i>Aspergillus</i> spp)	GM BAL	GM serum	BG serum	Rx/CT	PET/CT
16	NA	Positive (<i>A. niger</i>)	Positive (OD 11)	Negative	Positive (230 pg/mL)	Thickening with cavity containing fungus ball	Negative
17	Positive	Positive	Positive (OD 4.6)	Negative	Positive (327 pg/mL)	thickening in left upper lobe with cavity containing fungus ball	Positive (SUV max 6.9)
18	NA	Positive	NA	Positive (OD 1.1)	Positive (482 pg/mL)	basal bronchiectasis, pleural effusion	NA
19	NA	Positive	Positive (OD 6.3)	Negative	Positive (382 pg/mL)	Thickening with patent bronchi in right upper lobe with cavity containing fungus ball	Positive (SUV max 7.3)
20	positive	Negative	NA	Negative	Negative	Thickening with cavity containing fungus ball	Negative
21	NA	Positive	Positive (OD 4.6)	Negative	Positive (327 pg/mL)	Thickening with cavity containing fungus ball	Positive (SUV max 6.5)

BAL bronchoalveolar lavage, BG (1 $\rightarrow$ 3)- β -D-glucan assay, CT computed tomography, GM galactomannan assay, NA not available, OD optical density, PET positron emission tomography, Rx radiography, SUV standardised uptake value

for three patients it was not available, two patients had clinical conditions precluding the scan and 1 patient did not consent. The majority of patients (13/15, 86.6 %) showed hypermetabolic pulmonary lesions, which suggested the presence of an inflammatory process. In one of the two patients with aspergilloma and no hypermetabolic lesions, the fungal mass was removed by surgery and the patient was diagnosed with simple aspergilloma (i.e. aspergilloma with no tissue invasion by *Aspergillus* hyphae).

Treatment and outcomes

All 21 patients, including patient 1 diagnosed with simple aspergilloma during follow-up, initiated treatment with oral voriconazole according to the protocol of the study centre. Two patients discontinued voriconazole treatment after 3 days and 2 weeks, respectively, due to adverse events. One patient was treated with surgery and the other was switched to another antifungal agent (posaconazole). More than half of the patients stayed on treatment with voriconazole for at least 3 months (13/21, 61.9 %). Four patients (19.1 %) were lost to follow-up (2 at 3 months, 1 at 6 months, and 1 at 12 months).

Detailed treatment outcomes of the 21 patients are reported in Table 3. Disease resolution was achieved by 7/21 patients (33.3 %), after 3 months for 5 patients and after 6 months for 2 patients. Two of 21 patients yielded

negative precipitin tests. Of the 7 patients who achieved resolution, 3 were treated with voriconazole only, 3 received a combination of voriconazole and surgery, and 1 received surgical treatment only. Five patients treated with voriconazole for 3 to 6 months were substantially improved at 6 months, as shown by the resolution of clinical symptoms, reduction of pulmonary lesions, and decrease of inflammatory markers. Two of these patients maintained their improvement up to the last follow-up visit, 6 months after treatment discontinuation (patients four and ten), while one patient with improvement at 6 months had a disease relapse at 12 months. Therefore, 42.9 % (9/21) of all patients in this case series had a complete resolution or a substantial improvement of their condition at 12 months. Seven patients (33.3 %) died during follow-up due to their underlying diseases ($n = 6$) or in accidents ($n = 1$).

Treatment tolerability

Treatment with voriconazole was discontinued in 6 patients (28.5 %) due to adverse events [severe cutaneous adverse events ($n = 3$), liver toxicity ($n = 2$), hallucinations ($n = 1$)]. Severe cutaneous events (pemphigoid reaction) occurred after 4–5 months of treatment, while liver toxicity leading to treatment discontinuation developed immediately after voriconazole initiation in one patient with

Table 3 Summary of treatment outcomes

Patient	Therapy	3 months	6 months	12 months
1	Voriconazole discontinued due to liver toxicity, surgery	Complete recovery	Negative precipitin assay	
2	Voriconazole discontinued after 4 months due to skin toxicity	Complete recovery		
3	Voriconazole for 3 months	Complete recovery		
4	Voriconazole discontinued after 5 months due to skin toxicity	Stable	Improvement maintained	Improved
5	Voriconazole	Died after 20 days		
6	Voriconazole for 4 months	Stable	Died after 4 months	
7	Voriconazole discontinued after 4 months due to skin toxicity	Stable	Improved	Disease relapse
8	Voriconazole for 2 months	Lost		
9	Voriconazole, pneumonectomy	Postoperative empyema	Complete recovery	
10	Voriconazole for 3 months	Improved	Improvement maintained	Improved
11	Voriconazole for 3 months, discontinued due to liver toxicity	Stable	Died	
12	Voriconazole for 6 months	Stable	Improved	Died
13	Voriconazole for 3 months	Stable	Died	
14	Voriconazole for 3 months	Improved	Improvement maintained	Lost
15	Voriconazole for 2 months	Lost		
16	Voriconazole for 1 month	Died		
17	Voriconazole discontinued due to hallucinations and replaced by posaconazole, bronchial artery embolisation	Complete recovery	Negative precipitin assay	
18	Voriconazole, surgery	Improved	Complete recovery	
19	Voriconazole for 4 months	Improved	Died	
20	Voriconazole for <2 months with no changes, surgery	Complete recovery		
21	Voriconazole for 6 months	Improved	Lost	

chronic hepatitis and after 3 months of treatment in the other patient.

Discussion

In this case series, typical radiological manifestations of CPA, such as lung excavated thickening, were present in 71.4 % (15/21) of patients. In 12 out of 21 patients, pulmonary structure alterations (mostly tuberculosis sequelae or COPD) were present before diagnosis and thus these patients were predisposed to CPA. Another typical CPA-predisposing condition of this case series was mild immunodepression which was present in the majority of patients (85.7 %). The combination of clinical symptoms, radiological findings, and microbiological assessments led to the confirmation of CPA diagnosis in all patients, with the exception of one patient who was diagnosed with simple aspergilloma after surgery. Treatment with oral voriconazole for 3 to 6 months allowed 42.8 % of patients to achieve disease resolution or a substantial improvement. More than 60 % of patients could be treated with voriconazole continuously for up to 3 months, with no major tolerability problems.

The criteria used for confirming the diagnosis of CPA in this case series were based on those originally proposed by

Denning et al. in 2003 as well as by others more recently [4, 20, 21]. The criteria by Denning et al. and Felton et al. also require elevated inflammatory markers but we did not consider these diagnostic criteria because it is regarded as too non-specific. As pointed out in a recent case series, the clinical manifestations of the various CPA subtypes are overlapping and their distinction is not essential from a therapeutic perspective, as the treatment approach to these subtypes is the same [7]. However, it is important to distinguish simple aspergilloma (i.e. a mostly asymptomatic fungus ball that develops in a pre-existing pulmonary cavity and shows no radiological progression) as its prognosis and treatment are different (simple aspergilloma has a better prognosis than other CPA forms and can be treated by surgical resection) [7, 8]. In the present case series, one patient with simple aspergilloma was indeed successfully treated by surgical resection.

In agreement with the findings reported in the literature, the most common host factors predisposing to CPA were previous tuberculosis, COPD, and mild immunodepression [4, 8, 11, 22–25]. The potential contribution to the development of CPA of other, less known risk factors was suggested by this case series. These factors were cigar smoking and marijuana use, and the presence of a tracheostomy and endotracheal prosthesis. Marijuana smoking has been associated with various aspergillosis forms including CPA,

although the association appears to be uncommon [26–28]. Italian cigars, which are made of fermented tobacco, have also been suggested as additional risk factors for CPA. According to our observations, the presence of tracheostomy tubes and endotracheal prosthesis can be expected to significantly alter the anatomical barriers leading to increased spore inhalation and increased risk of *Aspergillus* colonisation.

Confirming the diagnosis of CPA is complicated by the fact that thorascopic or open-lung biopsies are rarely performed in patients with CPA due to the risk of complications associated with underlying pulmonary diseases. In addition, the isolation of *Aspergillus* spp. from sputum samples does not discriminate between simple colonisation and infection [21]. Most patients with CPA, including those with simple aspergilloma, have positive serum IgG antibodies to *Aspergillus* [5, 29]. In a recent study, this test was positive in >95 % of cases [11]. In another study, the test was positive in 89.3 % of cases compared to only 50 % positivity with the galactomannan assay [30]. The galactomannan diagnostic marker and the BG assay have been extensively studied for use in invasive fungal diseases. The galactomannan assay is approved for the diagnosis of invasive pulmonary aspergillosis [31]. However, the performance of these assays in CPA is less well documented and more controversial. In the present case series, and in agreement with the findings from other studies, the galactomannan assay on sera was negative in most patients, while it seemed more sensitive on BAL specimens [5, 32]. In a recent study, the detection of galactomannan antigen in BAL specimens was found to be more sensitive (85.7 %) and more specific (76.3 %) than the detection in the serum of CPA patients [33]. Furthermore, a recent study in 334 patients with CPA concluded that the serum galactomannan test cannot be used for the serological diagnosis of CPA [34]. In our case series, the serum assay for BG was positive for the majority of patients (76.1 %). The contrasting results obtained with the two diagnostic markers highlight the need for improved diagnostic tools in CPA, as well as the importance of interpreting the results of serological tests by taking into account the information provided by clinical, microbiological, and radiological assessments [5, 35].

Chest imaging revealed the presence of cavities containing in most cases a fungus ball in almost 70 % of patients. In the remaining patients, however, pulmonary lesions were less specific and less suggestive of fungal disease. To further investigate these pulmonary lesions, selected patients underwent assessments by [^{18}F]FDG-PET/CT. This technique allows identification of metabolically active cells, such as inflammatory or malignant cells, which accumulate [^{18}F]FDG resulting in a distinct image on PET [36]. This technique was recently evaluated in patients with

invasive fungal diseases and was demonstrated to be useful for the diagnosis and staging of this disease [36–38]. Of the 15 patients analysed here by [^{18}F]FDG-PET/CT, 13 were found to be positive (presence of hypermetabolic lesions), confirming the presence of an inflammatory process. The two patients whose [^{18}F]FDG-PET/CT findings were negative were also asymptomatic (with the exception of episodes of haemoptysis for which the two patients were referred to the study centre), suggesting that the correct diagnosis might be simple aspergilloma. One of the two patients underwent surgery, which confirmed the diagnosis of simple aspergilloma. These results suggest that [^{18}F]FDG-PET/CT may be useful for discriminating between simple aspergilloma and complex aspergilloma. This technique may also have potential for monitoring the response to antifungal treatment, as serum precipitins and BG assay often remain positive after stabilisation of radiological features.

Chronic pulmonary aspergillosis is a slowly progressive disease leading to lung destruction if untreated. The current consensus recommends treatment with antifungal agents, including voriconazole. So far, the evidence supporting the use of voriconazole for the treatment of CPA is limited and based on small studies. The outcomes of the present case series are in line with those described in the literature. In a prospective Japanese study of 71 non-immunocompromised CPA patients treated with voriconazole, 60.6 % of patients had a good response, 26.8 % had no response and 5.6 % had progression [17]. In a prospective multicentre trial of 41 patients with minimally or non-immunocompromised CPA, voriconazole therapy resulted in a 6-month global success rate of 53 % for chronic necrotising aspergillosis and 14 % for chronic cavitary aspergillosis (32 % overall) [16]. Sambatakou et al. found a 43 % complete or partial response in sub-acute invasive pulmonary aspergillosis and 80 % response in CPA in their prospective trial of 39 patients treated with voriconazole [14]. In a retrospective study of 24 patients with CPA, 58 % of patients had improved radiological findings and mycologic eradication following voriconazole therapy [22]. In our case series, long-term treatment with voriconazole was not tolerated by 6 of the 21 patients (28.5 %), with 3 cases of skin toxicity, 2 cases of hepatotoxicity (in 2 patients with impaired liver function), and 1 severe psychiatric episode. A similar profile of adverse events was reported in other studies with voriconazole [14, 16, 17, 22]. The high mortality rate, mostly due to the underlying conditions of the patients, makes it difficult to assess the effectiveness of long-term antifungal therapy. In patients with CPA, most of whom have a reduced life expectancy, it is difficult to establish a reasonable duration of treatment and to decide whether a prolonged treatment is better than a short one. Long-term treatment is controversial not only due to the poor

tolerability of triazole antifungal agents, but also because it has been associated with the development of resistant fungal strains [5, 39]. The development of resistance may also account for the limited improvement and the occurrence of relapse after long-term treatment [5, 39].

This study has several limitations including a small sample number, retrospective design, and absence of a control. Despite this, our study provides a glimpse into the real-life management of patients presenting with probable CPA, from diagnosis confirmation to long-term treatment with antifungal agents and follow-up. It may thus provide evidence-based guidance for the management of these difficult-to-treat patients.

Conclusions

The diagnosis of CPA is complex as it needs to be based on the combination of several factors. In addition, the manifestations of the disease overlap with those of other pulmonary conditions. CPA is a slowly progressive disease with a negative prognosis. Therapy with antifungal agents is recommended, although optimal treatment regimens still need to be defined. The outcomes of this case series show that long-term treatment (up to 6 months) with voriconazole was feasible and resulted in disease resolution or substantial improvement in a reasonable proportion of patients. However, poor tolerability of anti-fungal therapy and the mortality rate (mostly due to underlying conditions) remained substantial. The effectiveness of antifungal therapy for CPA needs to be further investigated. Improved CPA diagnostic procedures and assays for monitoring the response to treatment are also urgently needed.

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