VOLUME 25
NUMBER 4
APRIL 2021

PAGES 255–332
ISSN 1027 3719

The International Journal of Tuberculosis and Lung Disease

The Official Journal of the International Union Against Tuberculosis and Lung Disease

INT J TUBERC LUNG DIS 25(4):324–326

http://dx.doi.org/10.5588/ijtld.20.0735

LETTER

Risk factors for chronic pulmonary aspergillosis in post-TB patients

Dear Editor,

Chronic pulmonary aspergillosis (CPA) is estimated to affect 3 million people worldwide making it an under-recognised, but significant global health problem, conferring significant morbidity and mortality.[1] According to recent reports, globally around 373,000 patients develop CPA among people with pulmonary TB (PTB) sequelae each year.[1–4] Two studies from India showed that aspergillus antibodies were present in 23% and 26% of patients with chronic lung diseases.[5,6] A study from China[7] reported serum immunoglobulin G (IgG) antibodies to *Aspergillus* species in 4% of the healthy population. The occurrence of CPA in patients with pulmonary cavities has been estimated to be 22% based on one previous study.[4] The prevalence of CPA in PTB patients without pulmonary cavities was assumed to be 2%.[8] We therefore conducted a prospective observational study to determine the prevalence and clinical profile (Table 1) of CPA and to study the risk factors (Table 2) for the development of CPA among people with post TB sequelae in a tertiary hospital in northern India.

Each year, approximately 14,000 people with post-TB sequelae report to the respiratory outpatient Department of National Institute of Tuberculosis and Respiratory Diseases, New Delhi (NITRD). We conducted our study from 1 February 2016–31 October 2016 and included 100 people with symptoms of chronic cough (for more than 3 months); fever; haemoptysis; shortness of breath; chest pain or weight loss after completion of anti-tubercular treatment (ATT); and chest X-ray (CXR) abnormalities including cavitary pulmonary lesion with evidence of para-cavitary infiltrates, new cavity formation or expansion of cavity size over time, air crescent sign, pleural thickening, parenchymal destruction and/or fibrosis. We excluded people with active PTB, a history suggestive of asthma before the development of TB, using immunosuppressive medication or an immunosuppressive condition, human immunodeficiency virus seropositive cases, or pregnant women. The study was approved by the National Institute of Tuberculosis and Respiratory Diseases (NITRD/PGEC/2016/2711).

After history and clinical evaluation, all patients underwent postero-anterior CXR, sputum for acid-fast bacilli (AFB) smear microscopy, Xpert® RIF/MTB (Cepheid, Sunnyvale, CA, USA), potassium hydroxide (KOH) direct microscopy of sputum and fungal culture. Also, serum IgG antibodies to *Aspergillus* species were detected using PLATELIA Aspergillus IgG (Bio-Rad, Hercules, CA, USA); the cut-off value used in the kit is ≥10 IU/ml, considered positive as per the manufacturer's instructions. All CXRs were read by two independent expert clinicians and classified according to the USA National Tuberculosis Association criteria.[9] Discrepancies were resolved by consensus.

Patients were classified as CPA if they met the following four Global Action Fund for Fungal Infections criteria:[10]

1) Symptoms in form of haemoptysis and/or persistent cough, and/or weight loss; for more than 3 months' duration and
2) Progressive cavitation on chest imaging and/or intracavitary fungal ball and/or pleural thickening or peri-cavitary fibrosis or infiltrates all adjacent to cavities
3) Microbiological evidence of *Aspergillus* infection in the form of positive *Aspergillus*-specific IgG and/or sputum microscopy results showing hyphae consistent with *Aspergillus* and/or *Aspergillus* growth on >2 sputum or other respiratory samples.
4) Mycobacterial infection ruled out using smear, Xpert test and/or mycobacterial culture.

Of the enrolled 100 patients, 57 (57%) patients were diagnosed with CPA, of which 67% of CPA patients had cavities on CXR. Nineteen patients without cavities were diagnosed with CPA on the basis of progressive pleural thickening or parenchymal fibrosis on CXR and positive serology or sputum microscopy or culture for *Aspergillus* after ruling out other possible aetiologies. Small cavities might have been detected using CT scan, but this was not done.

Based on clinico-radiological evaluation and investigations; various risk factors were evaluated for the development of CPA (Table 2). The mean age of patients was 42.2 years; 96% were male. Of the study participants, 63% had symptoms (as per inclusion criteria) for 1–5 years, and 62% had been treated once for PTB, whereas 38% were treated for PTB more than once. On univariate analysis, extremely advanced severity on CXR, multiple number of ATT

Article submitted 25 September 2020. Final version accepted 7 January 2021.

Table 1 Patient microbiological parameters

Microbiological parameters	CPA ($n = 57$) n (%)	Non-CPA ($n = 43$) n (%)
Sputum microscopy (KOH) mount, positive	13 (22.8)	0
Sputum fungal culture, positive	23 (40.3)	0
Serum IgG antibodies-positive	45 (79)	0

CPA = chronic pulmonary aspergillosis; KOH = potassium hydroxide; IgG = immunoglobulin G.

courses taken, and presence of cavity were significantly associated with the development of CPA. On multiple logistic regression, the presence of cavity and multiple rounds of ATT courses taken were found to be independent significant risk factors for CPA. The presence of cavity on CXR increased the risk by more than 6x, and multiple number of ATT courses taken by more than 3x for the development of CPA. In the present study, low body mass index, socio-economic class, smoking and alcohol were not found to be significant risk factors for the development of CPA. In our literature search, we failed to find any studies that described multiple courses of ATT as a risk factor for developing CPA. A recent study has shown that the annual rate of CPA development over a 2-year follow-up period in post-TB sequelae patients with residual cavity was 6.5%.[2]

Among CPA patients, 23 (40.3%) had growth of Aspergillus in their sputum on two different occasions, of which 13 (22.8%) patients had septate hyphae on direct KOH microscopy. *Aspergillus fumigatus* was the most common species isolated, followed by *A. flavus*. Previous studies also observed that *A. fumigatus* was the predominant species isolated among CPA patients.[11,12] In the present study, 45% of total patients enrolled had a positive IgG antibody test. Many studies in the literature have shown that serological tests for *A. fumigatus* IgG antibodies have a higher sensitivity than culture for the diagnosis of CPA.[13,14] Patients having a single cavity with localized disease were referred for thoracic surgery opinion and patients with multiple cavities and bilateral or multi-lobar disease or pleural

Table 2 Risk factors associated with CPA

Risk factors	CPA ($n = 57$) n (%)	Non-CPA ($n = 43$) n (%)	P value	OR	95% CI Lower	95% CI Upper
Univariate analysis						
Age, years, mean ± SD	41.21 ± 10.65	42.92 ± 13.12	0.063	0.876	0.83	1.2
Sex						
Male	52 (91.2)	37 (86.0)	0.429	0.59	0.135	2.5
Female	5 (8.8)	6 (14.0)		1		
BMI, kg/m^2, mean ± SD	17.2 ± 2.58	19.1 ± 3.77	0.45	0.848	0.741	1.2
Socio-economic status			0.18	1.1	0.67	3.45
Lower	48 (84)	41 (95.3)				
Middle	8 (14)	2 (4.7)				
Upper	1 (2)	0 (0.0)				
Smoker			0.271	0.628	0.275	1.44
Yes	23 (40.0)	12 (27.9)				
No	34 (60.0)	31 (72.1)				
Alcohol abuse			0.219	0.6	0.221	1.413
Yes	15 (26.3)	10 (17.5)				
No	42 (73.7)	33 (82.5)				
Diabetes			0.800	1.238	0.238	6.454
Yes	3 (5.3)	3 (6.4)				
No	54 (94.7)	40 (93.6)		1.000		
Number of previous TB treatments			0.001	4.22	1.75	10.18
Single	25 (43.9)	33 (76.4)				
Multiple	32 (56.2)	10 (23.6)				
Total duration of illness, days, mean ± SD	30.67 ± 35.96	36.11 ± 35.13	0.285	1.006	0.995	1.017
Interval from completion of last ATT course and symptom presentation, years, mean ± SD	4.2 ± 1.8	3.6 + 2.1	0.13	0.3	−1.38	0.17
CXR features			0.37	1.5	0.622	3.63
Unilateral	12 (21)	15 (34.9)				
Bilateral	45 (79)	28 (65.1)				
Cavity			0.0001	5.9	2.48	14.04
No	19 (33.3)	33 (76.7)				
Yes	38 (66.7)	10 (23.3)				
Single/multiple (patients with any cavity)			0.54	0.65	0.16	2.65
Single	23 (60.1)	5 (50)				
Multiple cavity	15 (39.9)	5 (50)				
Multivariate logistic regression						
Number of previous TB treatments			0.044	3.41	1.42	8.22
Presence of cavity			0.0011	6.6000	2.6926	16.1780

CPA = chronic pulmonary aspergillosis; OR = odds ratio; CI = confidence interval; SD = standard deviation; BMI = body mass index; ATT = anti-TB treatment; CXR = chest X-ray.

thickening with extensive symptoms were started on oral itraconazole therapy (200 mg twice daily for 6 months).[1]

To the best of our knowledge, this is the first study from India to systematically evaluate the clinical profile and prevalence of CPA and predisposing risk factors in patients with post-TB sequelae. The observed prevalence of CPA among post-TB sequelae patients in the present study (57%) is higher than previous reported studies in post-TB sequelae patients across the globe.[4,6,8,15,16] As per the current definition of CPA, only those symptomatic post-TB sequelae patients with CXR abnormalities and with serum IgG positive with/without fungal smear/culture positivity were labelled as CPA.[10] This could be the reason for the reported high occurrence of CPA in the current study. The main limitation of this study was that the outcome of patients who were initiated on itraconazole therapy was not evaluated because long-term follow-up could not be done for these patients.

It is a matter of concern that unless post-TB patients with a high probability of CPA are investigated, the diagnosis of CPA may be missed and these patients may be started on inappropriate treatments. However, because the sample size was relatively small, larger studies are required to assess the true prevalence of CPA in people with post-TB sequelae.

R. Singla,[1] R. Singhal,[2] R. Rathore,[1] A. Gupta,[1] P. Sethi,[1] V. P. Myneedu,[2] A. Chakraborty,[3] V. Kumar[3]

[1]Department of Tuberculosis and Respiratory Diseases, [2]Department of Microbiology, and [3]Department of Tuberculosis and Chest Diseases, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India

Correspondence to: Ritu Singhal, Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases, Sri Aurobindo Marg, New Delhi 110030, India. e-mail: drritugo@gmail.com

Conflicts of interest: none declared.

References

1 Denning DW, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J 2016; 47(1): 45–68.
2 Page ID, et al. Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation. Eur Respir J 2019; 53(3): 1801184.
3 Wilopo BAP, Richardson MD, Denning DW. Diagnostic aspects of chronic pulmonary aspergillosis: present and new directions. Curr Fungal Infect Rep 2019 Nov 25; https://doi.org/10.1007/s12281-019-00361-7
4 Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull World Health Organ 2011; 89(12): 864–872.
5 Shahid M, Malik A, Bhargava R. Prevalence of aspergillosis in chronic lung diseases. Indian J Med Microbiol 2001; 19(4): 201–205.
6 Dhooria S, et al. Prevalence of Aspergillus sensitisation in pulmonary tuberculosis-related fibrocavitary disease. Int J Tuberc Lung Dis 2014; 18: 850–855.
7 Li H, et al. Role of the Aspergillus-specific IgG and IgM test in the diagnosis and follow-up of chronic pulmonary aspergillosis. Front Microbiol 2019; doi:10.3389/fmicb.2019.01438.
8 Agarwal R, Denning DW, Chakrabarti A. Estimation of the burden of chronic and allergic pulmonary aspergillosis in India. PLoS One 2014; 9(12): e114745.
9 National Tuberculosis Association. Diagnostic standards and classification of tuberculosis. New York, NY, USA: NTA, 1961: pp vi, 56.
10 Denning DW, et al. Case definition of chronic pulmonary aspergillosis in resource-constrained settings. Emerging Infect Dis 2018; 24(8):e171312
11 Kurhade AM, et al. Mycological and serological study of pulmonary aspergillosis in central India. Indian J Med Microbiol 2002; 20(3): 141–144.
12 Chawla K, et al. Clinico-microbiological profile of chronic pulmonary aspergillosis from a tertiary care centre in southern India. J Clin Diagn Res 2013; 7(12): 2712–2715.
13 Denning DW, et al. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. Clin Infect Dis 2003; 37 (Suppl 3): S265–280.
14 Volpe Chaves CE, et al. Accuracy of serological tests for diagnosis of chronic pulmonary aspergillosis: a systematic review and meta-analysis. PLoS One 2020; 15(3): e0222738.
15 Aspergilloma and residual tuberculous cavities—the results of a resurvey. Tubercle 1970; 51(3): 227–245.
16 Aspergillus in persistent lung cavities after tuberculosis. A report from the Research Committee of the British Tuberculosis Association. Tubercle 1968: 49(1): 1–11.