Chronic Pulmonary Aspergillosis - Case Series and Review of Indian Literature

Vikas Marwah, Robin Choudhary, Deepu K. Peter, Gaurav Bhati, Kunal Kumar, Akhil R, Shafin Babu

Department of Pulmonary, Critical Care and Sleep Medicine, Army Institute of Cardiothoracic Sciences, Pune, Maharashtra, India

Abstract

Aspergillus species, especially *Aspergillus fumigatus*, can cause varied pulmonary manifestations depending on the host immune status and duration of infection. Chronic pulmonary aspergillosis (CPA) is an under-reported entity, and its diagnosis remains a diagnostic challenge for clinicians. CPA can have varied presentations including chronic cavitary pulmonary aspergillosis (CCPA), subacute invasive pulmonary aspergillosis, and chronic fibrosing pulmonary aspergillosis. Underlying lung diseases such as chronic obstructive pulmonary disease and sequelae of pulmonary tuberculosis predisposes these individuals to CPA. These cases can present as chronic cough with hemoptysis even requiring emergency bronchial artery embolization. Here, we present a series of four CCPA cases who were diagnosed on the basis of clinico-radiological features and the *Aspergillus*-specific IgG antibody levels. A review of case series published in India is also presented.

Keywords: *Aspergillus*-specific IgG, chronic pulmonary aspergillosis, voriconazole

Introduction

Chronic pulmonary aspergillosis (CPA) includes a spectrum of manifestations such as chronic cavitary pulmonary aspergillosis (CCPA), subacute invasive pulmonary aspergillosis (IPA), and chronic fibrosing pulmonary aspergillosis (CFPA).[1,2] A disease duration of more than 3 months distinguishes CPA from acute and subacute pulmonary aspergillosis. These diseases are generally seen in individuals with prior structural lung diseases including sequelae of pulmonary tuberculosis, allergic bronchopulmonary aspergillosis, sarcoidosis, lung cancer, emphysema, and chronic obstructive pulmonary disease (COPD).[3,4] However, the disease entity of subacute IPA is also seen in individuals with variable degree of immunosuppression such as diabetes, human immunodeficiency virus (HIV), and alcoholism.[5,6] Herein, we present a case series of four cases of CCPA and a review of Indian literature.

Case Reports

Case 1

A 56-year-old man with morbid obesity was admitted to our hospital with multiple episodes of hemoptysis of about 50 ml each and shortness of breath for the last 4 years. He was a known case of Type 2 diabetes mellitus and primary hypertension. His diabetes mellitus was poorly controlled and he was on oral hypoglycemic drugs. His vital parameters were within normal limits. His general examination revealed bilateral pitting pedal edema. On evaluation, his laboratory data showed normal hemogram (hemoglobin 15.9 g/dl, total leukocyte count 7500/cumm, differential count – neutrophils 65%, lymphocytes 25%, platelets 2.5 lakhs/cumm), blood urea 40 mg/dl, and serum creatinine 1.6 mg/dl. His liver function tests and coagulation profile were normal. His electrocardiogram showed left ventricular hypertrophy. Echocardiography confirmed the same along with Grade I diastolic dysfunction. Chest radiograph revealed reticulonodular opacities in the right middle and lower zones. He underwent a computed tomogram of the chest which elucidated subsegmental collapse consolidation in the superior lingular segment of the left upper lobe and collapse consolidation in the right middle

Access this article online

Quick Response Code:

Website: www.ijrc.in

DOI: 10.4103/ijrc.ijrc_98_20

Address for correspondence: Dr. Robin Choudhary, Department of Pulmonary, Critical Care and Sleep Medicine, Army Institute of Cardiothoracic Sciences, Pune - 411 040, Maharashtra, India.
E-mail: robinch19@gmail.com

How to cite this article: Marwah V, Choudhary R, Peter DK, Bhati G, Kumar K, Akhil R, *et al*. Chronic pulmonary aspergillosis - Case series and review of Indian literature. Indian J Respir Care 2021;10:230-5.

Received: 11-09-2020 **Revised:** 04-02-2021

Accepted: 05-04-2021 **Published:** 14-06-2021

lobe [Figure 1a]. During the course of hospitalization, he had an episode of massive hemoptysis. Emergency bronchoscopic cold saline and adrenaline irrigation was performed which helped in the temporary control of hemoptysis. However, in view of persisting symptoms, his bronchoscopy was repeated, and his bronchial wash fluid and postbronchoscopic sputum was sent for microscopic studies and appropriate cultures. The microscopic studies revealed narrow septate fungal hyphae with acute angle branching, presumptively, *Aspergillus* species, and no malignant cells were seen. The *Aspergillus*-specific IgG was raised (45 mgA/l) in this patient.

He was commenced on antifungal agents (oral voriconazole with dosing of 400 mg twice daily for 24 h and 200 mg twice daily for 6 weeks). He was also administered injectable antifungals during the initial acute period. The patient showed significant improvement clinically and had no further episodes of hemoptysis. Repeat computed tomogram of the chest, after 6 weeks of antifungal treatment, showed that resolution of collapse consolidation of the right middle and inferior lingular segment of the left upper lobe and ground-glass attenuation in the superior lingular segment had also resolved [Figure 1b].

Case 2

An 83-year-old man, a reformed smoker, reported to our hospital with a history of recurrent episodes of hemoptysis of about 50 ml each for 1 month. On examination, he was afebrile with a respiratory rate of 18/min and was maintaining a saturation of 98% at room air. His complete blood counts and renal and liver function tests were within normal limits. His chest radiograph showed bronchiectatic changes in the right middle and lower lobes and in the lingula [Figure 2]. He was initially managed with injectable antibiotics and supportive management. However, he had an episode of life-threatening hemoptysis, for which he underwent emergency bronchial artery embolization (BAE). He continued to have streaky hemoptysis post-BAE. He was further evaluated for CPA, and his serum *Aspergillus*-specific antibody (IgG) was raised - 42.90 mgA/l (normal range <27 mgA/l). He was diagnosed as a case of CPA and was commenced on oral antifungal agents (voriconazole with dosing of 400 mg twice daily for 24 h and 200 mg twice daily for 6 weeks), to which he showed significant clinico-radiological response.

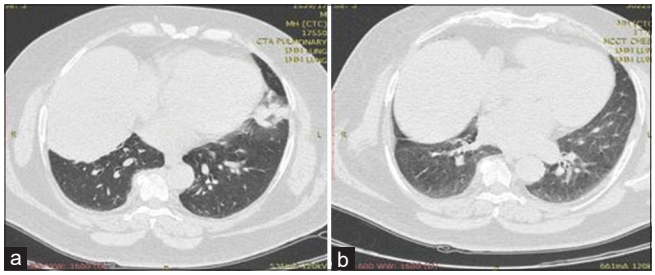

Figure 1: (a) High-resolution computed tomography of the chest on December 22, 2018, showing subsegmental collapse consolidation in the superior lingular segment of the left upper lobe. (b) High-resolution computed tomography of the chest on February 5, 2018, revealing good resolution of the consolidation of lingular segment of the left upper lobe

Case 3

A 24-year-old male with no known comorbidities presented with a history of fever and cough with mucoid expectoration of 3 weeks' duration. He gave a history of similar complaints 10 years and 2 years ago, for which he was treated with empirical antituberculous drugs for 6 months. On evaluation, he was afebrile and his vital parameters were within normal limits. His complete blood counts and renal and liver function tests were essentially normal. His chest skiagram showed fibronodular opacities in the right upper and middle zone [Figure 3a]. He underwent computed tomography of the chest which showed cylindrical bronchiectasis in the bilateral lower lobes (right > left) with air space consolidation with breakdown and thick-walled multiple cavities in the apical segment left lower lobe [Figure 3b and c]. He was extensively evaluated and underwent videobronchoscopy. The bronchoalveolar lavage (BAL) sample sent for acid-fast bacilli/mycobacteria growth indicator tube was negative for *Mycobacterium tuberculosis* and malignancy. Although the fungal stain of BAL fluid was negative, he was suspected to have chronic fungal infection and his serum *Aspergillus*-specific IgG was raised (>43.00 mgA/l). He was diagnosed as CPA and was started on oral voriconazole. He showed significant clinical response after 6 weeks of antifungal treatment. He is presently asymptomatic.

Case 4

A 65-year-old male reported with a history of cough with blackish sputum and weight loss for 1-month duration. He had similar complaints in the past 4 years, for which he was managed conservatively. On evaluation, he was found to have anemia (Hb - 9.3 mg/dl). His chest skiagram showed two cavitary lesions in the right upper and middle zone with surrounding consolidation. His computed tomography of the chest showed thick-walled cavitary lesion (4.7 cm × 4.8 cm × 8.2 cm), small multiple cavitary

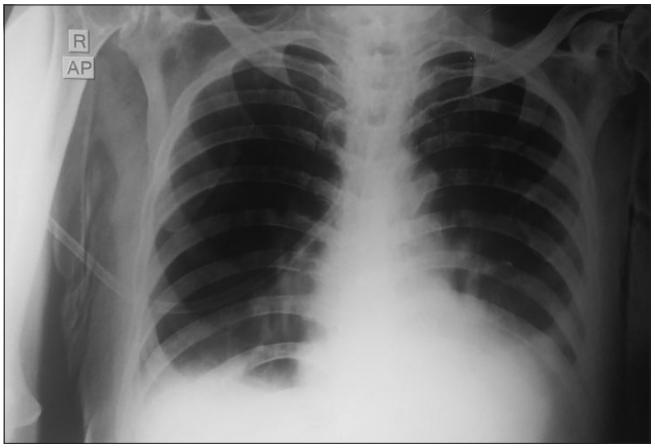

Figure 2: Chest radiograph showing bronchiectatic changes in the right middle and lower lobes.

nodules in the bilateral upper lobe, and multiple nodules in the right middle lobe and left lower lobe. He was initially started on empirical antituberculous drugs, but there was no improvement even after 4 months of antitubercular therapy. He underwent fiber-optic bronchoscopy and histopathological examination of his endobronchial biopsy showed areas of inflammatory infiltrates and necrosis with few fungal colonies, thin septate hyphae with acute angle branching, suggestive of aspergillosis. The hyphae showed frequent septations and regular branching and were seen at hematoxylin and eosin stain and highlighted by Gomori methamine silver stain [Figure 4a and b]. His *Aspergillus*-specific IgG was also raised (>44.5 mgA/l). He was managed as a case of CCPA and was commenced on liposomal injection amphotericin-B (dose - 5 mg/kg/day). However, he developed infusion reaction with injection amphotericin, and on evaluation, his electrocardiography showed ST-T changes, his Trop-T was positive, and two-dimensional echocardiography showed apical dysfunction and ballooning. He was diagnosed as a case of acute coronary syndrome with cardiogenic shock (Takotsubo syndrome) and was managed with continuous positive airway pressure and dobutamine infusion. Injection amphotericin-B was stopped and was switched over to injection caspofungin. He also developed coffee-colored aspirate in Ryle's tube, a drop in his hemoglobin levels, and signs of multiorgan failure. He was administered packed red cells and fresh frozen plasma. He was later intubated due to persistent tachypnea, rising arterial carbon dioxide and respiratory fatigue, and mechanically ventilated. He developed critical care myoneuropathy and underwent elective tracheostomy in view of prolonged ventilation. He was continued on injection caspofungin, oral voriconazole, and mechanical ventilatory support. He showed significant response to these and was later discharged with tracheostomy tube with speaking valve and oral voriconazole. He is presently asymptomatic, and his tracheostomy has been decannulated.

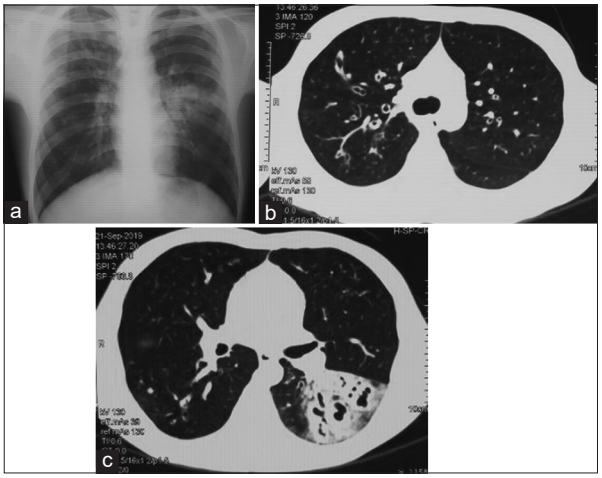

Figure 3: (a) Chest skiagram showing fibronodular opacities in the right upper and middle zone. (b) Computed tomography of the chest showing cylindrical bronchiectasis bilateral lower lobe. (c) Computed tomography of the chest showing air space consolidation with breakdown and thick-walled cavities in the apical segment left lower lobe

The characteristics of patients and outcomes are summarized in Table 1.

Discussion

Aspergillus species is ubiquitous in nature and has various manifestations depending on the duration of infection and immune status of the host. CPA is almost always caused by *Aspergillus fumigatus*, although *Aspergillus niger* and *Aspergillus flavus* have also been identified in certain patients.[7,8] CPA was first recognized as a fatal condition in 1842 in Edinburgh, United Kingdom. Patients with underlying pulmonary diseases such as COPD, posttuberculosis sequelae, cystic fibrosis, and bronchiectasis are more predisposed to develop CPA. Previously treated tuberculosis is one of the most common predisposing risk factors, worldwide.[9,10]

The affected individuals are generally middle-aged males who present with constitutional symptoms (weight loss, malaise, sweats, and anorexia), chronic productive cough, dyspnea, and occasional hemoptysis. Individuals with immunosuppression such as HIV or those on steroids can have rapid progression of disease.[10] All our patients were male and were more than 55 years of age except one, and they had underlying existing lung disorders such as COPD or posttuberculous sequelae.

Chronic forms of *Aspergillus* infection in the lung include chronic necrotizing pulmonary aspergillosis, CCPA, aspergilloma, and CFPA. The terminology of CPA has been developed to describe a spectrum of disease entities that have considerable overlap and variation in severity.[10,11] The most common form of CPA is CCPA, and it can lead to CFPA if not adequately treated. *Aspergillus* nodule and single aspergilloma constitute less common form of CPA.

On imaging, CPA is characterized by cavities, consolidation, and paracavitary opacities.[9] Single aspergilloma generally constitutes of a single pulmonary cavity with intracavitary fungal ball. CCPA is described radiologically with one or

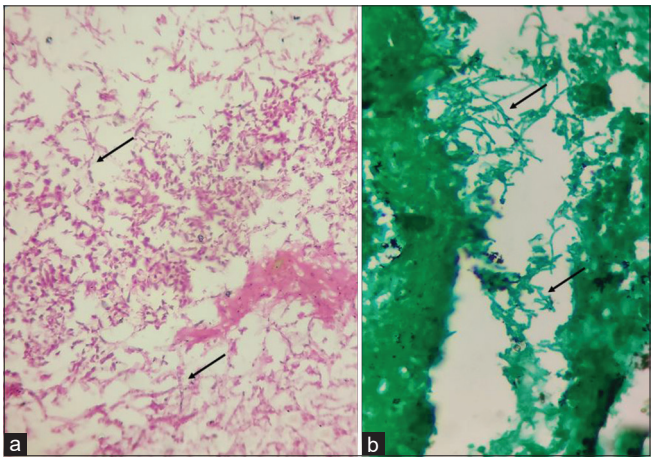

Figure 4: (a) Histopathological slide (H and E stain, ×400) showing thin septate hyphae with regular, acute angle branching (marked by arrows). (b) Histopathological slide (GMS stain, ×400) highlighting the fungal hyphae (marked by arrows)

Table 1: Clinico-radiological profile of the patients

Age (years)	Sex	Presenting complaints	CT findings	Serum IgG (mgA/l), (normal-<27)	Treatment
56	Male	Hemoptysis, dyspnea	Subsegmental collapse-consolidation in the superior segment of left upper lobe and right middle lobe	45	Voriconazole
83	Male	Hemoptysis	Bronchiectatic changes in right middle lobe, lingual, and lower lobes	42.90	Voriconazole
24	Male	Cough with expectoration	Bronchiectasis bilateral lower lobes, air space consolidation with breakdown and thick-walled cavities in the apical segment left lower lobe	43.00	Voriconazole
65	Male	Cough with expectoration, weight loss	Thick-walled cavitary lesion with cavitary nodules in the bilateral upper lobes, right middle lobe, and left lower lobe	>44.5	Caspofungin, voriconazole

CT: Computed tomography

more pulmonary cavities, which can be thin/thick walled with intraluminal aspergilloma or irregular intraluminal content which shows radiological progression over at least 3 months. CFPA generally shows severe fibrotic destruction of at least two lobes of the lung, which can appear as large cavities with surrounding fibrosis.[9-11]

The presence of *A. fumigatus* in the sputum sample is not significant due to ubiquitous nature of the fungus, but the presence of the same in the bronchoscopic fluid sample is more conclusive, especially culture growth of *Aspergillus*.[12] Detection of *Aspergillus* antibodies is indispensable for diagnosis off CPA since it differentiates between infection and colonization and has positive predictive value of 100%. *Aspergillus*-specific antibodies have a sensitivity of 80%–90%. Other serological tests include detection of serum galactomannan (sensitivity 77%) and β-D-glucan (sensitivity 20%), and newer diagnostics include *Aspergillus*-specific lateral flow device and serum galactoaminogalactan. The newer method of detection also includes real-time polymerase chain reaction which can detect even small amount of fungal DNA and can also be used to detect the resistance against antifungals such as azoles. All the patients in our study had raised *Aspergillus*-specific antibody (IgG).[10,12,13]

The mainstay of treatment of CPA is antifungal (triazoles) agents. Oral itraconazole/voriconazole can be given and show good response. CCPA generally show slow response and duration has to be 4–6 months for optimum response. Injectable antifungals such as amphotericin are indicated in progressive disease and where there is intolerance or resistance to oral treatment. Instillation of antifungals in the aspergilloma cavity is indicated for those cases where surgery is not an option to control recurrent hemoptysis. The agents include amphotericin-B, azole, sodium iodide, and nystatin and are generally delivered via a percutaneous catheter or needle under bronchoscopic cover. However, the response to this mode of therapy has been very variable. Surgical resection is a definitive treatment option and should be considered in all patients with severe hemoptysis and cases which are refractory to medical management. BAE is a lifesaving procedure and can also be used as a bridging modality before definitive surgery. The spectrum of surgical modalities includes lobectomy, segmental resection, pneumonectomy or thoracoplasty with simultaneous cavernostomy, and muscle transposition flap. One of our patients required injectable amphotericin for initiation period, while others were managed with oral voriconazole and they showed significant response.[10-12]

Moderate-to-severe hemoptysis warrants urgent BAE as a lifesaving measure. It also serves as temporary measure before surgery or definitive treatment. It is successful in 50%–90% of cases. Two of our cases required emergency BAE, and it was successful in both the cases.

Review of Indian literature

We also did a review of Indian literature and the case series of CPA published in India were included; however, single case reports and editorials were not included. A total of six case series were included in the review [Table 2]. One of the largest studies conducted in Northern India was by Sehgal *et al*., which included 269 patients with CPA. The median age was 44.3 years with male gender constituting 53.5%. Most common symptoms were cough (87.4%), and pulmonary tuberculosis was the most common underlying pulmonary disease in the study population (85.5%). *Aspergillus*-specific antibody (IgG >27 mgA/l) was raised in 94.4% of the study group, and the most common variant of CPA was found to be CCPA (79.9%).[14] In another study by the same author, 137 patients of CPA (diagnosis was based on clinical, radiological, and serological profile) and confirmed that *Aspergillus*-specific antibody (IgG) levels of more than 27 mgA/l had good sensitivity and excellent specificity in diagnosing CPA. In this study, they had also included culture of respiratory sample (sputum and BAL) and other immunological evidence in the form of serum or BAL galactomannan and *Aspergillus* precipitins. However, the composite sensitivity and specificity of *Aspergillus*-specific antibody (IgG) were higher than other variables.[15] In another observational and retrospective case series of 22 patients by Chawla *et al*., the clinical and microbiological profile of all the culture-positive cases of aspergillosis were studied. They concluded that *Aspergillus* species (especially *A. fumigatus*) is the most common organism causing chronic pulmonary infection.[16]

Table 2: Review of Indian literature of the case series of chronic pulmonary aspergillosis

Details of author	Study population	Median age (years)	Male: female	Clinical features	Underlying lung disease	Year of publication
Sehgal *et al*.	269	44.3	1.15:1	Chronic cough, weight loss, dyspnea	Pulm TB (85.5%)	2018
Sehgal *et al*.	137	43.6	1:1	Chronic cough, hemoptysis	Pulm TB (88%)	2018
Chawla *et al*.	22	52.5	1.2:1	Chronic cough, dyspnea	Bronchial asthma, chronic steroid use	2013
Agarwal *et al*.	31	37	1.3:1	Cough, dyspnea, hemoptysis, weight loss	Pulm TB (90%)	2013
Kurhade *et al*.	20	Not specified	Not specified	Not specified	Pulm TB, lung abscess	2002
Shahid *et al*.	88	49.9	5:1	Cough, fever, dyspnea	Bronchogenic carcinoma, pulm TB, bronchial asthma	2001

TB: Tuberculosis

In a prospective randomized control trial conducted by Agarwal *et al*., they confirmed the efficacy of itraconazole in the treatment of patients of CCPA. They conducted the trial on 31 patients after diagnosis of CCPA based on clinical, radiological, and microbiological evidence, and a total of 6 months of oral itraconazole (400 mg/day) was given to the test subjects. The overall response rate was measured on the basis of clinical response (improvement in cough, weight gain, and reduction in episodes of hemoptysis), radiological response (reduction in size/number of fungal ball, pulmonary infiltrates, and pleural fibrosis); and after 6 months, it was overall 76.5% in the itraconazole group as compared to control (35.7%). They also reported adverse effects in 47% of the patients in the itraconazole group, but none of them were serious enough to warrant discontinuation of itraconazole.[17]

In study conducted by Kurhade *et al*., the prevalence and predisposing factors of *Aspergillus* infection in 123 patients were evaluated, out of which 20 patients were confirmed of having CPA. The authors used culture and serological studies to confirm the infection and also tested for the antifungal susceptibility of amphotericin-B, itraconazole, and fluconazole in terms of their minimum inhibitory concentration, and itraconazole was found to be most effective. The authors confirmed that combination of culture and serology was best for confirmation of diagnosis of CPA.[18] In another prospective study by Shahid *et al*., they evaluated the prevalence of *Aspergillus* infection in 88 individuals with chronic lung disease. They conducted direct microscopy and fungal culture of BAL and antibodies against *Aspergillus* by immunodiffusion (ID) and enzyme-linked immunosorbent assay (ELISA). They also performed dot blot assay for anti-*Aspergillus* antibodies, which was confirmed by ID or ELISA. *Aspergillus* was isolated in culture from 13 (14.7%) cases of chronic liver disease, while 30.6% cases showed anti-*Aspergillus* antibodies by serological methods. *A. fumigatus* was the predominant species isolated. 17 (19.3%) cases of chronic lung disease showed antibody against *Aspergillus* by ID, 22 (25%) by ELISA, while 19 of 27 seropositive cases also showed positive results by dot blot assay. They confirmed that ELISA was more sensitive tool than ID for the detection of anti-*Aspergillus* antibodies, and it is also useful in the detection of *Aspergillus* infection in culture-negative cases.[19]

The case series from India are summarized in Table 2.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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