Clinical and laboratory profile of chronic pulmonary aspergillosis: a retrospective study

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Introduction Chronic pulmonary aspergillosis (CPA) is a type of semi-invasive aspergillosis seen mainly in immunocompetent individuals. These are slow, progressive, and not involved in angio-invasion compared with invasive pulmonary aspergillosis. The predisposing factors being compromised lung parenchyma owing to chronic obstructive pulmonary disease and previous pulmonary tuberculosis. As not many studies have been conducted in CPA with respect to clinical and laboratory profile, the study was undertaken to examine the profile in our population.

Patients and methods This was a retrospective study. All patients older than 18 years, who had evidence of pulmonary fungal infection on chest radiography or computed tomographic scan, from whom the *Aspergillus* sp. was isolated from respiratory sample (broncho-alveolar wash, bronchoscopic sample, etc.) and diagnosed with CPA from 2008 to 2016, were included in the study.

Results A total of 30 patients were included in the study. Most patients presented with pulmonary symptoms like cough with expectoration, hemoptysis, fever, breathlessness, and chest pain. Among the systemic comorbid conditions, diabetes mellitus was the most common (7/30), and nearly 50% (14/30) of the patients had a history of pulmonary tuberculosis. Among the hematological parameters, a significant difference was observed in hemoglobin, total leukocyte count, differential leukocyte count, and erythrocyte sedimentation rate. In all the four dead patients, the cause of death was respiratory failure and all patients were previously treated for pulmonary tuberculosis.

Conclusion When a patient with pre-existing lung disease like chronic obstructive pulmonary disease or old tuberculosis cavity presents with cough with expectoration, breathlessness, and hemoptysis, CPA should be considered as the first differential diagnosis.

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Introduction

Aspergillosis refers to a spectrum of infection or disease caused by fungi belonging to the genus *Aspergillus* sp. [1]. The most common pathogen causing the disease is *Aspergillus fumigatus*, followed by *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, etc. [2]. These fungi are ubiquitous in nature; thus, most of the humans are exposed to the airborne spores, making lung the primary organ of infection. The inhaled fungal spores germinate into hyphae in the lung. Depending on the immune status of the patients, these hyphae colonize in the respiratory tract and finally invade the pulmonary parenchyma [3]. The disease spectrum varies from noninvasive (allergic bronchopulmonary aspergillosis and aspergilloma) to invasive pulmonary aspergillosis and also disseminate through blood route [2]. Invasive aspergillosis is mainly seen in individuals with immunodeficient state like hematological malignancy, cancer chemotherapy, and AIDS [4]. Even, immunocompetent individuals are predisposed to aspergillosis, which includes previously treated pulmonary tuberculosis with residual cavity [5], chronic obstructive pulmonary disease (COPD) [6], uncontrolled diabetes mellitus, and chronic alcoholism.

The clinical features in patients with chronic pulmonary aspergillosis (CPA) vary from nonspecific symptoms like fever not responding to antibacterial therapy, cough with expectoration, dyspnea, to mild–severe hemoptysis [7] CPA has mainly three variety of presentations, that is, simple aspergilloma, chronic cavitary pulmonary aspergillosis, and chronic fibrosing pulmonary aspergillosis [8]. It is a challenging task for the clinical microbiologist to diagnose pulmonary aspergillosis, especially when septate hyphae are seen in respiratory sample of an immunocompetent individual, because of nonspecific symptoms, and colonization of respiratory tract is very common in them, even though gold standard test is histopathology, showing invasive, acute angled, branched, dichotomous septate hyphae with the fungal culture growing *Aspergillus* sp. from the sample from the same site [9].

Among the noninvasive diagnostic techniques, the high-resolution computed tomography of chest is more useful than the routine chest radiography, as it helps in early diagnosis and treatment [10]. Use of biomarkers like galactomannan and 1,3 β-D-Glucan in pulmonary aspergillosis is limited, as they are nonspecific and detectable in infection with other fungus also [11].

Diagnosis of CPA includes (a) clinical features, including symptoms like fever not responding to antibacterial therapy, loss of weight, cough with expectoration, dyspnea, and mild to severe hemoptysis; (b) radiological evidence of paracavitary infiltrates in pre-existing or new cavitations; and (c) laboratory evidence of increased inflammatory markers like erythrocyte sedimentation rate (ESR) and *Aspergillus* sp. isolation from respiratory samples or positive for serum *Aspergillus* precipitin test [12].

The suspicious of aspergillosis in immunocompetent individuals and early diagnosis and effective antifungal therapy can reduce the morbidity and mortality. The study was undertaken to assess the clinical and laboratory profile of the patients diagnosed with CPA in our center.

Patients and methods

This was a case–control study and was carried at the Department of Microbiology, Father Muller Medical College Hospital, Mangalore, India. The study was retrospective one. One of the investigators looked into the microbiology reports that confirmed the presence of *Aspergillus* sp. in the bronchoscopic sample from the year January 2008 to December 2016. Diagnostic criteria for CPA was as per European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and European Respiratory Society guideline for the management of CPA. All the patients had chronic cavitary pulmonary aspergillosis [13]. Patients with immunocompromised status like positive for HIV, HBV, HCV, cancer chemotherapy, systemic corticosteroid therapy, or any GVH disease were not considered. The patients' medical records were retrieved, and the demographic, clinical, laboratory parameters, and therapeutic details were collected, analyzed, and finally correlated with the outcome of the treatment. For controls, the investigators considered the laboratory details of healthy individuals who had come for a regular health check-up and were devoid of any acute or chronic illnesses. Care was taken to see that the age and sex matched with that of the test group.

The data from individual patients satisfying the inclusion criteria were noted down from individual files and entered into the Microsoft excel. The demographic details were categorized into frequency, whereas the hematological and biochemical data were calculated to obtain mean±SD. All these details are represented in each of the tables. For overall comparison, results of cases of CPA were compared with controls, that is, healthy adult individuals who had come for health checkup, and subjected to the Student *t* test. A *P* value of 0.05 was considered significant.

Results

A total of 30 patients were included in the study, among which 60% (18/30) were male and 40% (12/30) female. Most patients presented with pulmonary symptoms like cough with expectoration, hemoptysis, fever, breathlessness, and chest pain, as shown in Table 1. Among the systemic comorbid conditions, diabetes mellitus was the most common (7/30) and nearly 50% (14/30) of the patients had history of pulmonary tuberculosis (Table 1). On auscultation of the lung field, crepitations, and rhonchi were found in

Table 1 The host factors in the patients with chronic pulmonary aspergillosis

Symptoms	*N*=30 [*n* %]
Cough with expectoration	30 (100)
Hemoptysis	28 (93.33)
Fever	14 (46.67)
Breathlessness	13 (43.33)
Chest pain	7 (23.33)
Chills and rigors	5 (16.67)
Weight loss	2 (6.67)
Orthopnea	2 (6.67)
Wheeze	1 (3.33)
Pre-existing structural lung diseases	
Previous history of TB	14 (46.67)
Post TB–bronchiectasis	7 (23.33)
Post TB-fibrosis	1 (3.33)
COPD	5 (16.67)
Bronchial asthma	3 (10)
Systemic comorbidity	
Diabetes mellitus	7 (23.33)
Hypertension	3 (10)
Chronic kidney disease	1 (3.33)
Chronic liver disease	1 (3.33)
Cerebrovascular accident	1 (3.33)
Signs	
Crepitations	13 (43.33)
Rhonchi	6 (20)
Bronchial breath sounds	4 (13.33)
Respiratory failure	3 (10)
Bronchopneumonia	2 (6.67)
Empyema	1 (3.33)

COPD, chronic obstructive pulmonary disease; TB, tuberculosis.

13 (43%) and six (20%) patients, respectively. In our earlier observation, we found four of these cases of CPA were farm workers [14].

The location of fungal cavity with paracavitary infiltrates was seen in the upper lobes of right lung (15, 50%), followed by left lung (10, 33%) and bilateral lungs (5, 17%). Among the 14 cases of pulmonary tuberculosis, radiological evidence of post-tuberculosis bronchiectasis and fibrosis was seen in seven and one patient, respectively.

The bronchoscopic samples of these patients had microscopic evidence of septate branching hyphae, and culture on Sabouraud's dextrose agar grew *A. fumigatus* (28) and *A. flavus* (two). Among the hematological parameters, a significant difference was observed in hemoglobin, total leukocyte count, differential leukocyte count, and ESR, when compared with healthy individuals (Table 2). When the biochemical parameters were studied, no significant difference was observed in fasting blood sugar, liver function test, and renal function test, except serum albumin and albumin/globulin ratio was significantly less in patients with aspergillosis, indicating chronicity of the underlying disease. Nine patients were started on antifungal therapy. Itraconazole was prescribed to five and fluconazole and voriconazole to three and one, respectively. As these patients had underlying comorbid diseases, ceftriaxone and levofloxacin were started empiricially in 12 and five, respectively. The bronchodilator nebulization was administered to 18 patients who were in respiratory distress.

Among the patients we studied, four succumbed to death. The death was observed mainly in the elderly patients (mean age, 63.75±9.04) compared with the survived patients (mean age, 47.84±10.39). In all the four dead patients, the cause of death was respiratory failure and all patients were previously treated for pulmonary tuberculosis and had significant underlying bilateral lung cavities with reduced lung capacity.

When the laboratory parameters of the dead and alive patients' were compared, only a few parameters showed significant difference (Table 3). Among the hematological parameters, the percent of neutrophils was high and the platelet count was less in deceased

Table 2 Comparison of laboratory parameters among the healthy individuals and patients with chronic pulmonary aspergillosis

	Healthy individuals	Aspergillosis	*P* value
Hematology			
Hemoglobin (g/dl)	12.52±1.45 (9.2–15.9; *N*=93)	11.78±2.27 (7.5–16; *N*=29)	0.01
Total leukocyte count (cells/mm^3)	8448.17±5508.93 (2100–5400; *N*=93)	10 663.33±4686.56 (4500–18 300; *N*=29)	0.01
Neutrophils (%)	63.27±14.9 (36–92; *N*=93)	72.63±11.07 (47–89; *N*=29)	0.0007
Lymphocytes (%)	30.13±14.1 (5–76; *N*=93)	18.27±9.91 (4–40; *N*=29)	<0.0001
Eosinophils (%)	4.42±5.12 (1–26; *N*=93)	3.03±3.99 (1–17; *N*=29)	0.13
Monocytes (%)	2.42±1.67 (0–11; *N*=93)	6.07±3.52 (1–13; *N*=29)	<0.0001
Erythrocyte sedimentation rate (mm/1st h)	10.76±9.17 (1–63; *N*=59)	44.13±25.97 (5–93; *N*=29)	<0.0001
Platelet count (/mm^3)	225 175±86 707.1 (73 000–388 000; *N*=80)	272 489.7±113 531.7 (33 000–402 000; *N*=23)	0.07
l parameters			
Fasting blood sugar (mg/dl)	109.31±18.10 (73–155; *N*=105)	163.3±92.57 (76–435; *N*=20)	0.02
Total bilirubin (mg/dl)	0.62±0.41 (0.2–2.1; *N*=43)	1.25±1.54 (0.18–5.37; *N*=12)	0.19
Conjugated bilirubin (mg/dl)	0.22±0.12 (0.1–0.6; *N*=43)	0.96±1.43 (0.09–4.72; *N*=11)	0.15
Unconjugated bilirubin (mg/dl)	0.36±0.24 (0.1–1.1; *N*=43)	0.37±0.26 (0.1–0.98; *N*=11)	0.95
AST	28.37±12.11 (13–64; *N*=43)	59.5±43.79 (10–123; *N*=14)	0.02
ALT	25.13±20.3 (10–115; *N*=43)	52.36±54.44 (10–172; *N*=14)	0.09
ALP	69.56±18.17 (43–110; *N*=43)	132±159.8 (51–604; *N*=11)	0.18
Total protein (g/dl)	7.29±0.43 (6.4–8.2; *N*=43)	7.06±0.85 (5.52–8.42; *N*=11)	0.39
Albumin (g/dl)	4.3±0.45 (3.12–5.07; *N*=43)	3.66±0.69 (2.59–4.65; *N*=11)	0.01
Globulin (g/dl)	2.97±0.32 (2.4–3.5; *N*=43)	3.4±0.67 (2.3–4.3; *N*=11)	0.06
A/G ratio	1.47±0.26 (0.9–1.9; *N*=43)	1.14±0.36 (0.8–1.7; *N*=11)	0.01
Serum creatinine (mg/dl)	0.75±0.25 (0.5–1.4; *N*=45)	1.06±0.95 (0.5–5.28; *N*=23)	0.13
Blood urea (mg/dl)	20.74±8.39 (10–38; *N*=45)	27.4±18.04 (10–78; *N*=19)	0.13
Serum sodium	137.67±14.41 (137–143.8; *N*=45)	132.06±4.83 (122–140; *N*=17)	0.003
Serum potassium	4.27±0.38 (3.6–5.07; *N*=45)	3.8±0.69 (2.4–4.61; *N*=17)	0.01
Serum chloride	101.71±3.54 (95.8–106.2; *N*=45)	141.34±214.77 (80.4–977; *N*=17)	0.43

A/G, albumin to globulin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

Table 3 Comparison of laboratory parameters among patients with chronic pulmonary aspergillosis who survived and those who died

	Aspergillosis alive	Aspergillosis dead	*P* value
Age (years)	47.84±10.39 (26–69; *N*=26)	63.75±9.04 (50–75; *N*=4)	0.01
Random blood sugar (mg/dl)	164.08±86.67 (76–435; *N*=26)	215±83.82 (110–340; *N*=4)	0.3
Erythrocyte sedimentation rate (mm/1st h)	40.73±23.39 (5–85; *N*=26)	66.25±32.1 (13–93; *N*=4)	0.27
Hemoglobin (g/dl)	16.01±18.89 (8.5–110; *N*=26)	9.08±2.22 (7.5–12.9; *N*=4)	0.09
Total leukocyte count (cells/mm^3)	11 123.08±4597.35 (4500–18 300; *N*=26)	7675±2997.81 (5200–12 800; *N*=4)	0.14
Neutrophils (%)	71.04±11 (47–89; *N*=26)	83.25±8.44 (69–90; *N*=4)	0.05
Lymphocytes (%)	19.5±10.1 (4–40; *N*=26)	10.25±7.76 (4–23; *N*=4)	0.13
Eosinophils (%)	3.35±4.06 (1–17; *N*=26)	1.75±0.83 (1–3; *N*=4)	0.45
Monocytes (%)	6.12±3.64 (1–13; *N*=26)	4.75±1.09 (3–6; *N*=4)	0.48
Platelet count (/mm^3)	294 856±87 141.35 (126 000–402 000; *N*=19)	166 250±145 462 (33 000–402 000; *N*=4)	0.04
Total protein (g/dl)	7.1±0.87 (5.52–8.42; *N*=8)	6.61±0.81 (5.52–7.78; *N*=4)	0.46
Albumin (g/dl)	3.57±0.66 (2.59–4.65; *N*=8)	3.58±0.77 (2.59–4.65; *N*=4)	0.98
Globulin (g/dl)	3.54±0.65 (2.3–4.3; *N*=8)	3.00±0.36 (2.5–3.5; *N*=4)	0.19
A/G ratio	1.06±0.33 (0.8–1.7; *N*=8)	1.23±0.33 (0.9–1.6; *N*=4)	0.48
Total bilirubin (mg/dl)	1.57±1.72 (0.18–5.37; *N*=8)	1.22±0.92 (0.5–2.8; *N*=4)	0.73
Conjugated bilirubin (mg/dl)	1.19±1.53 (0.09–4.72; *N*=8)	0.84±0.87 (0.23–2.35; *N*=4)	0.71
Unconjugated bilirubin (mg/dl)	0.38±0.28 (0.1–0.98; *N*=8)	0.37±0.09 (0.26–0.5; *N*=4)	0.95
AST	49±38.87 (10–123; *N*=11)	115±39.1 (56–166; *N*=4)	0.02
ALT	41.55±43.82 (10–172; *N*=11)	102.75±56.54 (22–172; *N*=4)	0.04
ALP	154.22±162.13 (54–604; *N*=9)	89±44.13 (51–160; *N*=4)	0.48
Serum creatinine (mg/dl)	0.89±0.26 (0.5–1.56; *N*=20)	1.88±1.97 (0.5–5.28; *N*=4)	0.05
Blood urea (mg/dl)	25.63±16.71 (10–78; *N*=16)	34.5±18.41 (19–65; *N*=4)	0.39
Serum sodium	133.07±4.17 (125–140; *N*=14)	128.5±4.15 (122–133; *N*=4)	0.09
Serum potassium	3.94±0.52 (2.83–4.61; *N*=14)	3.31±0.82 (2.4–4.59; *N*=4)	0.09
Serum chloride	156.96±227.49 (86.3–977; *N*=14)	86.7±4.65 (80.4–92.9; *N*=4)	0.57

A/G, albumin to globulin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

patients. Similarly, biochemical parameters like serum creatinine and liver enzymes like aspartate aminotransferase, alanine aminotransferase were significantly high in the expired patients.

Discussion

According to WHO bulletin, it is estimated that ~1.2 million people are affected by CPA following treatment of pulmonary tuberculosis [5]. In an Indian study, it was estimated that 5-year estimated CPA prevalence rate (per 100 000) is 24 [15].

In a retrospective study in Korea that included 119 patients, more than two-thirds of the patients had past or concurrent pulmonary infection, either tuberculosis or nontubercular *Mycobacterium* sp. [12]. Similarly, pre-existing structural lung diseases like COPD (16.67%) and bronchial asthma (10%) were observed in our cases, which is similar to the study conducted in other population [16,17].

It is known that on entry of the *Aspergillus* spores in the lung, the cell-mediated immunity is activated, leading to leucocytosis in the host. These spores in the lung germinate into hyphae, and either colonize or invade the lung parenchyma, leading to pathological changes in the lung like infarction/hemorrhage, edema, and necrosis in the distal parenchyma [3]. Thus, it explains the common symptom of breathlessness, cough with expectoration, and hemoptysis in our patients, as seen in other studies [5]. The inflammatory markers like total leukocyte count and ESR have been elevated in the patients [12]. In our patients, significant anemia, leucocytosis, lymphocytosis, and increased ESR were observed when compared with healthy individuals (Table 1). As aspergillosis is seen in patient with chronic lung disease like COPD or old tuberculosis, they are anemic and have raised ESR. Leucocytosis and lymphocytosis was observed that may be contributed to inflammatory response to the fungal elements in the host [3]. When the fasting blood sugar, liver function test, and renal function test were compared, only serum albumin was significantly low in the patients, again indicating the chronicity of the pathology involved. An increase in ESR and reduced serum albumin level have been bad prognostic factors, as studied in the 70 cases of CPA in Korea [12].

The case fatality rate for invasive and localized pulmonary aspergillosis is 60.2 (97/161) and 29.5 (28/61), respectively [18]. According to the WHO estimate, the short-term and 5-year case fatality rate of CPA is 20–30% and 50%, respectively. In another study, mortality in CPA was noticed to be 39% in American population and less than 10% in European population [19]. In our study, four patients succumbed to CPA, who were significantly older than who survived with the disease. No significant difference was noticed in the hematological and biochemical parameters among the patients who succumbed to aspergillosis and who survived (Table 3). Only few parameters like serum creatinine and liver enzymes like aspartate aminotransferase and alanine aminotransferase were elevated. The limitation of this study was that this was a retrospective study, and a few details of the patients' were not available especially on the follow-up. Only nine of the 30 patients were started on antifungal therapy, and the remaining were not started with antifungal therapy; the reason for which is not known. The serological evidence of aspergillosis, that is, positive serum Aspergillus precipitin test/D-Glucan or fungal galactomannan was not able to study.

Conclusion

In conclusion, when a patient with history of treated pulmonary tuberculosis presents with productive cough and mild hemoptysis, CPA should be consider as the first differential diagnosis, especially in tropical countries. The mortality increases in CPA with age, poor nutritional status, and pre-existing lung diseases like COPD. Anemia, raised ESR, and reduced serum albumin can be used as worse prognostic factors for the patients with CPA.

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Conflicts of interest

There are no conflicts of interest.

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