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Original Article

Internal Medicine Section

Role of Aspergillus Specific IgG Titres as a Therapeutic Target for Chronic Pulmonary Aspergillosis: A Longitudinal Study

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ABSTRACT

Introduction: Chronic Pulmonary Aspergillosis (CPA) continues to be an enigma to clinicians in regions with a high prevalence of pulmonary tuberculosis and is often misdiagnosed as the latter, attributable to the significant overlap in symptoms and radiology. Moreover, although the diagnostic criteria for CPA have been standardised, the role of serological markers in monitoring disease activity and response to therapy is still not well characterised.

Aim: To understand the characteristics, risk factors and treatment outcomes in patients developing CPA and to determine the role of serological markers as indicators of disease activity.

Materials and Methods: The present longitudinal study was conducted in the Department of Respiratory Medicine, University College of Medical Sciences and its associated Guru Teg Bahadur Hospital, Delhi, India from February 2021 to June 2022. Study included 46 patients suspected of harbouring CPA attributable to their clinico-radiological presentation. The diagnosis of CPA was made using the established criteria. Patients with a confirmed diagnosis of CPA received oral azole antifungals for six months and were monitored at three monthly intervals for reduction in baseline parameters to determine treatment success/failure. Paired and unpaired parametric variables were compared using the t-test and non parametric methods were compared using the Chi-square test.

Results: The diagnosis of CPA was established in 31 (67.4%) patients of whom 74.2% were males and the mean age was 47.3±2.2 years. These patients had been symptomatic for 5.8±1.2 years. Underlying risk factors (such as the history of tuberculosis, chronic obstructive pulmonary disease, diabetes mellitus, history of long-term glucocorticoid use etc.) had been present for 6.9±1.3 years. Patients harboured an average of two risk factors with tuberculosis and diabetes mellitus being the most common local and systemic affliction, respectively. Patients with tuberculosis (p-value=0.001) and chronic steroid use (p-value=0.029) were significantly at higher risk of developing CPA. Six months of azole therapy led to significant reduction in specific IgG titres (p-value=0.001), and serum precipitins (p-value=0.004). Two patients on itraconazole relapsed within 12 months but were successfully treated with voriconazole.

Conclusion: Tuberculosis was the most significant local risk factor leading to the development of CPA, which developed soon after diagnosis of another systemic risk factor. Six months of azole therapy was adequate to induce remission of the disease, activity of which can be monitored though the measurement of serum IgG antibody titres.

Keywords: *Aspergillus fumigatus*, Chronic necrotising, Immunoglobulin G antibody, Itraconazole, Pulmonary tuberculosis

INTRODUCTION

Respiratory afflictions of *Aspergillus* species are now known to demonstrate as a wide spectrum ranging from asymptomatic colonisation to frankly invasive disease, the severity being a function of invasiveness of the mould vis-à-vis the immune status of the individual [1-3]. While the risk factors for the invasive forms of aspergillosis are well established, those leading to the more chronic, semi-invasive forms are less well understood. Chronic Pulmonary Aspergillosis (CPA) is a chronic and progressive pathology of the lung resulting from a chronic subclinical inflammation and destruction of the lung parenchyma due to chronic colonisation and invasion of the latter by Aspergillus occurring in the setting of previously diseased lung tissue albeit with a 'relatively' robust immune response. A host of local pulmonary disorders have been implicated as risk factors for the same of which mycobacterial lung infections are most common followed by Allergic Bronchopulmonary Aspergillosis (ABPA), Chronic Obstructive Pulmonary Disease (COPD), pneumothorax, lung cancer, pneumonia and sarcoidosis to name a few [4].

Baseline differences in the geographical distribution of the underlying risk factors imply a varied global epidemiology of CPA as well. While some European studies document COPD to the most common risk factor for CPA [5-7]. Others, particularly those from Asia implicate tuberculosis as the most prevalent risk factor, probably due to the commoner prevalence of the latter in this region [8-11]. Globally, African and Asian countries are estimated to be the hotbed for CPA developing secondary to tuberculosis. Given the fact that India is a high burden tuberculosis country and along with China comprises two-thirds of the global burden of tuberculosis, the same is hardly surprising; rather intriguing is why despite a high burden of tuberculosis, these two regions have such poor reporting of CPA when it is estimated that upto 6.4% of those treated for tuberculosis will eventually develop CPA [11]. It is estimated that high-burden countries for tuberculosis such as India could account for nearly 290,147 cases over five years [12].

The discrepancy between estimates and reported figures may be ascribed to the non specificity of symptoms and radiological findings. It can be seen from the results that cough, dyspnoea and haemoptysis, the most common symptoms of CPA also happen to be the symptoms of tuberculosis. Moreover, cavitation and fibrosis are the most common radiological lesions as also is the case with tuberculosis. Therefore, it is likely that a vast majority of sputum negative tuberculosis patients from high burden countries are actually missed cases of CPA. Hence, there is need for active case detection and a high index of suspicion in patients with risk factors [11,12].

The diagnosis of CPA is complex and one which relies on a multidisciplinary approach involving the pulmonologist, microbiologist, mycologist, immunologist and radiologist which is frequently not feasible in low-income areas [1].

The consensus with regards to management of the disease is to follow-up the progress of treatment and to perform a quantitative imaging procedure to assess radiological response [1]. Demonstration of the presence of serological markers such as Aspergillus specific Immunoglobulin G (IgG) titres hold a positive predictive value of 100% in favour of infection and is thus vital in the diagnosis of the disease, however, the role of IgG antibodies as prognostic markers is less clear notwithstanding their employment in previous studies for the same [1,5]. The present study was undertaken with the aim to understand the characteristics, risk factors, and treatment outcomes in patients who develop CPA and to determine the role of specific serological markers such as *Aspergillus fumigatus* specific IgG antibody titres in the follow-up of the disease.

MATERIALS AND METHODS

This longitudinal study was conducted in the Department of Respiratory Medicine, University College of Medical Sciences and its associated Guru Teg Bahadur Hospital, Delhi, India, from February 2021 to June 2022. The study was approved by the Institutional Ethics Committee (approval number IECHR-2021-51-7-R1]). Informed consent was obtained from all the patients before the enrolment.

Sample size calculation: It was done through the Cochrane formula. On an average, 45 patients are diagnosed with microbiologically negative pulmonary tuberculosis per quarter at the study institute. The required sample size for the present study to be recruited over a quarter, with 6% prevalence, 95% power, 0.05 significance level, and 5% error was calculated to be 30.

Inclusion criteria: Consecutive adult patients suspected of having CPA based on consistent risk factors (like tuberculosis, COPD, diabetes mellitus, history of long-term glucocorticoid use) and consistent radiological feature were enrolled and investigated for the possibility of the former as per the criteria proposed by Denning DW et al., and were included in the study [1].

Exclusion criteria: Patients with a more probable/confirmed alternative diagnosis or those with a critical presentation were excluded from the study.

Study Procedure

The patients underwent measurement of body weight, Body Mass Index (BMI), cell counts, liver and kidney function tests, measurement of serum precipitins and specific IgG antibodies against *Aspergillus (A.) fumigatus,* serum galactomannan, C-reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) in addition to X-ray chest and Computed Tomography (CT) thorax.

Those diagnosed with CPA served as the study group while those who did not confirm to the criteria were investigated for alternative diagnoses. The former were administered therapy with antifungal agents after detailed counselling about drug alternatives, their adverse effects, chances of recurrence etc. and were followed-up every three months after the initiation of therapy which was continued for atleast for six months. Patients were administered either of the two triazole antifungals in the form of capsules namely Itraconazole (ITZ) and Voriconazole (VRC), the former was administered with cola or lime juice in a dose of 200 mg twice a day while the latter was administered in a dose of 200 mg twice a day following the first loading dose of double the maintenance dose. The above-mentioned parameters were repeated at every follow-up visit and were used to guide further therapy.

Monitoring and Follow-up

Patients diagnosed with CPA were classified into one of the subtypes namely Chronic Cavitating Pulmonary Aspergillosis (CCPA), Chronic Necrotising Pulmonary Aspergillosis (CNPA) or Subacute Invasive Aspergillosis (SAIA), Chronic Fibrosing Pulmonary Aspergillosis (CFPA), aspergillus nodule or simple aspergilloma as per previously used definitions [1]. Patients were administered the antifungal agent as described above for atleast six months. Treatment outcome was defined as successful, if follow-up was associated with:

- Abatement of presenting symptoms,
- Radiological improvement,
- Normalisation of CRP or ESR levels,
- Reduction of IgG against A. fumigatus titres to the baseline (calculated from a pooled serum sample taken from healthy controls).

While failure was defined if any of the above were not achieved.

In case of the latter, patients were reassessed for the reasons of treatment failure and were shifted to a higher antifungal regimen; ITZ was to be replaced with VRC while VRC was to be replaced with amphotericin B. Patients treated successfully were followed-up six monthly with the above-mentioned investigations for one year to identify any relapse of CPA which was identified by:

(1) Recurrence of symptoms
(2) New radiological shadows consistent with CPA
(3) Improbability of other diagnoses
(4) IgG against A. fumigatus titres double from the last known value
(5) Elevation of CRP or ESR with or without isolation of fungi from the sputum sample or demonstration of galactomannan in serum.

Patients who stayed asymptomatic at the end of the study were discharged from regular hospital visits and advised to follow-up as needed.

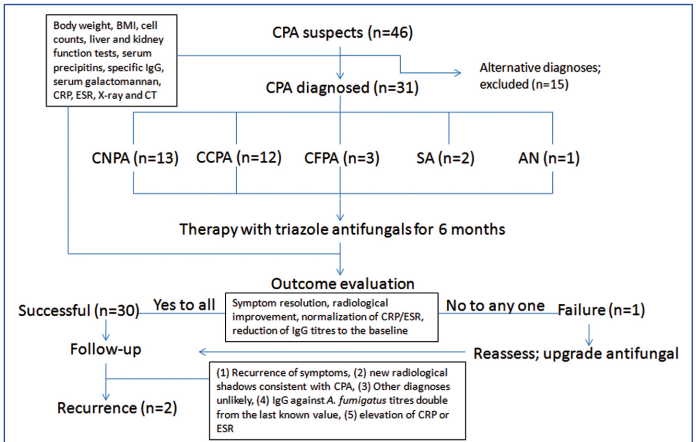
STATISTICAL ANALYSIS

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) software version 16.0 (SPSS Inc. Released 2007. SPSS for Windows, Chicago, IL, USA). Paired and unpaired parametric variables were compared using the t-test, non parametric methods were compared using the Chi-square test. The p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 46 patients were enrolled as CPA suspects in the study of which CPA was diagnosed in 31 (67.4%) patients. [Table/Fig-1] demonstrates the patient flow and clinical characterisation. Clinical characteristics of the study population are presented in [Table/Fig-2] which shows that the mean age of the study group was 47.3±2.2 years (range: 21-70 years), 23 (74.2%) were males, 16 (51.6%) were smokers with an average smoking history of 36.6 pack years while 5 (16.1%) were habitual of alcohol. Patients had been



[Table/Fig-1]: Schema depicting enrolment of participants, investigations and follow-up.
CPA: Chronic pulmonary aspergillosis; CNPA: Chronic necrotizing pulmonary aspergillosis; CCPA: Chronic cavitating pulmonary aspergillosis; CFPA: Chronic fibrosing pulmonary aspergillosis; SA: Subacute invasive aspergillosis; AN: Aspergillus nodule

symptomatic for 5.8±1.2 years with the most common symptoms being cough (n=22, 70.9%), dyspnoea (n=21, 67.7%) and haemoptysis (n=17, 54.8%). The right and left lungs were affected with nearly equal frequency, however, by the time the disease was diagnosed, 70.9% had bilateral lung involvement and more than 77% cases had more than one diseased lobe. Cavitation (n=27, 87.1%), aspergilloma (n=20, 64.5%) and parenchymal fibrosis (n=16, 51.6%) were the most frequent tomographic findings.

Characteristics	n (%)
Age (Years±SEM)	47.3±2.2 (21-70 years)
Sex	
Males	23 (74.2)
Smoking; Pack years	16 (51.6); 36.6
Symptoms	
Duration (years±SEM)	5.8±1.2
Cough	22 (70.9)
Dyspnoea	21 (67.7)
Haemoptysis	17 (54.8)
Fever	11 (35.5)
Weight loss	9 (29)
Chest pain	6 (19.4)
Involvement of lung	
Left	5 (16.1)
Right	4 (12.9)
Localisation	
Single lobe	7 (22.6)
>1 lobe	24 (77.4)
Radiological findings	
Cavity	27 (87.1)
Aspergilloma	20 (64.5)
Fibrosis	16 (51.6)
Bronchiectasis	13 (41.9)
Consolidation	11 (35.5)
Nodules	8 (25.8)
Pleural thickening	8 (25.8)
Pericavitary infiltrates	5 (16.1)
Air crescent	4 (12.9)

[Table/Fig-2]: Clinical characteristics of patients with chronic pulmonary aspergillosis (n=31).
SEM: Standard error of mean

In general, risk factors were present since 6.9±1.3 years. Although the local pulmonary pathology had been present for 9.4±6.9 years, the disease developed soon (1.4±0.6 years) after a systemic risk factor was diagnosed. On an average, 2.12 risk factors were present per patient. As shown in [Table/Fig-3], tuberculosis was the most common local pathology, present in 25 patients while diabetes mellitus, the most common systemic association, was seen in five patients; infrequent associations included solitary cases of bronchiectasis and Combined Pulmonary Fibrosis and Emphysema (CPFE) respectively. Amongst all the risk factors, tuberculosis (p-value=0.001) and chronic steroid use (p-value=0.029) were the most significantly associated with the development of CPA.

Underlying risk factor	n (%)
Tuberculosis	25 (80.6)
Chronic obstructive pulmonary disease	13 (41.9)
Diabetes mellitus	5 (16.1)
Allergic bronchopulmonary aspergillosis	5 (16.1)
Long-term glucocorticoid use	4 (12.9)
Bronchial asthma	4 (12.9)
Sarcoidosis	2 (6.5)
Bronchiectasis	1 (3.2)
Combined pulmonary fibrosis with emphysema	1 (3.2)

[Table/Fig-3]: Underlying risk factors in patients with chronic pulmonary aspergillosis.

At baseline, the mean weight was 48.6±1.8 kg and haemoglobin was 11.4±0.3 g/dL while the specific IgG and galactomannan titres were noted to be 57.6±5.6 MgA/dL and 0.55±0.15, respectively. Moreover, CRP was raised in 29 (93.5%), ESR in 16 (51.6%) and serum precipitating antibodies were demonstrated in 23 (74.2%). With regards to the aetiologic agent, fungus was isolated in 19 (61.3%) cases with *A. fumigatus* being identified in 16 (84%) of these cases. Additionally, *A. flavus* was isolated from 2 (10.5%) cases and an unidentified aspergillus species was isolated from a solitary case.

Among 31 CPA patients, 13 were classified as CNPA, 12 CCPA, three CFPA, two simple aspergilloma and one aspergillus nodule. 22 (70.9%) patients with CNPA, CCPA, CFPA and aspergillus nodule received ITZ, 7 (22.6%) received VRC while two patients with simple aspergilloma were followed-up every three months for clinicoradiological worsening, and positivity of CRP and doubling of specific IgG titres in order to identify development of CPA; they continued to be asymptomatic till 1 year. [Table/Fig-4] presents the effects of six months of specific antifungal therapy on the primary outcome variables. Both drugs exerted significant and comparable improvements in weight, BMI, Total Leucocyte Count (TLC), peripheral blood neutrophilia and lymphocytosis and blood urea. Also, significant reduction was noted in specific IgG titres and positivity of serum precipitins. Moreover, the secondary outcome variables namely number of patients to relapse and survival after treatment, showed that two patients, each with CCPA and CNPA previously treated on ITZ relapsed within 12 months but were successfully treated with VRC; while another patient, the solitary case of aspergillus nodule developed fatal invasive aspergillosis at three months into therapy and died. Another patient successfully treated with ITZ for CCPA succumbed to fatal haemoptysis due to an uncertain aetiology one year after being declared cured. Therefore, six months of treatment with antifungal triazoles was deemed satisfactory in 90% (26 of 29 patients) that received azole antifungals casesof CPA. No adverse effects serious enough to discontinue therapy were reported with either drug.

Parameter	Pretreatment (Mean±SEM)	Post-treatment (Mean±SEM)	p-value
Weight (Kg)	48.6±1.8	52.4±2.5	0.036*
BMI (Kg/m^2)	18.7±3.1	20.3±3.0	0.008*
TLC (×10^3/μL)	10.3±0.57	7.6±0.55	0.001*
Neutrophils (×10^3/μL)	6.7±0.2	6.1±0.3	0.002*
Lymphocytes (×10^3/μL)	2.2±1.9	2.7±1.8	0.038*
Blood urea (mg/dL)	32.5±2.5	26.5±1.9	0.009*
Specific IgG (MgA/L)	57.8±5.9	31.5±5.6	0.001*
Serum precipitins, n (%)#	23 (74.2)	16 (51.6)	0.004*

[Table/Fig-4]: Effect of triazole antifungal drugs on markers of disease activity.
*p-value <0.05 considered statistically significant; (%)# Depicts positive samples as a percentage of the total; SEM: Standard error of mean; BMI: Body mass index; TLC: Total leucocyte count

DISCUSSION

The present study aimed to identify the risk factors underlying the development of CPA and to determine the role of specific serological markers such as *Aspergillus fumigatus* specific Immunoglobulin G (IgG) antibody titres in the follow-up of the disease. Pulmonary tuberculosis was noted to be the most common underlying pathology in nearly 80% of the study population while diabetes mellitus with its prevalence in 12% patients was the most prevalent systemic condition. Moreover, while the local risk factors had been present for nearly a decade before the disease manifested, systemic associations such as diabetes mellitus and chronic steroid seemed to hasten the development of disease, with CPA manifesting in

about one year from the time the latter were diagnosed. Structural lung damage as seen after tuberculosis, has previously been shown to be a risk factor for fungal infections probably by overriding the local defence mechanisms of the lung [13,14]. Systemic immunosuppression as well is considered a risk factor for CPA but given the present study it would be interesting to investigate if development of systemic immunosuppressive conditions hastens the disease process.

C-reactive protein served as an important marker of disease activity, being elevated in more than 90% study population of the present study which is consistent with previously reported studies [7,11]. In fact raised CRP titres have been shown to be associated with an adverse outcome in CPA [11].

An interesting aspect of this study was measurement of *A. fumigatus*-specific IgG titres as a guide to therapy which, in contrast to the above-mentioned markers is a more direct, specific and quantifiable marker of disease activity. Although this measure has been previously used to judge disease activity after cessation of therapy, the same is restricted to individual studies and the criteria used have varied [1,8,15]. Most studies as well as guidelines rely on clinicoradiological improvement as the end point of treatment. However, the same could be subjective and non specific. Specific IgG measurement provides an objective and disease specific outcome parameter. In this study, specific IgG measurements were performed every three months till six months for which patients received therapy. During this period, the specific IgG titres nearly halved (reduction of 45%) from the mean pretreatment value of 57.8-31.5 MgA/L at the end of treatment. Thus, six months of therapy were found adequate in achieving reduction in specific IgG titres. Moreover, serial monitoring for the next 10 months indicated a relapse before significant radiological lesions developed, indicating therefore, that specific IgG titres is an important minimally-invasive objective marker of disease activity.

Limitation(s)

Assessment of outcomes dependent of the CPA subtype was not done. Also, no head-to-head comparison between the efficacy of voriconazole and itraconazole was done and antifungal susceptibility profiles of the isolated strains of *Aspergillus* species were not taken into account while determining therapy or declaring an ongoing treatment as a failure due to antifungal resistance. More systematic studies are needed to determine if the same therapeutic regimens suffice in all the disease subtypes and patients alike.

CONCLUSION(S)

Given a milieu of systemic immunosuppression, chronic pulmonary aspergillosis is not an uncommon development for diseases such as tuberculosis that induce structural lung damage. Moreover, 6 months of azole therapy is adequate to induce remission of the disease and is associated with favourable changes in non specific markers of disease activity such as body weight and peripheral leucocyte counts and a significant reduction of *Aspergillus fumigatus*-specific serum IgG antibody titres. Therefore, serial measurement of *Aspergillus fumigatus*-specific serum IgG antibody titres, which is commonly available and relatively inexpensive, can be employed as a specific serological marker to monitor the activity of chronic pulmonary aspergillosis.

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