Original Article

A retrospective study exploring chronic pulmonary aspergillosis in post-tuberculosis lung disease patients

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Background: Chronic pulmonary aspergillosis (CPA) complicates post-tuberculosis lung disease (PTLD), causing significant morbidity and mortality. Predictors for Aspergillus seropositivity and CPA in a PTLD population remain unclear. The objective of this study was to identify the clinical, radiological, physiological, and biochemical characteristics of patients presenting to an adult PTLD clinical service, who met full criteria for CPA, and to compare them to those who did not, as well as compare those with positive Aspergillus serology to those without.

Methods: This retrospective cross-sectional study, performed in a tertiary adult PTLD clinical service in South Africa, investigated the clinical, radiological, physiological and biochemical characteristics of patients who had Aspergillus serology performed and compared those with positive and negative serology, as well as those meeting CPA diagnostic criteria with those who did not.

Results: Over a 2-year period, 238 patients were seen in the PTLD clinic, of which 79 had registered Aspergillus immunoglobulin G (IgG) serology testing and computed tomography (CT) chest imaging performed. Twenty-six (32.9%) patients had positive Aspergillus serology and 20 (25.3%) met criteria for CPA. Current radiological definitions for CPA when applied in a blinded fashion, had a sensitivity of 80.8% and a specificity of 58.5% for Aspergillus seropositivity, with a positive predictive value of 48.8%. Having ≥4 episodes of previous pulmonary tuberculosis (PTB) was significantly associated with both Aspergillus seropositivity [odds ratio (OR) =10.9; 95% confidence interval (CI): 2.1–84.9] and CPA diagnosis (OR =15.5; 95% CI: 2.8–125.6). Haemoptysis was significantly more common in those with positive Aspergillus serology (OR =2.7; 95% CI: 1.4–5.2) and in those with CPA (OR =2.7; 95% CI: 1.4–5.4). Total immunoglobulin E (IgE) levels were significantly higher in those with Aspergillus seropositivity (P value =0.006) and in those with CPA (P value =0.03). Other symptoms, spirometric and laboratory findings were similar between groups.

Conclusions: Current radiological criteria are not sufficiently specific for the diagnosis of CPA in PTLD populations, necessitating wider use of Aspergillus serology. The significant overlap in clinical syndromes

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highlights a complicated yet poorly understood relationship between CPA and PTLD, with increased frequency of haemoptysis requiring further research.

Keywords: Post-tuberculosis lung disease (PTLD); chronic pulmonary aspergillosis (CPA); computed tomography scan (CT scan); haemoptysis; screening

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Introduction

According to the World Health Organization, an estimated 66 million people were effectively treated for active tuberculosis (TB) between 2000 and 2020, indicating an average treatment success rate of 85% with antimycobacterial agents (1). Despite achieving microbial cure, there remains a high burden of morbidity and mortality amongst TB survivors (2). Post-TB lung disease (PTLD) is a recognised consequence of pulmonary TB (PTB), with a growing body of evidence correlating previous TB disease with abnormal lung structure and function (2,3).

Chronic pulmonary aspergillosis (CPA) is a destructive lung disease caused by members of the Aspergillus genus, a common environmental fungal species (4,5). The five disease subtypes identified include simple aspergilloma formation, chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), Aspergillus nodules, and subacute invasive aspergillosis (SAIA) (4). CPA mainly affects individuals with prior or concurrent respiratory disease, with PTB being the most common predisposing condition (6). CPA affects approximately 3 million people worldwide and it is thought that about one in five post-TB patients with a residual cavity will develop CPA after treatment (6).

CPA is both a mimic and complication of treated PTB yet has been overlooked in settings where PTLD is common. The criteria for diagnosis of PTB, PTLD, and CPA have many overlaps including risk factors, symptomatology, and radiological findings predisposing to the misdiagnosis of patients. The Global Action for Fungal Infections (GAFFI) convened in 2016 to develop CPA diagnostic guidelines specific to resource constrained settings (7). Currently, the diagnosis of CPA is made utilising a combination of clinical, radiological, and serological tests, with Aspergillus IgG testing forming the cornerstone of diagnosis (7,8). Aspergillus antibody testing has shown >90% sensitivity and 85% specificity (9); however, it is likely that in low- to middle-income countries such as South Africa with a high burden of PTB and PTLD, lack of awareness, misdiagnosis, and a shortage of resources available for Aspergillus serological testing may result in underdiagnosis of CPA. Delayed or missed diagnoses and inappropriate or untimely treatment initiation may contribute to poor outcomes

Highlight box

Key findings

- This study highlights the significant clinical, biochemical, physiological, and radiological overlaps seen across patients with chronic pulmonary aspergillosis (CPA) and post-tuberculosis lung disease (PTLD).
- This study proves current radiological criteria are not sufficiently specific for the diagnosis of CPA in PTLD populations, necessitating wider use of Aspergillus serology.
- Haemoptysis was significantly more common in those with positive Aspergillus serology and in those with CPA, with the increased frequency of haemoptysis in this population group requiring further research.

What is known and what is new?

- CPA is understudied in Sub-Saharan Africa, and it is likely that in low- to middle-income countries such as South Africa with a high burden of pulmonary tuberculosis and PTLD, lack of awareness, misdiagnosis, and a shortage of resources available for Aspergillus serological testing may result in underdiagnosis of CPA.
- This study shows the significant overlap in the clinical, biochemical, radiological, and physiological profiles of CPA and PTLD patients, with current radiological criteria insufficient to distinguish the two conditions. Thus, highlighting the need for more frequent use of Aspergillus serology to confirm the diagnosis of CPA in PTLD.

What is the implication, and what should change now?

- This study will raise awareness for the necessity of maintaining a high index of suspicion and advocate for the use of Aspergillus serology as the cornerstone in making the appropriate and timely diagnosis of CPA in the PTLD population.

among the PTLD population.

The objective of this study was to identify the clinical, radiological, physiological, and biochemical characteristics of patients presenting to an adult PTLD clinical service, who met full criteria for CPA, and to compare them to those who did not, as well as compare those with positive Aspergillus serology to those without. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1062/rc).

Methods

Study population

This was a retrospective cross-sectional study inclusive of patients with a diagnosis of PTLD and registered Aspergillus IgG serology who attended the adult outpatient pulmonology service at Tygerberg Hospital, a tertiary referral center in South Africa, between 1 September 2020 and 31 October 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval to conduct the study was granted by Stellenbosch University Health Research Ethics Committee (Reference Number N22/11/151) and individual consent for this retrospective analysis was waived.

Data collection

Clinical and demographic data was extracted from the pulmonology clinic archive storage and Tygerberg Hospital electronic content management system. CPA diagnosis conferred to GAFFI guidelines, defined as respiratory symptoms for >3 months, chest imaging suggestive of CPA, and a positive Aspergillus immunoglobulin G (IgG) assay (8,9). Evidence of previous PTB was confirmed by either microbiological data or documented history of previous PTB. Serum IgG to Aspergillus fumigatus was measured using the ImmunoCAP Allergen m3 lateral flow assay with a value of >66.45 mg/L considered positive. Spirometry testing was performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) Guidelines with application of population specific reference ranges (10). Spirometric values included were forced expiratory volume in one second (FEV_1) measured in litres and as a percentage of predicted normal value, forced vital capacity (FVC) measured in litres and as a percentage of predicted normal value, and the ratio measure FEV_1/FVC. Radiological features of CPA on computed tomography (CT) imaging of the chest in accordance with international definitions (see Table S1) were assessed by two radiologists blinded to serological results and clinical details. In brief, the presence of simple aspergilloma, CCPA, CFPA, aspergillus nodule, and SAIA were individually assessed for each patient, and a final assessment of either "CPA suggestive" or "CPA not suggestive" was made. In the event of discordance between the two radiologists on any of the fields, a consensus read was held in the presence of a third reader until consensus was achieved.

Statistical analysis

Statistical analysis was done using R version 4.X.X (Vienna, Austria) (11). Continuous variables were summarised as a median and interquartile range (IQR) or a mean and standard deviation, and categorical variables were summarised as proportions. Odds ratios (ORs) were calculated using generalised linear models and are reported with 95% confidence intervals (CIs). An alpha of 0.05 was considered statistically significant. No correction for multiple testing was done. Annualized rates of change in FEV_1 and FVC values were performed by taking the difference between an individual's initial spirometry measurements and those taken at least 6 weeks later. This difference was divided by the length of the time interval in days between measurements and multiplied by 365 days. Distributions of annualized rates of change were visualised and compared.

Results

Patient characteristics

Between 1 September 2020 and 31 October 2022, 238 patients attended the PTLD clinical service, of whom 79 patients with registered Aspergillus IgG serology and CT chest imaging were included. Median age was 44 (IQR: 36, 51) years and 42 (53.2%) were female. The median number of previous PTB episodes was 2 (IQR: 1, 3). Respiratory symptoms were reported by 73 patients (92.4%), and 43 (54.4%) had imaging suggestive of CPA. A total of 26 patients (32.9%) tested positive for IgG to Aspergillus (*Table 1*). There were no statistical differences in the age and sex of those who tested positive for Aspergillus IgG compared to those who tested negative. The odds of having Aspergillus seropositivity was greater among

Table 1 Baseline characteristics of study population stratified by Aspergillus IgG serology

Baseline characteristics	Aspergillus IgG positive (n=26)	Aspergillus IgG negative (n=53)	OR (95% CI)	P value
Demographics				
Total	26 (32.9)	53 (67.1)	–	–
Age, years	44.1 (34.5, 49.8)	44.0 (37.0, 52.2)	–	–
Female	13 (50.0)	29 (54.7)	–	–
Risk factors				
Never-smoker	11 (42.3)	17 (32.1)	0.7 (0.3–1.9)	–
Ever-smoker	15 (57.7)	33 (62.3)	Ref	
Ex-smoker	11 (42.3)	13 (24.5)	–	–
Current smoker	4 (15.4)	20 (37.7)	–	–
Unknown	(0.0)	3 (5.7)	–	–
Pack years	20 (14, 30)	17 (8, 21)	–	–
Cannabis	2 (7.7)	5 (9.4)	–	–
Methamphetamine	1 (3.8)	1 (1.9)	–	–
Methaqualone	0	2 (3.8)	–	–
Inhaled corticosteroids	0	5 (9.4)	–	–
Oral steroids	0	2 (3.8)	–	–
HIV-positive	3 (11.5)	14 (26.4)	0.4 (0.1–1.3)	–
Receiving ARVs	3 (11.5)	14 (26.4)	–	–
Previous episodes of PTB				
1×	8 (30.8)	29 (54.7)	Ref	
2×	6 (23.1)	14 (26.4)	1.6 (0.4–5.4)	–
3×	4 (15.4)	7 (13.2)	2.1 (0.5–8.8)	–
≥4×	7 (26.9)	3 (5.7)	10.9 (2.1–84.9)	–
Symptoms				
Haemoptysis	10 (38.5)	8 (15.1)	2.7 (1.4–5.2)	–
Cough	17 (65.4)	28 (52.8)	0.8 (0.5–1.5)	–
Loss of weight	4 (15.4)	9 (17.0)	1.3 (0.6–2.7)	–
Chest pain	5 (19.2)	8 (15.1)	1.1 (0.5–2.2)	–
Dyspnoea	22 (84.6)	39 (73.6)	1.1 (0.6–2.2)	–
mMRC	2 (1, 3)	2 (1, 3)	–	–
Blinded radiological assessment consistent with				
CCPA[†]	14 (53.8)	16 (30.2)	5.4 (1.7–19.4)	–
CFPA[†]	1 (3.8)	1 (1.9)	6.2 (0.2–175.4)	–
Simple aspergilloma[†]	6 (23.1)	5 (9.4)	7.4 (1.7–36.7)	–
Radiology compatible with CPA (total) [†]	21 (80.8)	22 (41.5)	–	–
Radiology not compatible with CPA[†]	5 (19.2)	31 (58.5)	–	–

Table 1 (*continued*)

Table 1 (*continued*)

Baseline characteristics	Aspergillus IgG positive (n=26)	Aspergillus IgG negative (n=53)	OR (95% CI)	P value
Spirometry				
Normal	0	1 (2.0)	–	–
Obstructive	4 (16.0)	3 (5.9)	–	–
Low FVC	10 (40.0)	26 (51.0)	–	–
Obstruction with low FVC	10 (40.0)	20 (39.2)	–	–
No class	1 (4.0)	1 (2.0)	–	–
FVC % pred	58.1 (44.7, 77)	58.5 (43.9, 74.7)	–	0.83
FEV_1 % pred	44.3 (35.9, 55.7)	44.7 (32.8, 60.3)	–	0.71
FEV_1/FVC	61.3 (49.8, 74.7)	71 (54, 81.9)	–	0.23
Laboratory results				
Aspergillus IgG titre (normal value)	151.5 (111.5, 192)	14.1 (5.7, 27.8)	–	–
Total IgE	309 (116.5, 471), n=18	59.8 (24.3, 180.5), n=40	–	0.006
Total IgG	18.2 (17.3, 20.2), n=8	18.2 (15.9, 24.8), n=27	–	–
Total IgA	3.1 (1.7, 3.2), n=7	3.8 (3.2, 5.1), n=28	–	–
Total IgM	1.4 (1.2, 1.8), n=8	1.2 (0.9, 1.7), n=28	–	–
ESR	35 (8, 55.5), n=11	58 (32, 80.3), n=24	–	0.045
CRP	16 (6.5, 67.3), n=18	20 (6, 80.8), n=38	–	0.79

Numbers are presented as n (%) or median (interquartile range). Normal = FEV_1/FVC >0.7, percentage predicted FVC >80%, percentage predicted FEV_1 >80%. Obstructive = FEV_1/FVC <0.7, percentage predicted FVC >80%, percentage predicted FEV_1 <80%. Low FVC = FEV_1/FVC >0.7, percentage predicted FVC <80%, percentage predicted FEV_1 variable. Obstruction with low FVC = FEV_1/FVC <0.7, percentage predicted FVC <80%, percentage predicted FEV_1 <80%. Aspergillus IgG (mg/L) (>66.45 considered positive). Total IgE (kU/L) >100 kU/L extremely high levels of antibody. Total IgG (g/L) (7.0–16.0). Total IgA (g/L) (0.7–4.0). Total IgM (g/L) (0.4–2.3). ESR (mm/h) (0–20). CRP (mg/L) (<10). †, the radiological features of CPA on CT imaging of the chest were assessed by two independent radiologists blinded to patient serological results and clinical details. The suspected presence of simple aspergilloma, CCPA, CFPA, nodule and SAIA were individually assessed and a final assessment of "compatible with CPA" or "not compatible with CPA" was made. IgG, immunoglobulin G; OR, odds ratio; CI, confidence interval; ref, reference; HIV, human immunodeficiency virus; ARV, anti-retroviral therapy; PTB, pulmonary tuberculosis; mMRC, modified Medical Research Council dyspnoea scale; CCPA, chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IgA, immunoglobulin A; IgM, immunoglobulin M; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography; SAIA, subacute invasive aspergillosis.

those who had four or more previous episodes of PTB (OR =10.9; 95% CI: 2.1–84.9).

Diagnosis of CPA

Of those with positive Aspergillus serology, one patient reported no respiratory symptoms and five patients did not have imaging suggestive of CPA, thus were excluded as they did not meet CPA criteria. Twenty patients met all criteria for CPA diagnosis (*Figure 1*).

Differences between Aspergillus IgG serology positive and negative patients (Table 1)

Clinical history

There was no difference in smoking status between groups. Eleven patients reported illicit substance use. Three patients (11.5%) with positive Aspergillus serology were human immunodeficiency virus (HIV) positive, compared to 14 (26.4%) with negative serology (OR =0.4; 95% CI: 0.1–1.3). All HIV-positive patients were documented to be on antiretrovirals, but viral load and cluster of differentiation

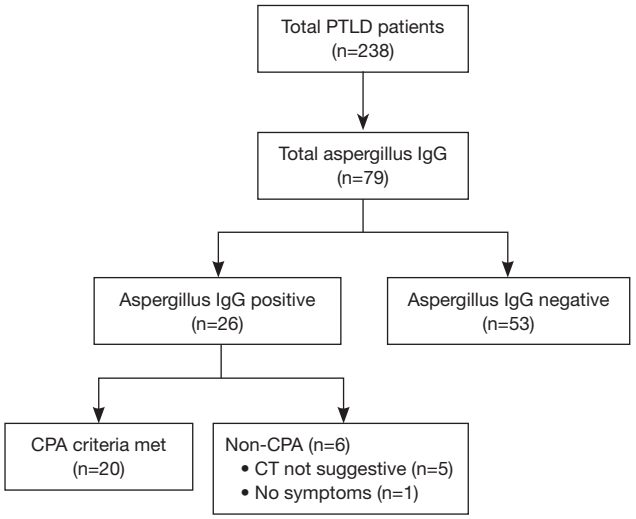

Figure 1 Consort diagram of study population. PTLD, post-tuberculosis lung disease; IgG, immunoglobulin G; CPA, chronic pulmonary aspergillosis; CT, computed tomography.

4 (CD4) counts were not documented. No statistical significance was observed between groups regarding use of inhaled or oral steroids.

Dyspnoea and cough were the most prevalent symptoms amongst the study population, yet there were no associations with Aspergillus seropositivity, however haemoptysis was significantly more common in the positive serology group (OR =2.7; 95% CI: 1.4–5.2).

Radiological findings

In total 43 (54.4%) patients had CT imaging suggestive of CPA, of whom only 21 (26.6%) had positive serology. Of those with positive serology (n=26), five patients did not have CT imaging findings suggestive of CPA (19.2%). The weighted Kappa value for agreement on the blinded radiological read was 0.41. CCPA was the most the frequently reported imaging finding, and of 30 (38%) patients identified, 14 (53.9%) had positive serology and 16 (30.2%) did not (OR =5.4; 95% CI: 1.7–19.4). Simple aspergilloma was reported in 11 (13.9%) patients, of whom only six had positive serology. CFPA was reported in 2 (2.5%) patients, of whom one had positive serology. No patient had findings suggestive of SAIA or Aspergillus nodules.

The sensitivity and specificity for CT imaging and positive Aspergillus serology were 80.8% and 58.5%, respectively, while the positive predictive value (PPV) and negative predictive value (NPV) were 48.8% and 86.1%, respectively (*Table 2*).

Table 2 Sensitivity and specificity of CT imaging for Aspergillus seropositivity

Parameters of accuracy	Value
True positive, n (%)	21 (80.8)
False negative, n (%)	5 (19.2)
False positive, n (%)	22 (41.5)
True negative, n (%)	31 (58.5)
Positive predictive value (%)	48.8
Negative predictive value (%)	86.1
Sensitivity (%)	80.8
Specificity (%)	58.5

CT, computed tomography.

Spirometry findings

Seventy-six patients had spirometry performed. Of those with positive serology, none had normal spirometry, 10 (40%) had a low FVC, 4 (16%) had an obstructive pattern, and 10 (40%) had obstruction with low FVC. A similar distribution of patterns was seen in those with negative serology. Median percentage predicted values for FVC, FEV_1, and FEV_1/FVC showed no statistical differences between groups.

Laboratory results

The median Aspergillus specific IgG in those who tested positive was 151.5 (IQR: 111.5, 192) mg/L. Inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were raised in the overall study population with lower values seen in those with positive serology. Median ESR was 35 (IQR: 8.0, 55.5) mm/h in the positive serological group and 58 (IQR: 32, 80.3) mm/h in the negative serological group (P=0.045). Median CRP was 16 (IQR: 6.5, 67.3) mg/L in the positive serological group compared to 20 (IQR: 6, 80.8) mg/L in the negative serological group (P=0.79). Total IgA, IgM and IgG values were similar across groups; however, total IgE was significantly higher in those with positive Aspergillus IgG serology. Median total IgE in those with positive Aspergillus serology was 309 (IQR: 116.5, 471) kU/L compared to 59.8 (IQR: 24.3, 180.5) kU/L in those with negative Aspergillus serology (P=0.006).

Differences between patients with and without a CPA diagnosis (Table 3)

In our study, 23.1% (6/26) of patients with positive serology

Table 3 Baseline characteristics of study population stratified by chronic pulmonary aspergillosis diagnosis

Baseline characteristics	CPA (n=20)	Non-CPA (n=59)	OR (95% CI)	P value
Demographics				
Total	20 (25.3)	59 (74.7)	–	–
Age, years	43.7 (32.2, 50.1)	44.2 (37.1, 51.8)	–	–
Female	11 (55.0)	31 (52.5)	–	–
Risk factors				
Never-smoker	11 (55.0)	17 (28.8)	0.4 (0.1–1.0)	–
Ever smoker	9 (45.0)	39 (66.1)	Ref	
Ex-smoker	7 (35.0)	17 (28.8)	–	–
Current smoker	2 (10.0)	22 (37.3)	–	–
Unknown	0 (0.0)	3 (5.1)	–	–
Pack years	8 (7, 10)	20 (15, 30)	–	–
Cannabis	1 (5.0)	6 (10.2)	–	–
Methamphetamine	0	2 (3.4)	–	–
Methaqualone	0	2 (3.4)	–	–
Inhaled corticosteroids	0	5 (8.5)	–	–
Oral steroids	0	2 (3.4)	–	–
HIV-positive	3 (15.0)	14 (23.7)	0.6 (0.1–2.0)	–
ARVs	3 (15.0)	14 (23.7)	–	–
Previous episodes of PTB[†]				
1×	6 (30.0)	31 (52.5)	Ref	
2×	4 (20.0)	16 (27.1)	1.3 (0.3–5.2)	–
3×	2 (10.0)	9 (15.3)	1.1 (0.2–6.1)	–
≥4×	7 (35.0)	3 (5.1)	15.5 (2.8–125.6)	–
Symptoms				
Haemoptysis	8 (40.0)	10 (16.9)	2.7 (1.4–5.4)	–
Cough	15 (75.0)	30 (50.8)	1.2 (0.7–2.4)	–
Loss of weight	4 (20.0)	9 (15.3)	1.7 (0.8–3.5)	–
Chest pain	4 (20.0)	9 (15.3)	1.0 (0.5–2.2)	–
Dyspnoea	17 (85.0)	44 (74.6)	1.4 (0.7–2.9)	–
mMRC	2 (1, 3)	2 (1, 3)	–	–
Imaging consistent with				
CCPA	14 (70.0)	16 (27.1)	–	–
CFPA	1 (5.0)	1 (1.7)	–	–
Simple aspergilloma	5 (25.0)	6 (10.2)	–	–
None	–	36 (61.0)	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Baseline characteristics	CPA (n=20)	Non-CPA (n=59)	OR (95% CI)	P value
Spirometry				
Normal	0	1 (1.8)	–	–
Obstructive	2 (10.5)	5 (8.8)	–	–
Low FVC	9 (47.4)	27 (47.4)	–	–
Obstruction with low FVC	7 (36.8)	23 (40.4)	–	–
FVC % pred	56.3 (43.1, 67.5)	59.1 (44.8, 75.4)	–	0.23
FEV_1 % pred	39.2 (36.5, 53.9)	45.5 (32, 58.5)	–	0.34
FEV_1/FVC	70.2 (55.4, 81.4)	69.2 (50.1, 81.7)	–	0.78
Laboratory results				
Aspergillus IgG	156 (115, 193.5)	16.7 (6.6, 40.8)	–	–
Total IgE	318 (116, 600), n=13	70.6 (24.5, 182), n=45	–	0.03
Total IgG	18.9 (18, 22.2), n=6	18.1 (15.4, 24.7), n=29	–	–
Total IgA	2.2 (1.3, 3.3), n=5	3.8 (3.1, 5.1), n=30	–	–
Total IgM	1.5 (1.0, 1.9), n=6	1.2 (0.9, 1.6), n=30	–	–
ESR	33 (5, 70), n=9	50.5 (32.8, 78), n=26	–	0.14
CRP	17 (8, 68), n=13	20 (6, 80.5), n=43	–	0.32

Numbers are presented as n (%) or median (interquartile range). †, one patient who met criteria for CPA had unknown number of episodes of previous PTB. Normal = FEV_1/FVC >0.7, percentage predicted FVC >80%, percentage predicted FEV_1 >80%. Obstructive = FEV_1/FVC <0.7, percentage predicted FVC >80%, percentage predicted FEV_1 <80%. Low FVC = FEV_1/FVC >0.7, percentage predicted FVC <80%, percentage predicted FEV_1 variable. Obstruction with low FVC = FEV_1/FVC <0.7, percentage predicted FVC <80%, percentage predicted FEV_1 <80%. Aspergillus IgG (mg/L) (>66.45 considered positive). Total IgE (kU/L) >100 kU/L extremely high levels of antibody. Total IgG (g/L) (7.0–16.0). Total IgA (g/L) (0.7–4.0). Total IgM (g/L) (0.4–2.3). ESR (mm/h) (0–20). CRP (mg/L) (<10). CPA, chronic pulmonary aspergillosis; OR, odds ratio; CI, confidence interval; ref, reference; HIV, human immunodeficiency virus; ARV, anti-retroviral therapy; PTB, pulmonary tuberculosis; mMRC, modified Medical Research Council dyspnoea scale; CCPA, chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; IgG, immunoglobulin G; IgE, immunoglobulin E; IgA, immunoglobulin A; IgM, immunoglobulin M; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

did not meet criteria for CPA. Twenty (25.3%) patients met full criteria, of which 11 (55%) were female, with a median age of 44 (IQR: 32, 50) years. The odds of meeting criteria for CPA were greater among those with four or more reported infections with PTB (OR =15.5; 95% CI: 2.8–125.6).

Clinical history

The odds of meeting criteria for CPA were lower among never-smokers compared to those with a history of smoking (OR =0.4; 95% CI: 0.1–1.0). Of those meeting criteria for CPA, 3 (15%) were HIV-positive, compared to 14 (23.7%) patients with HIV who did not meet CPA criteria (OR =0.6; 95% CI: 0.1–2.0). There was no association with the use of oral or inhaled corticosteroids among those meeting and not meeting CPA criteria.

The relative frequencies of dyspnoea, cough, chest pain, and weight loss were similar among those with CPA and without CPA, with a specificity of only 10.2% for respiratory symptoms and CPA diagnosis (sensitivity was 100% by definition). However, a diagnosis of haemoptysis was more frequent in those with CPA (OR =2.7; 95% CI: 1.4–5.4).

Radiological findings

Of those meeting criteria for CPA, the most common radiological diagnosis was CCPA (n=14, 70%), followed by simple aspergilloma (n=5, 25%). CFPA was suggestive on

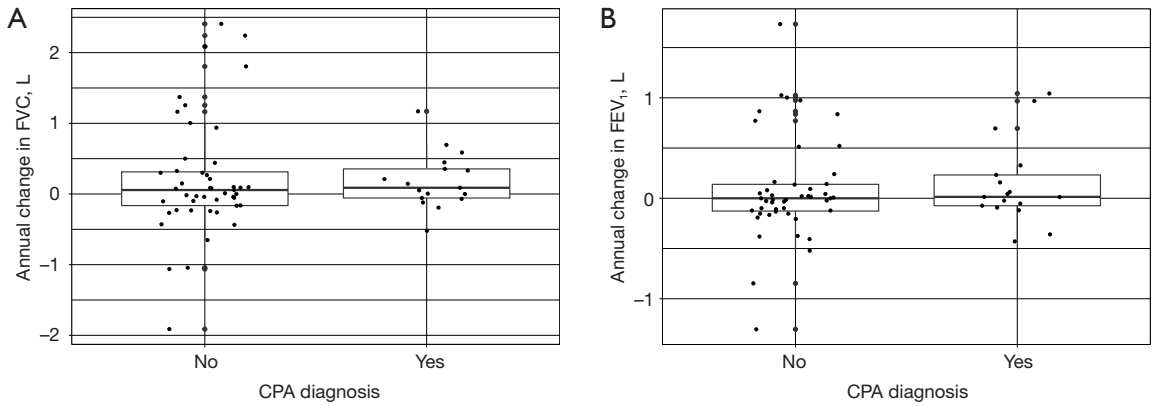

Figure 2 Annualized rate of change in lung function measures FVC (A) and FEV_1 (B) among those with and without a CPA diagnosis. FVC, forced vital capacity; CPA, chronic pulmonary aspergillosis; FEV_1, forced expiratory volume in one second.

imaging in one patient meeting criteria for CPA.

The specificity of CT imaging in CPA was 61% (sensitivity was 100% by definition).

Spirometry findings

No cross-sectional spirometric differences were observed in those meeting CPA criteria compared to those who did not. The annualised rate of change in FVC and FEV_1 measurements are displayed in *Figure 2*. Median change in FVC was 88 mL (IQR: −57, 355 mL) and 56 mL (IQR: −164, 313 mL) for those with and without a CPA diagnosis, respectively (*Figure 2A*). Median change in FEV_1 was 14 mL (IQR: −74, 232 mL) and 0 mL (IQR: −127, 139 mL) for those with and without a CPA diagnosis, respectively (*Figure 2B*). There were no significant differences in the proportion of individuals who lost greater than 100 mL annually in either FEV_1 or FVC measures across those with and without a CPA diagnosis, 3 (18%) versus 15 (32%) and 3 (18%) versus 14 (30%), respectively.

Laboratory results

Among those meeting CPA criteria, median Aspergillus IgG was 156 (IQR: 115, 193.5) mg/L compared to 16.7 (IQR: 6.6, 40.8) mg/L for those not meeting criteria. The specificity for positive Aspergillus IgG serology in CPA diagnosis was 89.8% (sensitivity was 100% by definition). Inflammatory markers, CRP and ESR, and total IgA, IgM and IgG levels were similar in both CPA and non-CPA groups; however, total IgE levels were significantly higher in those meeting CPA criteria compared to those not meeting CPA criteria (P value =0.03).

Discussion

In this study evaluating differences between CPA and PTLD in patients with previous TB, we found a complicated relationship between the two diagnoses. There were large overlaps in the risk factors, clinical, radiological, and physiological parameters, with only serology for Aspergillus distinguishing the two. Radiology patterns conventionally used to define CPA were commonly found in PTLD and could not be used to reliably discriminate between those with CPA and those without. Further, a quarter of patients with positive Aspergillus serology did not fulfill other traditional criteria for CPA.

Amongst the 79 PTLD patients reviewed, one-third had positive Aspergillus serology, higher than the 19.5% reported in Kenya among TB patients with persistent respiratory symptoms (12). This discordance is likely due to selection bias, as only patients with clinical indications or suspicion of CPA had Aspergillus serology performed in our cohort. Positive Aspergillus serology in combination with compatible symptomatology and radiological evidence is currently the preferred method for diagnosing CPA (7-9). Using this case definition developed by GAFFI, we found that one-quarter of our highly selected population met criteria for CPA. This is consistent with current global prevalence estimates of CPA in post-TB patients, ranging from 21–35%, with variation attributed to geographical location and associated burden of PTB (13).

In exploring predictors for Aspergillus seropositivity and CPA diagnosis in the PTLD population, demographics, risk factors, symptomatology, and biochemical profiles of the groups showed few discriminating differences. HIV

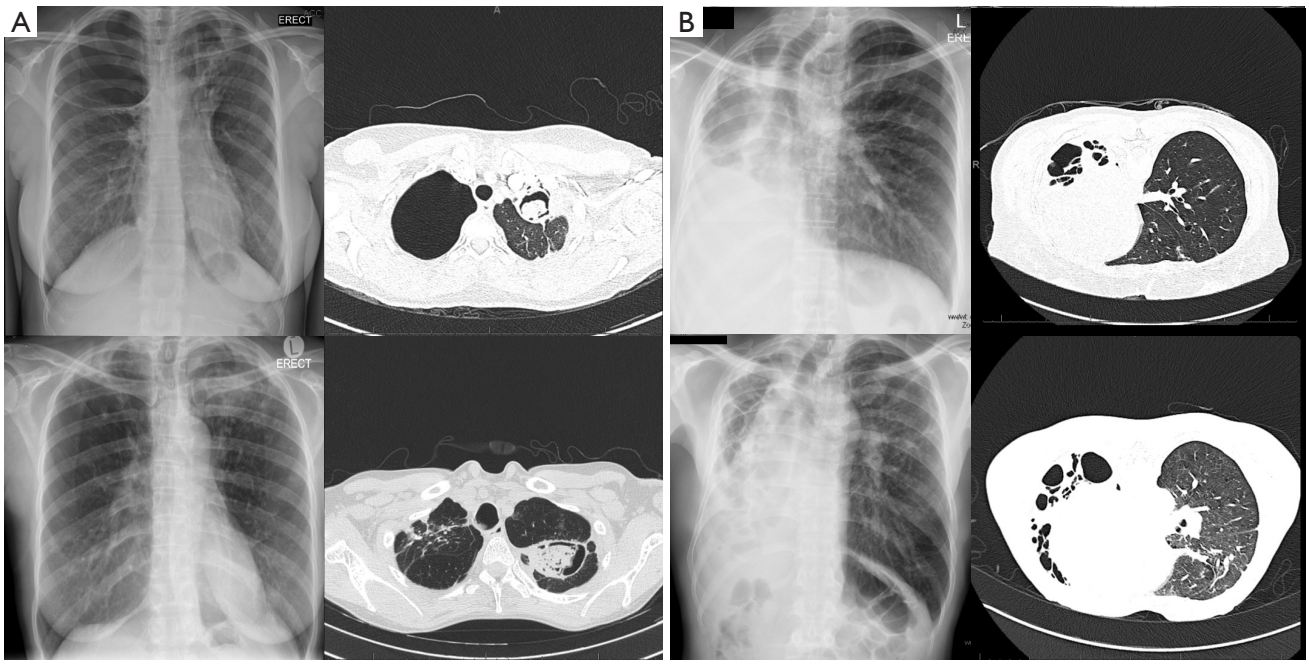

Figure 3 Radiological comparison of simple aspergilloma (left) and CCPA (right) in those with positive Aspergillus serology compared to those with negative Aspergillus serology. (A) Top panels: simple aspergilloma reported radiologically, Aspergillus IgG negative (30-year-old female). Bottom panels: simple aspergilloma reported radiologically. Aspergillus IgG positive (50-year-old female). (B) Top panels: CCPA reported radiologically. Aspergillus IgG negative (50-year-old female). Bottom panels: CCPA reported radiologically. Aspergillus IgG positive (60-year-old male). CCPA, chronic cavitary pulmonary aspergillosis; IgG, immunoglobulin G.

diagnosis was less common among those with positive Aspergillus serology and CPA, although not statistically significant. Importantly, haemoptysis was more common in those with both positive Aspergillus serology and CPA, a finding requiring further study. Life-threatening haemoptysis is an important adverse outcome in PTLD, and this finding suggests Aspergillus co-infection may be aetiological. Additionally, multiple prior PTB infections appeared to have significantly increased odds for developing CPA. Given the pathophysiology of CPA infection and the increased severity of lung damage observed with repeat PTB infection, this relationship might be expected (2). It is highly possible that some episodes of reported TB may have indeed been misdiagnosed CPA triggering "empiric re-treatment". We were unable to confirm microbiological diagnosis for every episode of TB in all patients to support this hypothesis. Further studies will need to explore this topic.

Radiology remains a cornerstone of CPA diagnosis, though in our cohort we found that 51.2% of patients who met radiological criteria for CPA in a blinded read did not have positive serology and thus did not meet CPA diagnostic criteria. Thus, in our context, current radiological CPA definitions have a false positive rate of 41.5%, with a specificity of only 58.5% for a positive Aspergillus IgG (*Table 3* and *Figure 3*). Radiological consensus showed moderate agreement between readers, and we would recommend refining definitions for CCPA and CFPA to improve consensus between radiologists. As demonstrated in our cohort, CPA pathologies have many overlaps with chest imaging findings seen in both PTB and PTLD. This makes differentiating CPA from PTB and PTLD on radiological evidence alone difficult. It is unclear why certain clinical patterns of PTLD appear similar to CPA in the absence of Aspergillus exposure. One hypothesis is that the radiological criteria for CPA are not sufficiently specific. Alternatively, exposure to other non-Aspergillus fungi may cause "CPA-like" radiological changes seen in our population. Further, the lateral flow assay used measures antibodies to Aspergillus fumigatus and has poor sensitivity to other Aspergillus species, which may further indicate missed infection with non-fumigatus Aspergillus species (14). Importantly, almost half of patients with simple aspergillomas reported on CT scan did not have positive

Aspergillus serology (*Figure 3*). The reasons are unclear, but may include lack of immune IgG response to fungal antigen, mycetoma of non-Aspergillus aetiology, or an alternate misdiagnosis (e.g., blood clot).

In our study, 96% of patients had abnormal spirometry. Low FVC and obstruction with low FVC were the most prevalent spirometric patterns observed amongst the study population, with no differences between those with and without CPA. Lung physiology in PTLD is complex, with literature showing that patients with PTLD can develop both chronic airflow obstruction and restriction (15). Further, patients with CPA have heterogenous spirometry attributed to various underlying lung pathologies frequently seen in CPA and lung damage caused by Aspergillus infection itself (16). The high prevalence of abnormal lung function in this study may be due to referral bias, as only those referred to the tertiary health centre were included in the study. Nonetheless, the high prevalence of abnormal lung physiology raises concern for current and future morbidity experienced by this population.

Of those meeting criteria for CPA, >80% were HIV-negative. This is in keeping with current literature, with observed reports showing CPA to be more common amongst immunocompetent patients (17,18). This may be explained by cavitatory PTB being more common in the HIV-negative population, with a study in Malawi showing that HIV-negative patients were almost twice as likely as HIV-positive patients to present with cavitation (OR =1.97; 95% CI: 1.20–3.23) (17). Cavitation poses a cumulative risk over time for CPA, as Aspergillus spores inhaled from the environment settle in poorly ventilated cavities, leading to fungal colonization and chronic inflammation (19). An additional proposed explanation for these differences has been postulated that HIV-infected patients may not mount a sufficient immune response to produce antibodies during Aspergillus infection, particularly those with low CD4 counts (18).

Amongst our PTLD patients, >90% of patients reported chronic respiratory symptoms. The symptoms in our cohort had similar frequencies across groups, with only haemoptysis as a useful discriminator for both Aspergillus seropositivity and CPA. Those with CPA were more than twice as likely to present with haemoptysis than those without CPA. One element of the diagnostic criteria for CPA requires the presence of respiratory symptoms for >3 months; however, our data challenges this paradigm, as both CPA and non-CPA PTLD patients had similar chronic clinical manifestations (7). The use of symptoms may improve sensitivity of diagnosis for CPA in general PTLD populations; however, our study proves that specificity remains problematic, especially in referred PTLD patient groups such as ours. Further, it is plausible that PTLD patients with symptomatic CPA are likely misdiagnosed as having TB recurrence at the primary care level where access to serological testing is limited.

Our study demonstrated polyclonal hypergammaglobulinemia and raised inflammatory markers across the study population, likely reflecting a paralleled state of chronic inflammation in both CPA and PTLD patients. Interestingly, total IgE titres were significantly higher in those with Aspergillus seropositivity and in those meeting CPA criteria. Our study adds to the emerging data on IgE titres in CPA, where high total IgE levels and Aspergillus sensitization has been seen in CPA, though its significance is still unclear. Kosmidis *et al.* observed that CPA patients with a high total IgE titre had more favourable treatment outcomes, with outcomes defined by clinical and or radiological improvement or stability (20). In contrast, a study by Sehgal *et al.* did not observe any differences in outcomes at 6 months in those with high total IgE, although it was observed that those with higher IgE titres had a significantly longer time to relapse compared to those with low IgE (21).

There are important limitations to our study. Our cohort represents a single tertiary centre in South Africa and may not be representative of other populations. Our sample size was relatively small, and the non-significant numerical differences observed may prove significant in larger population samples. Additionally, as mentioned, the study population was subject to selection bias as Aspergillus serology was only performed in patients where CPA was considered. This is of importance, as even in this highly selected group only a quarter met the criteria for CPA.

Despite these challenges, our study highlights the difficulties faced in diagnosing CPA in populations with a high burden of PTB and PTLD. The significant clinical, biochemical, physiological, and radiological overlaps seen across patients with CPA and PTLD necessitate a high index of suspicion and advocates for the use of Aspergillus serology as the cornerstone for making appropriate and timely diagnoses in this population, especially as radiological criteria when used alone are disappointing. Missed CPA diagnoses likely leads to poor outcomes in the PTLD population as CPA frequently progresses to cause significant loss of lung function, haemoptysis, and increased mortality (22). Further research is needed to determine the prevalence of CPA among more general PTLD patients and

in patients seeking health care. Further, research is needed as to whether CPA-like damage in PTLD patients may be caused by other non-Aspergillus fungi, and if radiological diagnostic criteria can be improved to better discriminate between CPA and non-CPA PTLD. In addition, further research on mycological examination of respiratory samples in combination with Aspergillus serology for CPA diagnosis may aid in identifying the fungal species responsible for CPA and allow for possible optimisation of antifungal treatment. Finally, longitudinal studies are needed to compare those with CPA and non-CPA PTLD to determine long-term outcomes and predictors thereof, and whether interventions such as anti-fungal therapy improve prognosis for these patients, especially given their high cost. Patients with positive serology who do not meet CPA criteria may form the most important group in observing the natural history of developing CPA and may offer opportunities for early intervention before lung damage accrues.

Conclusions

Lung destruction and the sequalae thereof is common to both PTLD and CPA patients, with current radiological criteria insufficient to distinguish the two conditions. The significant overlaps seen in the clinical, biochemical, radiological, and physiological profiles of these patients calls for more frequent use of Aspergillus serology to confirm the diagnosis of CPA in PTLD. Currently, only those with a high probability of CPA are being investigated in specialized centres, likely leading to missed CPA diagnoses and potentially poorer outcomes amongst the PTLD population. Further clinical and epidemiological research is warranted to better our diagnostic and therapeutic approach in this high risk PTLD population.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1062/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval to conduct the study was granted by Stellenbosch University Health Research Ethics Committee (Reference Number N22/11/151) and individual consent for this retrospective analysis was waived.

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