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CHRONIC PULMONARY ASPERGILLOSIS IN PATIENTS WITH ACTIVE PULMONARY TUBERCULOSIS WITH PERSISTING SYMPTOMS IN UGANDA

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Abstract

Background—The occurrence of chronic pulmonary aspergillosis (CPA) among drug sensitive pulmonary tuberculosis (PTB) patients on optimal therapy with persistent symptoms was investigated.

Methods—We consecutively enrolled participants with PTB with persistent pulmonary symptoms after 2 months of anti-TB treatment at Mulago Hospital, Kampala, Uganda between July 2020, and June 2021. CPA was defined as a positive *Aspergillus*-specific IgG/IgM immunochromatographic test (ICT), a cavity with or without a fungal ball on chest x-ray (CXR), and compatible symptoms >3 months.

Results—We enrolled 162 participants (median age 30 years; IQR: 25 — 40), 97 (59.9%) were male, 48 (29.6%) were HIV-infected, and 15 (9.3%) had prior PTB. Thirty-eight (23.4%) sputum

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Disclosure

There is no conflict of interest to disclose.

samples grew *A. niger* and 13 (8.0%) *A. fumigatus* species complexes. Six (3.7%) participants had intra-cavitary fungal balls, and 52 (32.1%) had cavities. Overall, 32 (19.8%) participants had CPA. CPA was associated with prior PTB (adjusted odds ratio (aOR): 6.61, 95% CI: 1.85 — 23.9, p=0.004), and far advanced CXR changes (aOR: 4.26, 95%CI: 1.72 — 10.52, p=0.002). The *Aspergillus* IgG/IgM ICT was positive in 10 (31.3%) participants with CPA.

Conclusions: CPA may cause persistent respiratory symptoms in up to one-fifth of patients after intensive treatment for PTB. The *Aspergillus* IgG/IgM ICT positivity rate was very low and may not be used alone for the diagnosis of CPA in Uganda.

Keywords

Pulmonary Tuberculosis; Persistent symptoms; Chronic Pulmonary Aspergillosis; Uganda

INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a heterogenous, destructive and debilitating parenchymal lung disease that predominantly occurs in patients with underlying pulmonary diseases or damage [1]. Pulmonary tuberculosis (PTB) is an important risk factor for CPA [2,3], with an estimated 1.2 million cases of CPA estimated to complicate treated PTB globally [4].

Patients with CPA frequently present with prominent pulmonary and systemic symptoms, such as chronic productive cough, hemoptysis, chest pain, weight loss, fevers, and fatigue, which are clinically indistinguishable from PTB symptoms leading to delayed and/or misdiagnosis [5]. In addition, chest imaging findings in CPA such as fibrosis and cavitation overlap with PTB lesions, and may therefore be unrecognized and left untreated, leading to poor outcomes [5]. Radiological phenotypes of CPA include 1) *Aspergillus* nodule – presenting as an isolated single or multiple pulmonary nodules, 2) simple aspergilloma – with a single well defined cavity with an intracavitary aspergilloma (fungal ball), 3) chronic cavitary pulmonary aspergillosis (CCPA) - a chronic cavitary disease with enlargement of existing cavities and formation of new cavity with or without a fungal ball and no demonstrable hyphal invasion of the parenchyma, and 4) chronic fibrosing pulmonary aspergillosis (CFPA), a late stage disease characterized by marked paracavitary and pleural fibrosis [6].

Uganda is a high TB burden country with an estimated TB prevalence of about 253 per 100,000 population [7]. Patients with active TB may have persistent respiratory symptoms during or after successful completion of their treatment. Currently, it is unclear how often persistent symptoms in patients with treated TB are related to CPA. Most of the existing data available is on patients who have completed TB treatment and there is limited data on those still receiving treatment who present with persistent respiratory symptoms. For example, in a laboratory-based study on persons living with HIV in Uganda, *Aspergillus*-specific IgG antibodies were elevated in 9% of the participants at the end of TB treatment[8]. However, a full diagnostic work-up for CPA was not performed in them. In a population-based study of previously treated PTB patients in Northern Uganda, about 6.5% of the participants developed CPA within 2 years of TB treatment. [9]

The goal of the intensive TB treatment phase (first 2 months) with 4 active anti-TB agents is to sterilize sputum and alleviate clinical symptoms [10]. Therefore, we hypothesized that persistent symptoms of PTB after the intensive phase of drug sensitive PTB treatment may be due to co-existent or incident CPA. The aim of this study was 2-fold. First, we determined the prevalence and factors associated with CPA among patients with drug sensitive PTB with persistent symptoms after 2 months of anti-TB therapy, and secondly, we evaluated the diagnostic performance of an *Aspergillus*-specific IgG/IgM immunochromatographic test (ICT) for the diagnosis of CPA in Uganda.

METHODS

Study design

This was a cross-sectional study conducted at the National TB control center of Mulago National Referral Hospital (MNRH), Kampala, Uganda between 1st July 2020 and 30th June 2021.

Study Setting

The TB Unit at MNRH serves as the national TB treatment center in Uganda. The unit uses a mixed model of care, whereby, 1) very sick patients are hospitalized at the start of their TB treatment until clinically stable, and 2) outpatient care where patients continue treatment from the community under supervision. The unit manages about 1,500 TB patients annually, making it the largest treatment center in the country.

Study population

We enrolled all eligible patients 18 years and older with microbiologically confirmed drug sensitive PTB (DS-PTB) using GeneXpert MTB/RIF and persisting pulmonary and/or systemic symptoms despite 2 months of standard anti-TB treatment. Patients on second line anti-TB regimens, pregnant women, critically ill patients, and those with extra-pulmonary TB were excluded.

Sample size estimation and study procedure

Using previous data on a 12% seroprevalence of *Aspergillus* IgG among patients with active TB in Uganda [8], at 95% confidence interval (CI), power of 80% and type I error of 5%, a sample size of 162 participants was estimated.

For all eligible participants, a trained medical officer collected data on clinical and demographic characteristics such as age, sex, HIV status, clinical symptoms, duration of TB treatment, prior history of TB diagnosis, occupation, income, and education status using a standardized semi-structured questionnaire. Participants were consecutively recruited until required sample size was reached.

Chest radiograph imaging and interpretation

A chest radiography (CXR) for each participant was performed at enrolment and interpreted by a qualified radiologist. The scale for grading severity of disease on CXR was defined specifically for this study by the radiologist. Minimal, moderate, and far advanced disease

was classified based on involvement of one, two or more zones respectively and coupled to unilateral or bilateral lung disease. Two horizontal lines were used to divide the lungs into 3 regions (upper, middle, and lower) giving a total of 6 zones. Severity within each zone was then scored as 0 for no disease, 1 for less than 50% disease and 2 for greater than 50% disease. Unilateral zonal severity was reported as: 0 for no disease, 1–4 for mild disease, 5–8 for moderate disease, and 9–12 for severe disease. Lung zonal predominance was reported as: Upper zone, middle zone, lower zone, upper and middle, upper and lower, middle and lower, and upper, middle, and lower zone predominant. Presence of a cavity elevated the severity classification. Cavity size was recorded as the maximum diameter on planar imaging. A CXR was suggestive of CPA if it showed cavities, pericavitary infiltrates, a fungal ball (intracavitary content), pericavitary fibrosis, or pleural thickening.

Aspergillus IgG/IgM serology and sputum cultures

Blood samples were obtained for *Aspergillus*-specific IgG/IgM assay. *Aspergillus*-specific IgG/IgM ICT (LD Bio, Lyon, France) was performed according to the manufacturer's instruction [11] and interpreted visually by a trained medical mycologist. Sputum samples were collected for high volume sputum (HVS) cultures to isolate *Aspergillus* species as previously described [12]. All isolates were identified phenotypically and reported as species complex.

Diagnosis of chronic pulmonary aspergillosis

CPA was defined as the presence of persistent respiratory symptoms (at least a cough or hemoptysis lasting for 3 months or more), suggestive CXR findings (cavities, pericavitary infiltrates, a fungal ball (intra-cavitary content), pericavitary fibrosis, or pleural thickening), and evidence of *Aspergillus* infection (a positive HVS culture and/or *Aspergillus* IgG/IgM ICT) consistent with the Global Fungal Infection Forum II diagnostic criteria for CPA in resource-limited settings [13]. The data from each patient was carefully evaluated by the lead investigator (MN) who made a provisional diagnosis of CPA. Two trained medical mycologists (FB and RK) experienced in the diagnosis of CPA independently evaluated MN's provisional diagnosis and any discrepancy was resolved by an expert in CPA (DWD).

Data analysis

Categorical variables were summarized using proportions and percentages. Means and standard deviation were calculated for normally distributed continuous variables. To compare different variables or different categories, the chi square test, and student t test were applied after testing appropriate assumptions. For the regression analysis, the outcome variable of CPA diagnosis was dichotomized as 1 "yes CPA" 0" No CPA". Univariate analysis was conducted for each independent variable and the outcome of CPA diagnosis. Factors with a $p< 0.25$ or previously known in the literature like age, sex of an individual, previous treatment for pulmonary Tuberculosis were considered for the multivariable regression mode. We assessed interaction through forming two-way interaction terms and performing likelihood ratio tests. Variables considered in the initial multivariable model were entered into a backward stepwise regression model. Confounding was assessed by considering a 10% or more change in the odds ratio with a model with the variable and one without. The goodness of fit of the model was assessed using the Hosmer-Lemeshow

goodness of fit test. The odds ratios with their 95%CI are presented. A p<0.05 was considered statistically significant. STATA version 14.0 was used for data analysis.

Ethics

The Makerere University School of Biomedical Science Research and Ethics Committee (SBS-795) and the Uganda National Council for Science and Technology (HS739ES) approved the study protocol. All study participants provided informed written consent. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

Results

Baseline clinical and radiological characteristics of the participants

Of the 162 participants enrolled, 97 (60.0 %) were male with a median age for all participants of 30 (IQR: 25 — 40) years. Forty-eight (29.6%) participants were living with HIV and 15 (9.3%) were previously treated for PTB. Fifty-two (32.1%) participants had history of alcohol use and 13 (8.0%) had a history of smoking tobacco. There was only 1 (0.6%) participant with history of COPD, bronchial asthma, and chicken pox each. None of the participants had a known history of sarcoidosis, whooping cough, or lung cancer.

All participants had chronic productive cough. Other frequent symptoms were, chest pain (92.6%, n=150), night sweats (90.7%, n=147), weight loss (51.8%, n=84), fatigue (46.3%, n=75), shortness of breath (41.4%, n = 67), loss of appetite (36.4%, n=59), and fever (19.1%, n=31). Twenty (12.4%) participants had hemoptysis (Table 2).

Twenty-nine (17.9%) participants had normal CXR findings. However, 63 (38.9%) participants had far advanced disease, and 70 (52.6%) had pathology in both lungs. Six (3.7%) participants had fungal balls, 52 (32.1%) had cavities, and 58 (35.8%) had pleural thickening (Table 3).

Prevalence of chronic pulmonary aspergillosis

Overall, 32/162 (19.8 %) participants had CPA (Figure 1). Overall, 11 (6.8%) participants tested positive on the *Aspergillus* IgG/IgM ICT (Figure 2). Thirty-eight (23.4%) sputum samples grew *A. niger* and 13 (8.0%) grew *A. fumigatus* species complexes (Figure 3). Nineteen (50%) of the 38 participants whose sputum samples grew *A. niger* complex had CPA. Comparatively, 7 (53.8 %) of 13 participants whose sputum samples grew *A. fumigatus* complex had CPA. Isolation of *Aspergillus* species was higher in CPA cases compared to non-CPA cases (19/32 (59.4%) *versus* 19/130 (14.6%), p <0.001). At multivariable analysis, factors statistically significantly associated with CPA were as follows; prior PTB (aOR: 6.61, 95%CI: 1.85 — 23.9, p=0.004), and far advanced CXR changes (aOR: 4.26, 95%CI: 1.72 — 10.52, p<0.002), (Table 1). Figures 4 and 5 illustrates imaging findings in a non-CPA and CPA cases, respectively.

Aspergillus IgG/IgM ICT positivity rate

The *Aspergillus* IgG/IgM ICT was positive in 10 participants with CPA (10/32, 31.3%) and 1 participant without CPA (1/126, 0.8%) (p<0.001).

DISCUSSION

We found CPA in about 20% of the participants with persistent respiratory symptoms after 2 months of standard anti-TB treatment — the intensive phase. The aim of the intensive phase of PTB treatment is to rapidly achieve sputum *M. tuberculosis* culture conversion and alleviate pulmonary and systemic symptoms by using a combination of 4 anti-mycobacterial agents [14]. Our findings suggest that CPA is a possible cause of persistent symptoms in microbiologically confirmed PTB patients on effective anti-TB regimen. In addition, our data showed that the odds of having CPA was about 7-fold higher in subjects with prior treated PTB compared to those receiving PTB treatment for the first time and over 4-fold higher in patients with far advanced CXR changes compared to those with normal or minimal CXR changes. Therefore, these group of patients should be targeted for a full evaluation for CPA. CPA is a treatable disease and early diagnosis and commencement of appropriate antifungal therapy significantly improves health-related quality of life of these patients [15].

A recent study evaluating over 1,200 cases of CPA in Africa identified current active or previous PTB as an underlying structural lung disease in over 70% of the cases [16]. A few epidemiological studies from across Africa and other countries in Asia have reported varying CPA prevalence based on the population of TB patients studied. In an earlier study from Northern Uganda among post-TB patients, the prevalence of CPA was about 5% [9]. In Nigeria, among patients with predominantly smear-negative PTB, about 9% of the participants had CPA at the end of their TB therapy[17]. In addition, among GeneXpert/smear-negative participants at their end of TB therapy in Indonesia, CPA was found in 22% of the participants [18]. In Iran, among 124 patients with TB (94 with current TB and 30 with previous TB) in Iran, 3 (2.4 %) had simple aspergilloma and 14 (11.3 %) CCPA [19]. In a more recent community-based study at Vietnam National Lung Hospital, 38 (54.3%) of 70 post-TB patients had CPA [20]. The findings from these studies suggests that CPA prevalence varies depending on the population of TB patients studied. Of concern is the relatively high occurrence of CPA in patients being treated for PTB without microbiological confirmation, which could imply a misdiagnosis of CPA for a smear negative PTB, and the possibility of incident CPA during PTB therapy as suggested by the current study. Therefore, CPA should be considered not only in previously treated patients, but also in those currently receiving therapy for PTB with suggestive clinical features. CPA should also be a differential diagnosis in those with GeneXpert/smear negative sputum and should be investigated especially when symptoms persist. [21]

Aspergillus serology is central in the diagnosis of CPA [22]. Current clinical practice guidelines recommend it as a key test for the diagnosis of CPA [23]. However, in this study, we found only about 31% of CPA patients to have a positive *Aspergillus* IgG serological test. This is in contrast with a previous report by Denning and colleagues where *Aspergillus* antibodies were elevated in nearly all patients [1]. Recent studies have shown

varying prevalence of *Aspergillus* positivity among CPA patients. In Nigeria, only 8.9% of CPA patients had a positive *Aspergillus* IgG [17], in Vietnam it was 89% [20], in Iran 44% and in Indonesia 80% [18]. These could be due to the varying *Aspergillus* platforms used, *Aspergillus* species isolated, the timing of the surveys (during or after PTB treatment) and genetics of the varying study population studied. The LD Bio *Aspergillus* IgG/IgM has recently been validated for serological diagnosis of CPA at the point of care with excellent sensitivity and specificity [24]. In Indonesia, the sensitivity of this ICT assay was 80% with a corresponding specificity of 70% [18]. On the other hand, the sensitivity and specificity for the LDBio *Aspergillus* ICT were 91.6% and 98.0%, respectively in a cohort of CPA patients at the National Aspergillosis Centre in the UK[24]. There is evidence that *Aspergillus* IgG cut off values vary with population, and performance on the *Aspergillus* ICT is not an exception to the rule. We recently showed that Aspergillus IgG/IgM ICT used in this study had a 0% sensitivity in patients with fungal asthma, despite having a 91% sensitivity in a Caucasian population [25]. Therefore, standardization of these serology platforms in the Ugandan population is urgent and justified.

Patents with CPA are often heavily symptomatic [26]. All the patients in our study had chronic productive cough. Surprisingly, only about 12% of our study participants had hemoptysis. In the largest ever review of CPA patients in Africa, almost 60% reported hemoptysis, significantly contributing to their death [16]. Hemoptysis is a common cause of death, even in developed countries, and bronchial artery embolization or surgery may be required to arrest bleeding [27]. In a recent systematic review by Bongomin and colleagues [28], among nearly 900 CPA patients managed surgically in Africa, post-operative mortality was as low as 5%, suggesting a possible role of surgery in the management of CPA in Africa were antifungal agents are not widely available. However, when antifungals are available, affordable and accessible to the patients, and there is no indication for surgery, itraconazole or voriconazole are the preferred first line agents for the management of CPA [6]. Antifungal agents alleviate symptoms, improve quality of life and overall survival [29,30].

A common post-PTB sequela is traction bronchiectasis, which is associated with *Aspergillus* bronchitis [31]. These patients are usually highly symptomatic, but do not have cavitary changes or pleural thickening on chest imaging. However, they will usually have positive *Aspergillus* cultures of sputum and may have *Aspergillus* IgG detectable in serum [31]. Patients with *Aspergillus* bronchitis usually respond to antifungal therapy [31]. Some of the patients with probable CPA in this study may have *Aspergillus* bronchitis, depending on the precise imaging findings. This is an area for further evaluation.

This study has some limitations. This was a single center study, involving mainly patients from the central region of Uganda and may not be representative of the entire Uganda population. All isolates of *Aspergillus* were identified phenotypically, therefore, there was a possibility of misidentification of phenotypically indistinguishable species. Future multicenter studies recruiting nationally representative participants are recommended. There are no established diagnostic criteria for PTB-associated CPA, as previous criteria do not recognize CPA to occur during active PTB. In addition, there is no known diagnostic cut off for *Aspergillus* IgG suitable for the diagnosis of CPA in Ugandans and the *Aspergillus* IgG/IgM has not been previously validated among Ugandans, posing a risk of diagnostic

inaccuracy, because diagnostic performance may vary by race and ethnicity. Also, we were unable to do bronchoscopies to further enhance recovery of *Aspergillus* and for biomarker assays on bronchoalveolar lavage sample. Lastly, we performed culture on a single sputum sample and positive cultures may have been from contaminations, particularly that a high proportion of cultures were positive for *A. niger*. Radiological phenotypes of CPA are defined using chest CT; therefore, we have missed some important imaging findings by using only CXR.

In conclusion, CPA is highly prevalent among active PTB patients with persistent respiratory symptoms, especially those with history of prior PTB treatment and those with advanced CXR changes in Uganda. CPA screening may be considered among this subset of patients. *A. niger* was a common species of *Aspergillus* in our setting. *Aspergillus* IgG/IgM LFA positivity rate was very low and thus may not be used singly for the diagnosis of CPA in Uganda.

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References

1. Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic Cavitary and Fibrosing Pulmonary and Pleural Aspergillosis: Case Series, Proposed Nomenclature Change, and Review. Clin Infect Dis. 2003;37(s3):S265–S280. doi:10.1086/376526 [PubMed: 12975754]
2. Bongomin F Post-tuberculosis chronic pulmonary aspergillosis: An emerging public health concern. Chowdhary A, ed. PLOS Pathog. 2020;16(8):e1008742. doi:10.1371/journal.ppat.1008742 [PubMed: 32817649]
3. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J. 2011;37(4):865–872. doi:10.1183/09031936.00054810 [PubMed: 20595150]
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. doi:10.2471/BLT.11.089441 [PubMed: 22271943]
5. Baluku JB, Nuwagira E, Bongomin F, Denning DW. Pulmonary TB and chronic pulmonary aspergillosis: clinical differences and similarities. Int J Tuberc Lung Dis. 2021;25(7):537–546. doi:10.5588/ijtld.21.0034 [PubMed: 34183098]
6. Denning DW, Cadranel J, Beigelman-Aubry C, et al. Chronic pulmonary aspergillosis: Rationale and clinical guidelines for diagnosis and management. Eur Respir J. 2016;47(1):45–68. doi:10.1183/13993003.00583-2015 [PubMed: 26699723]
7. World Health Organization. Uganda Tuberculosis Profile; 2018. www.who.int/tb/data.

8. Kwizera R, Parkes-Ratanshi R, Page ID, et al. Elevated Aspergillus-specific antibody levels among HIV infected Ugandans with pulmonary tuberculosis. BMC Pulm Med. 2017;17(1):149. doi:10.1186/s12890-017-0500-9 [PubMed: 29162063]
9. Page ID, Byanyima R, Hosmane S, et al. Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation. Eur Respir J. 2019;53(3). doi:10.1183/13993003.01184-2018
10. Horsburgh CR, Barry CE, Lange C. Treatment of Tuberculosis. N Engl J Med. 2015;373(22):2149–2160. doi:10.1056/NEJMra1413919 [PubMed: 26605929]
11. Piarroux RP, Romain T, Martin A, et al. Multicenter evaluation of a novel immunochromatographic test for anti-aspergillus IgG detection. Front Cell Infect Microbiol. 2019;9(JAN):1–7. doi:10.3389/fcimb.2019.00012 [PubMed: 30719427]
12. Vergidis P, Moore CB, Novak-Frazer L, et al. High-volume culture and quantitative real-time PCR for the detection of Aspergillus in sputum. Clin Microbiol Infect. December 2020. doi:10.1016/j.cmi.2019.11.019
13. Denning DW, Page ID, Chakaya J, et al. Case definition of chronic pulmonary aspergillosis in resource-constrained settings. Emerg Infect Dis. 2018;24(8):e1–e13. doi:10.3201/eid2408.171312
14. Grace AG, Mittal A, Jain S, et al. Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis. Cochrane Database Syst Rev. 2019;2019(12). doi:10.1002/14651858.CD012918.pub2
15. Al-Shair K, Atherton GT, Harris C, Ratcliffe L, Newton PJ, Denning DW. Long-term antifungal treatment improves health status in patients with chronic pulmonary aspergillosis: A longitudinal analysis. Clin Infect Dis. 2013;57(6):828–835. doi:10.1093/cid/cit411 [PubMed: 23788240]
16. Olum R, Osaigbovo II, Baluku JB, Stemler J, Kwizera R, Bongomin F. Mapping of chronic pulmonary aspergillosis in africa. J Fungi. 2021;7(10):790. doi:10.3390/jof7100790
17. Oladele RO, Irurhe NK, Foden P, et al. Chronic pulmonary aspergillosis as a cause of smear-negative TB and/or TB treatment failure in Nigerians. Int J Tuberc Lung Dis. 2017;21(9):1056–1061. doi:10.5588/ijtld.17.0060 [PubMed: 28826456]
18. Rozaliyani A, Rosianawati H, Handayani D, et al. Chronic Pulmonary Aspergillosis in Post Tuberculosis Patients in Indonesia and the Role of LDBio Aspergillus ICT as Part of the Diagnosis Scheme. J Fungi. 2020;6(4):318. doi:10.3390/jof6040318
19. Hedayati MT, Azimi Y, Droudinia A, et al. Prevalence of chronic pulmonary aspergillosis in patients with tuberculosis from Iran. Eur J Clin Microbiol Infect Dis. 2015;34(9):1759–1765. doi:10.1007/s10096-015-2409-7 [PubMed: 26003310]
20. Nguyen NTB, Le Ngoc H, Nguyen NV, et al. Chronic Pulmonary Aspergillosis Situation among Post Tuberculosis Patients in Vietnam: An Observational Study. J Fungi. 2021;7(7):532. doi:10.3390/jof7070532
21. Kwizera R, Katende A, Bongomin F, Nakiyingi L, Kirenga BJ. Misdiagnosis of chronic pulmonary aspergillosis as pulmonary tuberculosis at a tertiary care center in Uganda: a case series. J Med Case Rep. 2021;15(1):140. doi:10.1186/s13256-021-02721-9 [PubMed: 33781313]
22. Page ID, Richardson M, Denning DW. Antibody testing in aspergillosis - Quo vadis? Med Mycol. 2015;53(5):417–439. doi:10.1093/mmy/myv020 [PubMed: 25980000]
23. Bongomin F, Govender NP, Chakrabarti A, et al. Essential in vitro diagnostics for advanced HIV and serious fungal diseases: international experts' consensus recommendations. Eur J Clin Microbiol Infect Dis. 2019;38(9):1581–1584. doi:10.1007/s10096-019-03600-4 [PubMed: 31175479]
24. Stucky Hunter E, Richardson MD, Denning DW. Evaluation of LDBio Aspergillus ICT Lateral Flow Assay for IgG and IgM Antibody Detection in Chronic Pulmonary Aspergillosis. J Clin Microbiol. 2019;57(9). doi:10.1128/JCM.00538-19
25. Hunter ES, Page ID, Richardson MD, Denning DW. Evaluation of the LDBio aspergillus ICT lateral flow assay for serodiagnosis of allergic bronchopulmonary aspergillosis. Kniemeyer O, ed. PLoS One. 2020;15(9 September 2020):e0238855. doi:10.1371/journal.pone.0238855 [PubMed: 32976540]

26. Bongomin F, Asio LG, Baluku JB, Kwizera R, Denning DW. Chronic Pulmonary Aspergillosis: Notes for a Clinician in a Resource-Limited Setting Where There Is No Mycologist. J Fungi. 2020;6(2):75. doi:10.3390/jof6020075

27. Bongomin F, Harris C, Hayes G, Kosmidis C, Denning DW. Twelve-month clinical outcomes of 206 patients with chronic pulmonary aspergillosis. Chotirmall SH, ed. PLoS One. 2018;13(4):e0193732. doi:10.1371/journal.pone.0193732 [PubMed: 29634721]

28. Bongomin F, Olum R, Kwizera R, Baluku JB. Surgical management of chronic pulmonary aspergillosis in Africa: A systematic review of 891 cases. Mycoses. 2021;64(10):1151–1158. doi:10.1111/myc.13359 [PubMed: 34363630]

29. Al-Shair K, Muldoon EG, Morris J, Atherton GT, Kosmidis C, Denning DW. Characterisation of fatigue and its substantial impact on health status in a large cohort of patients with chronic pulmonary aspergillosis (CPA). Respir Med. 2016;114:117–122. doi:10.1016/j.rmed.2016.03.020 [PubMed: 27109821]

30. Agarwal R, Vishwanath G, Aggarwal AN, Garg M, Gupta D, Chakrabarti A. Itraconazole in chronic cavitary pulmonary aspergillosis: A randomised controlled trial and systematic review of literature. Mycoses. 2013;56(5):559–570. doi:10.1111/myc.12075 [PubMed: 23496375]

31. Chrdle A, Mustakim S, Bright-Thomas RJ, Baxter CG, Felton T, Denning DW. Aspergillus bronchitis without significant immunocompromise. Ann N Y Acad Sci. 2012;1272(1):73–85. doi:10.1111/j.1749-6632.2012.06816.x [PubMed: 23231717]

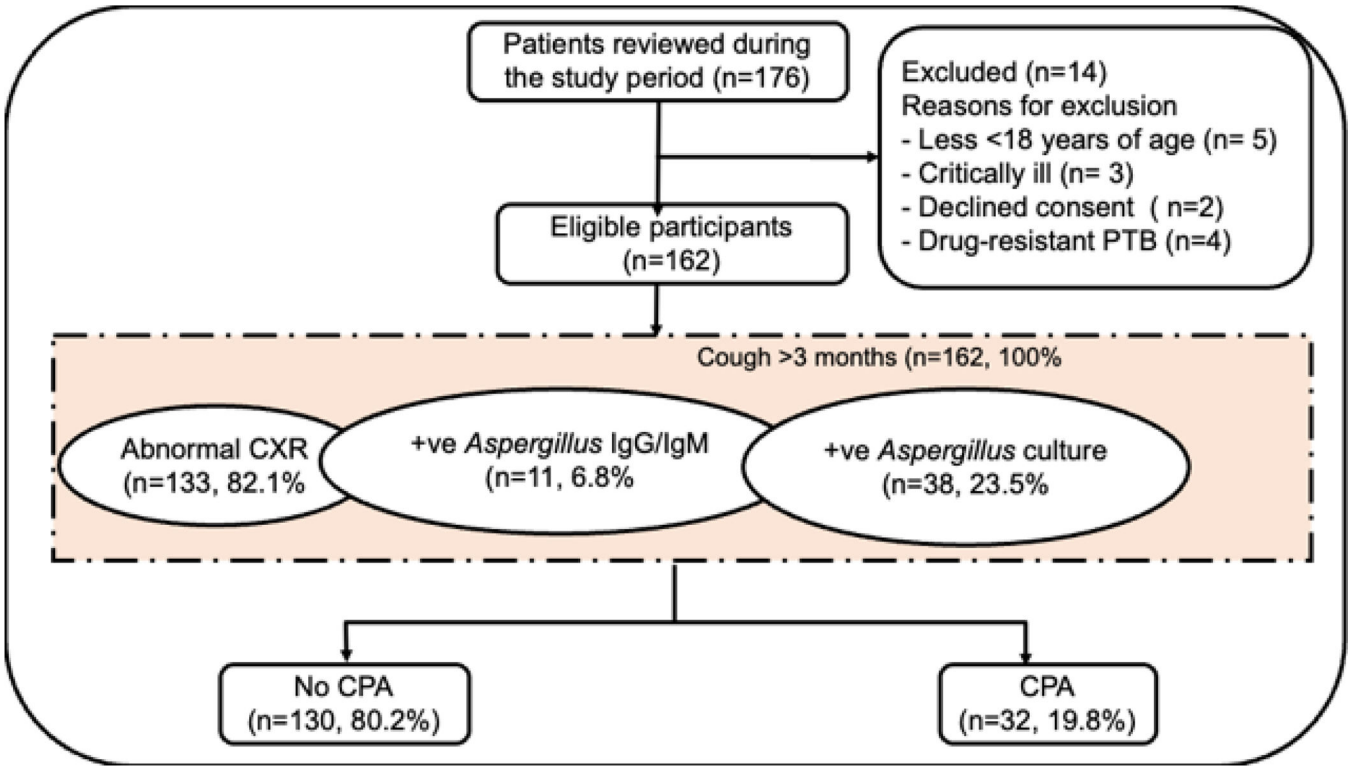

Figure. 1. Study enrollment

Figure 2. A positive *Aspergillus* IgG/IgM ICT

Figure 3. A positive *Aspergillus fumigatus* fungal culture

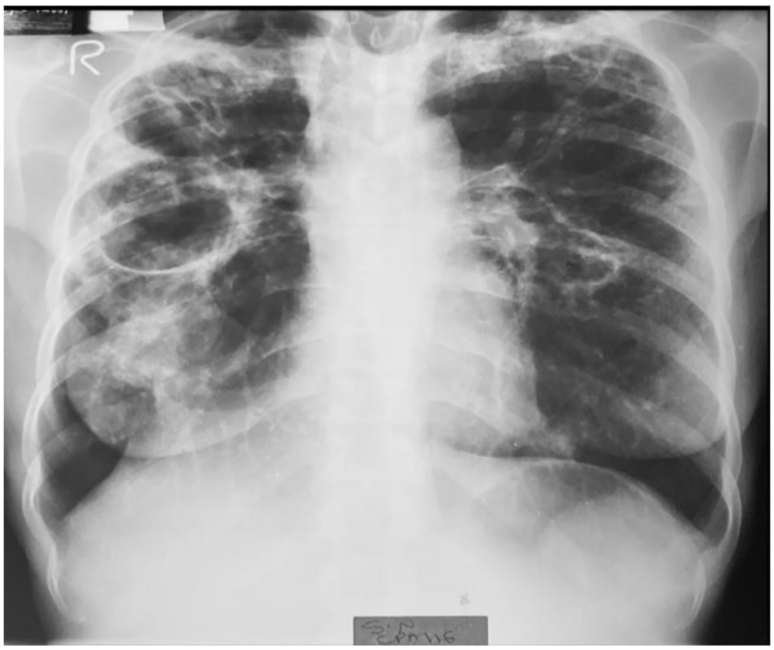

Figure 4. A CXR of a CPA negative case

Thirty-six-year-old female who was enrolled with complaints of a persistent cough, fevers, nights sweats, and chest pain after 2 months of PTB therapy. She had no prior TB treatment history. She was HIV negative. CXR showed multiple bilateral cavities, extensive air space infiltrates, and fibrosis. *Aspergillus* LFD was negative and fungal culture showed no significant growth

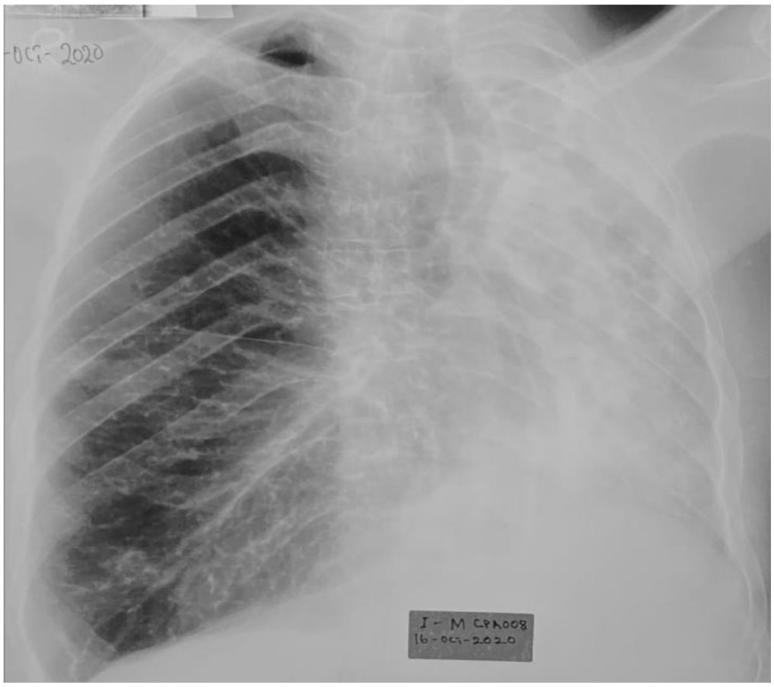

Figure 5. A CXR of a confirmed CPA case.

A 43-year male who was enrolled with complaints of a persistent cough, weight loss, and nights sweats after 2 months of PTB therapy. He had previously been treated for PTB 7 years ago and cured. He was HIV positive with a CD4 count of 423 cells/microlitre and a viral load of less than 50 copies/ml. He had history of smoking (1.5 pack years), and history of alcohol abuse. CXR showed far advanced disease with left lung collapse, and right linear opacities. *Aspergillus* LFD was positive and fungal culture grew *A*. fumigatus.

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Table 1

Factors associated to CPA in active PTB

Characteristics	All, (%)	CPA negative n (%) n=130	CPA positive n(%) n=32	Crude OR, (95 %CI)	P value	Adjusted OR, (95 %CI)	P value
Smoking status							
No	149 (92.0)	122(93.9)	27 (84.4)	Reference			
Yes	13 (8.0)	8 (6.1)	5 (15.6)	2.82 (0.85–9.31)	0.088		
Currently working							
No	98 (60.5)	81 (62.3)	17(53.1)	Reference			
Yes	64 (39.5)	49 (37.7)	15 (46.9)	1.45 (0.67–3.18)	0.343		
HIV							
Negative	114 (70.4)	90 (69.2)	24 (75.0)	Reference		Reference	
Positive	48 (29.6)	39 (30.8)	8 (25.0)	0.75 (0.31–1.81)	0.523	0.75 (0.28–2.01)	0.567
Sex							
Male	97 (60.0)	73 (55.6)	24(75.0)	Reference		Reference	
Female	65 (40.0)	57 (43.8)	8(25.0)	0.43 (0.18–1.02)	0.056	0.69 (0.26–1.88)	0.478
Prior TB							
No	147 (90.7)	123 (94.6)	28 (75.0)	Reference		Reference	
Yes	15 (9.3)	7 (5.4)	8 (25.0)	5.85(1.94–17.67)	0.002	6.66(1.85–23.9)	0.004
Alcohol intake							
No	110 (58.0)	92 (70.8)	18 (56.2)	Reference			
Yes	52 (32.0)	38 (29.2)	14 (43.8)	1.88 (0. 85–4.17)	0.075		
Age categorized (n=161)							
<40	119 (74.0)	99 (76.7)	20(62.5)	Reference		Reference	
40–49	21 (13.0)	17 (13.2)	4 (12.5)	1.16 (0.35–3.83)	0.802	0.72 (0.16–3.23)	0.670
50 and above years	21 (13.0)	13 (10.1)	8(25.0)	3.05 (1.12–8.31)	0.030	2.32 (0.72–7.49)	0.157
Measles							
No	143 (88.3)	116(89.2)	27 (84.4)	Reference			
Yes	19 (11.7)	14 (10.8)	5 (15.6)	1.53(0.51–4.63)	0.447		
Disease extent on Chest X-ray (n=162)	16 (9.9)						
Normal/minimal moderate advanced disease	99 (69.8)	88 (67.7)	11(34.4)	Reference		Reference	
Far advanced disease	63 (30.2)	42 (32.3)	21(65.6)	4.0 (1.77–9.05)	0.001	4.26(1.72–10.52)	0.002

Table 2

Table of other clinical characteristics

Characteristics	All, (%)	CPA positive n (%) n=32	CPA negative n(%) n=130	P-value
Shortness of breath	67 (41.4)	10 (27.8)	57 (45.2)	0.061
Weight loss	84 (51.8)	18 (56.3)	66 (50.8)	0.900
Fatigue				
yes	75 (46.3)	15 (46.9)	60 (46.1)	0.899
Fever				
yes	31 (19.1)	5 (15.6)	26 (20.0)	0.669
Loss of appetite				
yes	59 (36.4)	11 (34.4)	48 (36.9)	0.663
Shortness of breath				
yes	67 (41.4)	9 (28.1)	58 (44.6)	0.061
Hemoptysis				
Yes	20 (12.4)	7 (21.9)	13 (10.0)	0.142
Night sweats				
Yes	105 (64.8)	18(56.3)	87 (66.9)	0.086
Chest pain				
Yes	150 (92.6)	29 (90.6)	121 (93.1)	0.016
Wheezing				
Yes	15 (9.3)	12 (9.2)	3 (9.4)	0.828

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Table 3

Table showing how X ray findings vary by CPA diagnosis

Characteristic	All, n(%)	CPA positive n (%) n=32	CPA negative n(%) n=130	P value
Disease location, n=133				
Right chest	36 (27.1)	10 (25.7)	26 (25.7)	
Left chest	27 (20.3)	9 (28.1)	18 (17.8)	
both	70 (52.6)	13 (40.6)	57 (56.4)	0.273
Number of lung zones involved by disease (n=162)				
0	29 (17.9)	0 (0.0)	29 (22.3)	
1	19 (11.7)	2 (6.2)	17 (13.1)	
2	34 (21.0)	10 (31.2)	24 (18.5)	
3	26 (16.1)	8 (25.0)	18 (13.8)	
4	19 (11.7)	5 (15.6)	14 (10.8)	
5	11 (6.8)	1 (3.0)	10 (7.7)	
6	24 (14.8)	6 (25.0)	18 (13.8)	0.009
Infiltrates in upper lung field, n=100				
Present in the right side	31 (21.8)	9 (32.1)	22 (30.5)	
Present in the left side	28 (25.2)	9 (32.1)	19 (26.4)	
Present in both	41 (53.0)	10 (35.7)	31 (43.1)	0.771
Fibrosis/volume loss (n=83)				
Present in the right side	40 (48.2)	12 (42.9)	28 (50.9)	
Present in the left side	29 (34.9)	11 (39.3)	18 (32.7)	
Present in both	14 (16.9)	5 (17.9)	9 (16.4)	0.778
Cavity n=52				
Present in the right side	28 (53.8)	7 (36.8)	21 (63.6)	
Present in the left side	20 (38.5)	11 (57.9)	9 (27.3)	
Present in both	4 (7.7)	1 (5.3)	1 (9.0)	0.096
Milliary disease, n=3				
1	1 (33.3)	0 (0.0)	1 (33.3)	
3	2 (66.7)	0 (0.0)	2 (66.7)	
Adenopathy n=15				

Characteristic	All, n(%)	CPA positive n (%) n=32	CPA negative n(%) n=130	P value
Present in the right side	1 (6.7)	1 (33.3)	0 (0.0)	
Present in the left side	3 (20.0)	0 (0.0)	3 (25.0)	
Present in both	11 (73.3)	2 (66.7)	9 (75.0)	0.275
Pleural thickening, n=58				
Present in the right side	26 (44.8)	9 (40.9)	17 (47.2)	
Present in the left side	20 (34.5)	8 (35.4)	12 (33.3)	
Present in both	12 (20.7)	5 (22.7)	7 (19.4)	0.883
Pleural effusion, n=23				
Present in the right side	12 (52.2)	4(50.0)	8 (53.3)	
Present in the left side	9 (39.1)	4(50.0)	5 (33.3)	
Present in both	2 (8.7)	0 (0.0)	2 (13.3)	0.695
Fungal ball, n=6				
Present in the right side	5 (83.3)	2 (66.7)	3 (100.0)	
Present in the left side	1 (16.7)	1 (33.3)	0 (0.0)	1.00
Nodular disease, n=27				
Present in the right side	2 (7.4)	0 (0.0)	2 (9.5)	
Present in the left side	2 (7.4)	1(16.7)	1 (4.8)	
Present in both	23 (85.2)	5 (83.3)	18 (85.7)	0.659
Other findings, n=10				
Present in the right side	5 (50.0)	1 (50.0)	4 (50.0)	
Present in the left side	2 (20.0)	0 (0.0)	2 (25.0)	
Present in both	3 (30.0)	1 (50.0)	2 (25.0)	1.00