

## Pulmonary TB and chronic pulmonary aspergillosis: clinical differences and similarities

J. B. Baluku,<sup>1,2</sup> E. Nuwagira,<sup>3</sup> F. Bongomin,<sup>4</sup> D. W. Denning<sup>5</sup>

<sup>1</sup>Division of Pulmonology, Kiruddu National Referral Hospital, Kampala, <sup>2</sup>Directorate of Programs, Mildmay Uganda, Wakiso, <sup>3</sup>Department of Internal Medicine, Mbarara University of Science and Technology, Mbarara,

<sup>4</sup>Department of Medical Microbiology & Immunology, Faculty of Medicine, Gulu University, Gulu, Uganda;

<sup>5</sup>Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

### SUMMARY

**BACKGROUND:** Pulmonary TB (PTB) and chronic pulmonary aspergillosis (CPA) are both progressive and debilitating parenchymal lung diseases with overlapping risk factors, symptomatology and radiological findings that often result in misdiagnosis of either disease.

**METHODS:** We undertook a narrative review approach to describe the clinical and radiological manifestations of CPA and PTB and highlight the salient features that differentiate these two closely related maladies.

**RESULTS:** CPA is a frequent complication of treated PTB. In fact, 15–90% of CPA cases occur in patients with residual lung lesions following treatment for PTB. While CPA predominantly affects older patients with underlying lung diseases, both PTB and CPA present with clinically indistinguishable symptoms. Chest imag-

ing findings of cavitation and fibrosis are common to both diseases. However, lymphadenopathy, miliary pattern and pleural effusion are predictive of active PTB, while aspergilloma, pleural thickening and paracavitary fibrosis are more common in CPA. *Aspergillus*-specific IgG serology has a central role in differentiating PTB (both active and healed) from CPA with a high sensitivity and specificity.

**CONCLUSION:** *Aspergillus*-specific IgG serology is key in differentiating PTB and PTB relapse from CPA. It may be worthwhile developing clinical predictive scores that can be used in low-income settings to differentiate active TB, post-TB disease and TB+CPA co-infection.

**KEY WORDS:** tuberculosis; clinical features; CPA; differential diagnosis; differences

TB CAUSED BY *Mycobacterium tuberculosis* is the leading cause of death from an infectious agent globally, accounting for 1.4 million deaths among HIV-negative and HIV-positive individuals in 2019.<sup>1</sup> Although the global TB treatment success for drug-susceptible TB is high, at 85%,<sup>1</sup> acute and chronic complications of TB contribute significant disability and mortality even after TB treatment “success”.<sup>2</sup> There has been a modest decline in global TB-related mortality in the recent past, of 14%, between 2015 and 2019<sup>1</sup> (compared with a 9% difference between 2006 and 2016<sup>3</sup>). However, this estimate does not account for the excess TB mortality occurring after a TB treatment outcome has been documented. After completion of TB treatment, previously treated patients are three times more likely to die than individuals without TB, and this is independent of age, sex, country income and type of TB<sup>4</sup> or drug resistance profile.<sup>5</sup>

The lung is the most common site of TB infection, observed in 83% of patients with active TB.<sup>6</sup>

However, active pulmonary TB (PTB) is characterised by immune-mediated lung inflammation, cavitation and fibrosis that result in an array of lung parenchymal structural defects even after TB cure.<sup>7</sup> For this reason, there are growing calls for programmatic follow-up of TB patients after TB cure or treatment completion.<sup>8,9</sup> These calls draw attention to the several post-TB pulmonary complications that occur due to structural changes in the lung (such as chronic obstructive airway disease, bronchiectasis and fibrosis), psychosocial morbidities and respiratory infections.<sup>9,10</sup>

Predominantly caused by *Aspergillus fumigatus*, chronic pulmonary aspergillosis (CPA) is an important post-TB respiratory infection and a complication in 6–25% of patients with post-TB cavities.<sup>11</sup> In fact, 15–90% of patients with CPA have a history of prior PTB treatment.<sup>12</sup> About 450,000 deaths are attributed to CPA worldwide; these mostly arise due to pulmonary haemorrhage, bacterial co-infections or respiratory failure.<sup>13</sup> CPA comprises a constellation

Correspondence to: Joseph Baruch Baluku, PO Box 26343, Kampala, Uganda. email: [bbjoe18@gmail.com](mailto:bbjoe18@gmail.com); [joseph.baluku@mildmay.or.ug](mailto:joseph.baluku@mildmay.or.ug)

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of clinical syndromes ranging from a single pulmonary nodule, simple pulmonary aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA) to chronic fibrosing pulmonary aspergillosis (CFPA), which tend to occur among apparently immunocompetent individuals with underlying structural lung disease.<sup>14</sup> CPA requires a criterion-based diagnosis, i.e., duration of illness of  $\geq 3$  months, mycological and serological evidence of *Aspergillus* infection, compatible chest imaging and clinical symptomatology, and exclusion of alternative diagnoses.<sup>14</sup> The early features of CPA are typically asymptomatic, and screening would identify patients earlier.

An attendant problem of diagnosing CPA among patients with and without active TB or post-TB lung disease is the overlap of the geographical distribution, risk factors, symptomatology, clinical signs and radiological findings of *Aspergillus* and TB infection.<sup>15</sup> Moreover, a recent systematic review and meta-analysis found the prevalence of *Aspergillus* co-infection among PTB patients,<sup>16</sup> that is, the simultaneous presence of pulmonary *M. tuberculosis* infection and *Aspergillus* spp. in sputum, bronchial alveolar lavage specimens, or serological evidence of *Aspergillus* spp. with or without meeting the diagnostic criteria for CPA, in Asian and African countries to be 3.3–37%; this was associated with low body mass index, diabetes, smoking and male sex, which are known risk factors of TB.<sup>17</sup> In this review, we present similarities and differences between CPA and PTB to help clinicians in arriving at a proper diagnosis for either disease to allow early commencement of targeted treatment and improve treatment outcomes.

#### Ethical considerations

Ethical approval and informed consent were not required, as this is a review article.

### GEOGRAPHICAL OVERLAP OF TB AND CPA

There is considerable overlap between the global distribution of TB, *Aspergillus*/TB co-infection and post-TB CPA, and indeed, both are global diseases. In 2019, 10 million people fell ill with TB (84% of those notified had PTB), of whom the South-East Asia (44%) and Africa (25%) regions contributed the majority of cases.<sup>1</sup> India contributed the majority of global TB cases (26%).<sup>1</sup> During active TB infection, *Aspergillus* co-infection is not uncommon. The prevalence of the co-infection is reported to be high in Africa (17.7%) and Asia (14.7%), with India posting a prevalence of 5–25%.<sup>16</sup> In other high TB burden countries, co-infection is reported to be prevalent in 11.3% in Pakistan, 5.2% in Kenya<sup>18</sup> and 33.3% in Cameroon.<sup>19</sup> In Japan, an intermediate TB burden country, 14% of patients with CPA were reported to have active TB disease.<sup>20</sup>

The global estimate of the number of cases of CPA is not well documented due to lack of programmatic reporting of these cases. One deterministic model, based on the number of TB cases reported in 2005, estimated an annual incidence of over 370,000 cases of CPA after successful TB treatment globally.<sup>21</sup> In tandem with global TB cases, estimates based on the model suggest that the majority of CPA cases came from the South East Asian and African regions, with India accounting for the majority of cases among individual countries.<sup>21</sup> Using this model, the incidence of post-TB CPA is estimated to be 14.5 cases per 100,000 per year in Ethiopia, a high TB burden country.<sup>22</sup> In India, another modelling study estimates up to 170,000 incident cases of post TB CPA.<sup>23</sup> In Nigeria, another high TB burden country, 8.7% of TB patients in their last month of TB therapy or those with smear-negative TB were reported to have CPA.<sup>24</sup> In Indonesia, about 13% of patients completing TB therapy had CPA.<sup>25</sup> Among patients with underlying respiratory diseases and long-standing respiratory signs and symptoms in Cuba, 44.7% had confirmed CPA, 4.8% of whom had PTB.<sup>26</sup> In Pakistan, previous TB was the cause of CPA in 87% of cases at one tertiary institution,<sup>27</sup> and 39/100,000 cases of CPA are estimated nationally.<sup>28</sup> A study in northern Uganda, a high TB-HIV burden country, reported a CPA prevalence of 4.2% among patients with previous TB.<sup>29</sup>

### RISK FACTORS FOR TB AND CPA

As shown in Table 1, there is an overlap in the risk factors for CPA among patients with active TB, those without TB and TB patients without CPA. Underlying lung disease, especially TB,<sup>27,30</sup> is the most predominant risk factor for CPA. All patients with CPA had at least one underlying lung disease in a cohort of 70 patients in Korea.<sup>30</sup> Underlying structural lung disease is not a predominant risk factor for PTB. While chronic lung diseases such as chronic obstructive pulmonary disease (COPD) may be associated with increased risk for TB,<sup>31</sup> there is substantial evidence linking previous active TB to increased risk of chronic lung diseases as well.<sup>32</sup> A study of 126 cases with CPA in the United Kingdom reported that previous mycobacterial infection (including non-tuberculous mycobacteria [NTM]) was the most common underlying condition found in 30% of the cases; allergic bronchopulmonary aspergillosis (ABPA) was found in 12%, while COPD/emphysema, pneumothorax, history of treated lung cancer and pneumonia were each found in  $<10\%$  of the cases.<sup>12</sup> Similarly, previous TB (87%) and ABPA (12%) were the most common underlying lung pathology in cases of CPA in Pakistan.<sup>27</sup> In that study, steroid use (37%) and diabetes (28%) were the most common non-pulmonary conditions. Steroid use and cavitary-type

**Table 1** Risk factors of CPA and TB

| Risk factors for CPA and TB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | References            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Risk factors of <i>Aspergillus</i> infection and CPA among patients with active TB and other mycobacterial infections <ul style="list-style-type: none"> <li>• Age of <math>\geq 40</math> years</li> <li>• Smoking</li> <li>• Diabetes</li> <li>• Low body mass index</li> <li>• Male sex</li> <li>• Steroid use</li> <li>• Cavitory disease</li> </ul>                                                                                                                                                                                                                                                                                                                                   | 16,33                 |
| Risk factors for CPA without active TB <ul style="list-style-type: none"> <li>• Underlying lung pathology: previous TB, ABPA, COPD, emphysema, pneumothorax, previous lung cancer, interstitial lung disease, previous thoracotomy, postoperative pulmonary complications</li> <li>• Age <math>\geq 60</math> years</li> <li>• Male sex</li> <li>• Smoking</li> <li>• Diabetes</li> <li>• Sarcoidosis</li> <li>• Low body mass index</li> <li>• <i>Mycobacterium abscessus</i> complex</li> <li>• Fibro-cavitory non-tuberculous mycobacterium</li> <li>• Steroid use</li> <li>• Receiving both chemotherapy and radiotherapy for lung cancer</li> <li>• Genetic susceptibility</li> </ul> | 12,25,27,34, 35,73–75 |
| Risk factors for TB without CPA <ul style="list-style-type: none"> <li>• Immune suppressive states such as HIV, immunosuppressive therapy, including tumour necrosis factor-alpha inhibitors and steroid use</li> <li>• Malnutrition</li> <li>• Age <math>&lt; 2</math> years and 15–55 years</li> <li>• Male sex</li> <li>• Diabetes</li> <li>• Health care workers</li> <li>• Tobacco smoking</li> <li>• Alcohol use</li> <li>• Low socio-economic status</li> <li>• Genetic susceptibility</li> </ul>                                                                                                                                                                                   | 1,17,38,76            |

CPA = chronic pulmonary aspergillosis; ABPA = allergic bronchopulmonary aspergillosis; COPD = chronic obstructive airway disease.

NTM were found to be risk factors for CPA among patients with NTM in Japan.<sup>33</sup> In a large cohort of 566 patients who underwent treatment for NTM in South Korea, older age, male sex, steroid use, low body mass index (BMI), COPD, fibro-cavitory NTM and *M. abscessus* complex were associated with incident CPA.<sup>34</sup> After lung cancer surgery, low BMI, underlying interstitial lung disease, smoking, thoracotomy, receiving both chemotherapy and radiotherapy, and post pulmonary complications predict incident CPA.<sup>35</sup> While alcohol use is associated with increased TB risk, it was not associated with CPA among patients with TB co-infection in India.<sup>36</sup> Also, whereas low socio-economic status is widely recognised as a risk factor for TB infection and disease, the effect of socio-economic status on the risk for CPA (independent of TB) is not well documented.<sup>37</sup> Patients with CPA are more likely to be older ( $\geq 40$  years), while active TB is traditionally known to be

more common in infants ( $< 4$  years), during adolescence (15–19 years) and those aged 20–30 years.<sup>38</sup> However, the 2020 WHO global TB report shows a peak in incident TB cases in those aged 15–55 years globally and in the  $> 65$  years age group in the East Mediterranean and West Pacific regions.<sup>1</sup> CPA is very rare in children,<sup>39</sup> and this could be attributed to the low incidence of cavitory TB, which tends to occur in older children.<sup>40</sup>

## CLINICAL FEATURES OF TB AND CPA

CPA and TB have similar clinical manifestations and patients with post-TB CPA are often misdiagnosed as having TB recurrence, especially in low-resource settings, where diagnostics are a challenge. Respiratory symptoms of TB often persist in as many as 60% of TB survivors after completion of treatment and cure even without CPA.<sup>41,42</sup> In a Ugandan cohort, patients who were mostly subsistence farmers residing in traditional grass-roofed homes continued to experience symptoms of breathlessness, easy fatigability, chest pain and cough up to 2 years post-TB treatment.<sup>43</sup> While these symptoms could suggest TB relapse, 5% of these patients had confirmed CPA at follow-up.

Symptoms alone have varied sensitivity and specificity for either disease. One systematic review found that in the diagnosis of TB, the sensitivity and specificity of “any cough” and “any symptom” (including cough, haemoptysis, fever, night sweats and weight loss) was respectively 57% and 80%, and 77% and 68%.<sup>44</sup> Although prolonged cough ( $> 2$ –3 weeks) had high specificity (95%), its sensitivity for TB was very low (35%). Patients with CPA are usually middle-aged and present with fever, malaise, fatigue and weight loss, in addition to chronic cough and haemoptysis.<sup>45</sup> In post-TB individuals, those with CPA are more likely to present with cough or haemoptysis, fatigue and dyspnoea than those without CPA.<sup>25,46</sup> Table 2 shows the frequency of respiratory symptoms among patients with CPA with and without concurrent active TB. To note, 6–23% of patients with CPA, especially those with *Aspergillus* nodules, may be asymptomatic.<sup>47,48</sup> With regard to clinical signs, Jakribettu et al. found that patients with CPA had crepitations (43%), rhonchi (20%) and bronchial breath sounds (13%) in a cohort of 30 patients in India.<sup>49</sup> These signs are often encountered in active PTB, and are unlikely to be specific or sensitive to either disease. Figure 1 shows the overlap of symptoms of CPA and TB.

A combination of symptoms, laboratory and imaging findings is more likely to improve diagnostic accuracy. Among post-TB individuals, a combination of positive *Aspergillus* serology, chest radiology showing cavitation or pleural thickening and symptoms had a sensitivity and specificity of respectively

**Table 2** Frequency of symptoms of CPA among patients with and without active TB

| Symptom                 | Frequency of symptoms<br>in CPA without active TB<br>% | References           | Frequency of symptoms<br>in CPA with active TB <sup>77</sup><br>% |
|-------------------------|--------------------------------------------------------|----------------------|-------------------------------------------------------------------|
| Cough                   | 39–100                                                 | 25–27,30,46–49,78,79 | 100                                                               |
| Haemoptysis             | 13–93                                                  | 25,27,30,46–49,78–80 | 36                                                                |
| Fatigue                 | 14–58                                                  | 25,26,46             | 64                                                                |
| Sputum production       | 6–93                                                   | 30,47,48,78,79       | 93                                                                |
| Fever                   | 17–47                                                  | 27,48,49,79          | 43                                                                |
| Breathlessness/dyspnoea | 7–43                                                   | 25–27,46,48,49,79    | Not specified                                                     |
| Chest pain/discomfort   | 4–30                                                   | 25–27,46,48,49,79    | Not specified                                                     |
| Asymptomatic            | 6–23                                                   | 47,48                | Not specified                                                     |
| Weight loss             | 0–51                                                   | 25–27,30             | 57                                                                |
| Anorexia                | 10                                                     | 26,27                | Not specified                                                     |
| Chills and rigors       | 17                                                     | 49                   | Not specified                                                     |
| Orthopnoea              | 7                                                      | 49                   | Not specified                                                     |
| Wheezing                | 3                                                      | 49                   | Not specified                                                     |

CPA = chronic pulmonary aspergillosis.

92.3% and 98.5% for CPA.<sup>43</sup> Among patients with suspected TB, a combination of any symptom with characteristic chest X-ray findings has a sensitivity of 90–100% and specificity of 69–92% for TB.<sup>44</sup>

### RADIOLOGICAL FEATURES OF TB AND CPA

Imaging is essential in the diagnosis of both PTB and CPA. In fact, CPA phenotypes are classified based on radiological findings: single or multiple nodules (*Aspergillus* nodules), single cavity with a fungal ball (simple aspergilloma), multiple enlarging cavities with or without fungal ball (CCPA), or CCPA with features of extensive para-cavitary or pleural fibrosis (CFPA).<sup>14</sup>

Radiological features such as infiltrates, cavitation, bronchiectasis, pleural thickening, fibrosis and nodular appearances are common to both CPA and PTB (Figure 1).<sup>50,51</sup> Moreover, both diseases have apical

and middle lobe predominance (Figures 2 and 3). A systematic review of computed tomography (CT) imaging findings among survivors of PTB found varying frequencies of chest pathology: cavitation (7.4–34.6%), fibrosis (70.0–92.6%), bronchiectasis (35.0–86.0%), pleural thickening (0.1–50.0%), nodules (25.9–55.8%), consolidation (3.7–19.2%) and emphysema (15.4–45.0%);<sup>52</sup> it is unclear whether some patients in these studies had CPA as well. This makes differentiating TB relapse and other post-TB disease from post-TB CPA difficult. However, while adenopathy and pleural effusion are more common in patients with active TB (Figure 2), the presence of intra-cavitary fungal ball, pleural thickening, and paracavitary fibrosis are more commonly seen in patients with CPA (Figure 3). Among patients with CPA diagnosed in Indonesia, patients with CPA had more cavitation (100% vs. 50%), paracavitary fibrosis (50% vs. 11%) and fungal ball (20% vs.

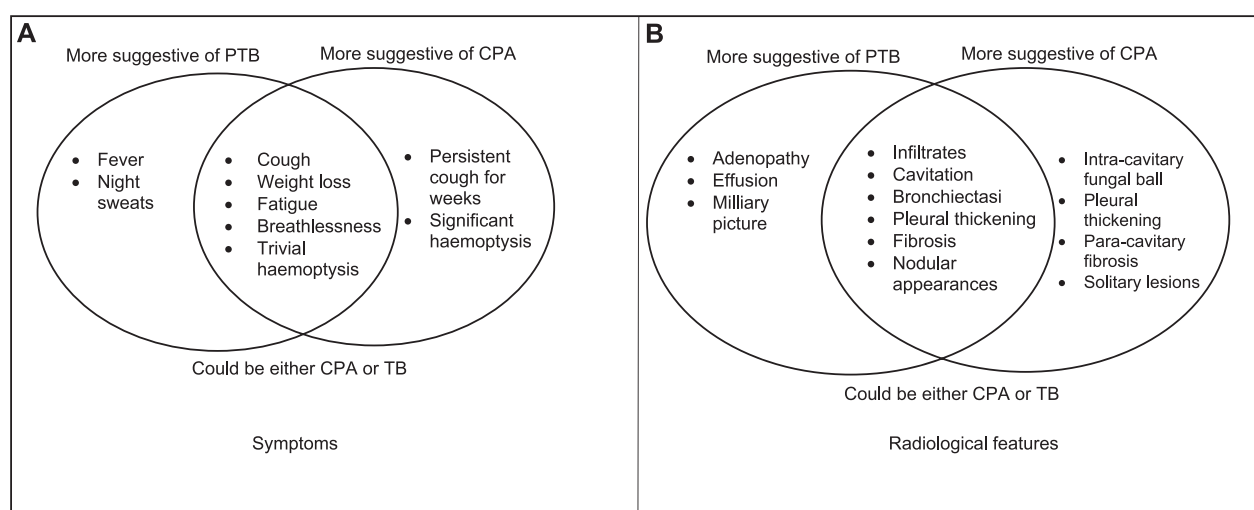


**Figure 1** Figure 1 showing symptoms and radiological findings of CPA and PTB. **Panel A** (symptoms): Many of the symptoms of TB and CPA are similar and both infections can occur together. This figure indicates those symptoms that are common to both infection, and those which are much more common in TB or in CPA, but this is not universally true and is a generalisation. **Panel B** (radiological features): This figure shows that several radiological features are common to both CPA and PTB and those more common to either disease may not be very specific. PTB = pulmonary TB; CPA = chronic pulmonary aspergillosis.

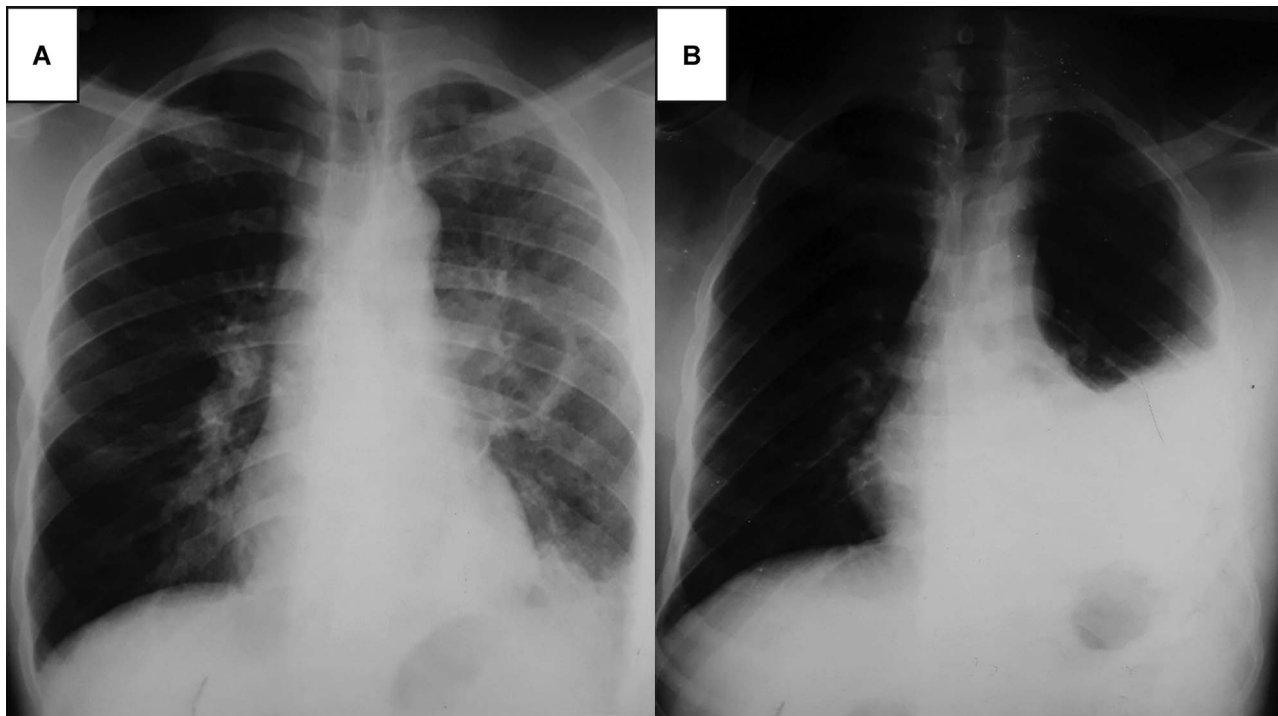


**Figure 2** Panel A) Chest X-ray showing a thin-walled cavity without intra-cavitary material in the left middle lung zone with minimal ipsilateral pleural effusion in a patient with microbiologically confirmed PTB. **Panel B** shows a chest X-ray of a patient with massive left-sided pleural effusion.

3%) than post-TB patients without CPA.<sup>46</sup> A similar observation was reported among Ugandan patients, where fungal ball (64.3% vs. 3.4%), cavitation (100% vs. 35.6%), paracavitary fibrosis (100 vs.

35.6%) and pleural thickening (100% vs. 23.7%) were more common in patients with CPA than in those without.<sup>43</sup> The presence of cavitation or pleural thickening had a negative predictive value of 100% in

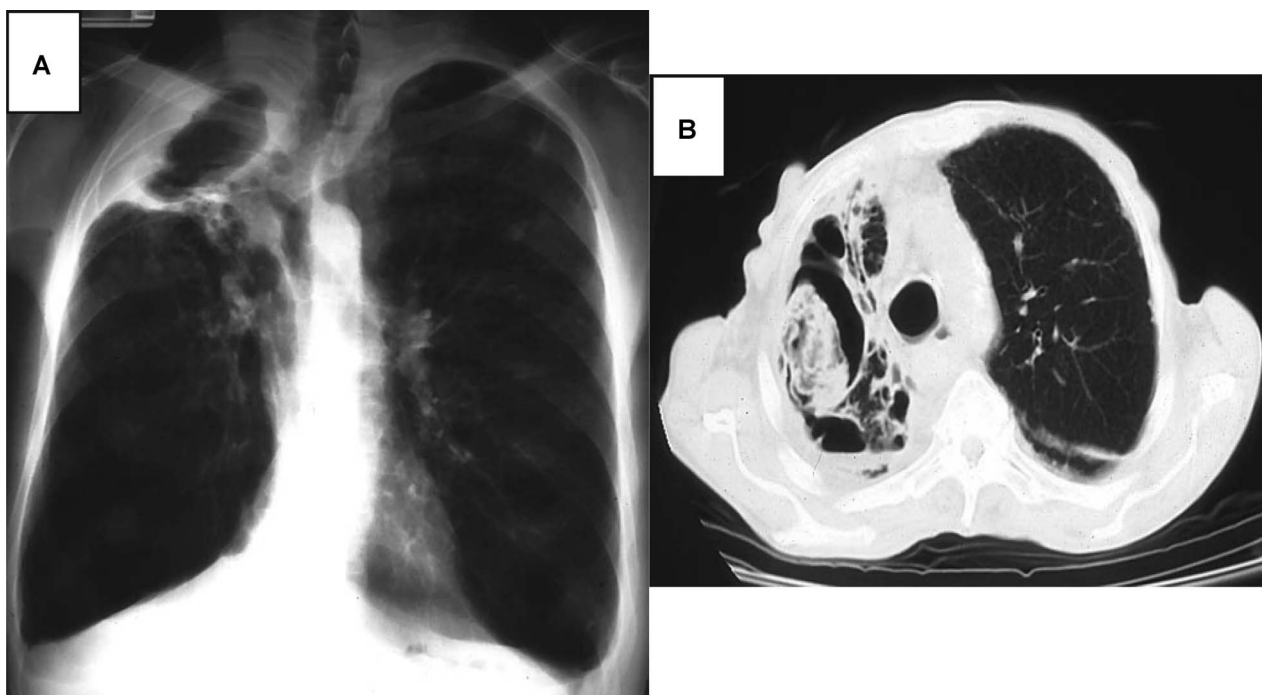


**Figure 3** A) A chest X-ray and **B)** a chest CT scan of the same patient showing a right apical thick-walled cavity with extensive paracavitary fibrosis and intracavitary material. In this case, *Aspergillus*-specific IgG was positive (titre 350 mg/L) and high-volume sputum culture was positive for *Aspergillus fumigatus*. Sputum Xpert was negative. This is consistent with the diagnosis of CCPA.

predicting CPA among patients with post-TB CPA in Uganda.<sup>43</sup> In China, among patients with CPA, 81% of chest CT abnormalities were solitary lesions.<sup>48</sup> Because of the striking similarities and slight differences in the radiological and clinical manifestations of PTB and CPA, mycobacteriological work up including GeneXpert® (Cepheid, Sunnyvale, CA, USA), sputum culture and microscopy (for PTB), and mycological culture, microscopy and *Aspergillus*-specific IgG (for CPA) are key to differentiating TB from CPA.

### LABORATORY DIAGNOSTICS IN TB AND CPA

The laboratory diagnosis of PTB has been revolutionised by the advent of nucleic-acid amplification tests (NAATs), which have the capability to detect *M. tuberculosis* complex, as well as resistance to first- and second-line anti-TB agents. The Xpert® MTB/RIF, Xpert MTB/RIF Ultra (Cepheid), first and second-line probe assays (for drug susceptibility testing [DST]), Loopamp™ MTBC assay (Human Diagnostics Worldwide, Wiesbaden, Germany), Truenat™ MTB Plus (Molbio Diagnostics, Verna, India) and Truenat™ MTB-RIF Dx for rifampicin resistance (Molbio) have been endorsed by the WHO for the diagnosis of PTB.<sup>53</sup> Compared to traditional microscopy, NAATs have higher sensitivity and specificity, lower turnaround times and DST capability. Nevertheless, their uptake in high-burden developing countries has been slow due to the high cost and need for technical expertise and infrastructure that is often inexistent at lower health facilities in these settings, where sputum microscopy is still the predominant diagnostic modality.<sup>54</sup> Therefore, the use of sputum microscopy (with Ziehl–Neelsen or Auramine staining) and sputum culture on liquid or solid media for phenotypic DST is still widely used in low-resource settings.<sup>55</sup> Although the lateral flow urine lipoarabinomannan (LF-LAM) assay has low sensitivity for mycobacterial lipoarabinomannan antigen among HIV-positive individuals with (sensitivity is 42%) and without (sensitivity is 35%) TB symptoms, LF-LAM is recommended to be used in combination with existing TB diagnostic tests among HIV-positive individuals with signs and symptoms of TB, or those who are seriously ill, those with advanced HIV, or those with severe immune suppression (CD4 <200 cells/mm<sup>3</sup>).<sup>56</sup> TB serological tests have been reported to have very varied sensitivity (0–100%) and specificity (31–100%), and are therefore not recommended for TB diagnosis.<sup>57</sup>

Serological tests are a cornerstone of CPA diagnosis and are part of the diagnostic criteria.<sup>14</sup> Serological evidence of *Aspergillus* spp. can be demonstrated using immunodiffusion (ID), counter-immunoelectrophoresis (CIE), conventional enzyme-linked immunosorbent assay (ELISA) or lateral flow devices

(LFDs) that are inexpensive and easy to use.<sup>58</sup> *Aspergillus* LFDs (Figure 4A) have revolutionised CPA diagnosis in resource-limited settings.<sup>59</sup> ELISA has a higher diagnostic accuracy with a sensitivity and specificity of (respectively 93% and 97%) than ID/CIE (respectively 64% and 99%).<sup>60</sup> A hospital-based study has recently shown the sensitivity and specificity of *Aspergillus*-specific IgG for CPA diagnosis to be respectively 84.1% and 89.6%, and the antigen levels were correlated with response to anti-fungal treatment.<sup>61</sup> However, a key challenge is the lack of a universally accepted optimal cut-off. In a large prospective study in Taiwan, the respective seroprevalence of *Aspergillus* spp. using the cut-offs of 50, 40, 27 and 20 mg of antigen-specific antibodies per litre (mgA/L) were respectively 17%, 23%, 43% and 56% among individuals with previous TB compared to 9%, 15%, 27% and 41% among patients with active TB.<sup>62</sup> There is a need for consensus on universal or population-specific cut-offs for the diagnosis of CPA. One approach would be to consider standard deviations from a given population's mean *Aspergillus*-specific IgG level. Mycological evidence of *Aspergillus* spp. can be ascertained using traditional direct microscopy of clinical specimens and subsequent mycological culture, or using polymerase chain reaction, a molecular method where small amounts of DNA is amplified.<sup>58</sup> Serum and bronchial alveolar lavage fluid galactomannan and  $\beta$ -D-glucan antigen assays have a low diagnostic accuracy in CPA.<sup>63</sup> Similarly, conventional sputum culture has a low yield, with sensitivity less than 50%. However, high-volume culture – which necessitates inoculation of up to a millilitre of sputum sample onto Sabouraud agar – has a diagnostic accuracy comparable to or better than PCR.<sup>64</sup> This allows antifungal (triazole) susceptibility testing and guides choices of antifungal treatment (Figure 4B).

### TREATMENT OF TB AND CPA

The management of TB and CPA as separate disease entities is well-established. In drug-susceptible PTB, a standard regimen consisting of a 2-month intensive phase with rifampicin, isoniazid, pyrazinamide and ethambutol, followed by a 4-month continuation phase with rifampicin and isoniazid is recommended.<sup>65</sup> Oral itraconazole (or voriconazole) is recommended in the medical management of CCPA for a period of  $\geq 6$  months; patients with simple aspergilloma benefit from surgical resection if they have normal lung function.<sup>14</sup> Long-term therapy with triazoles may be indicated in CFPA, while uncomplicated pulmonary *Aspergillus* nodules require a “watch and wait” approach.<sup>14,66</sup> In the event of concurrent CPA and mycobacterial infection, the co-administration of rifamycins and itraconazole is associated with significant drug-drug interactions in

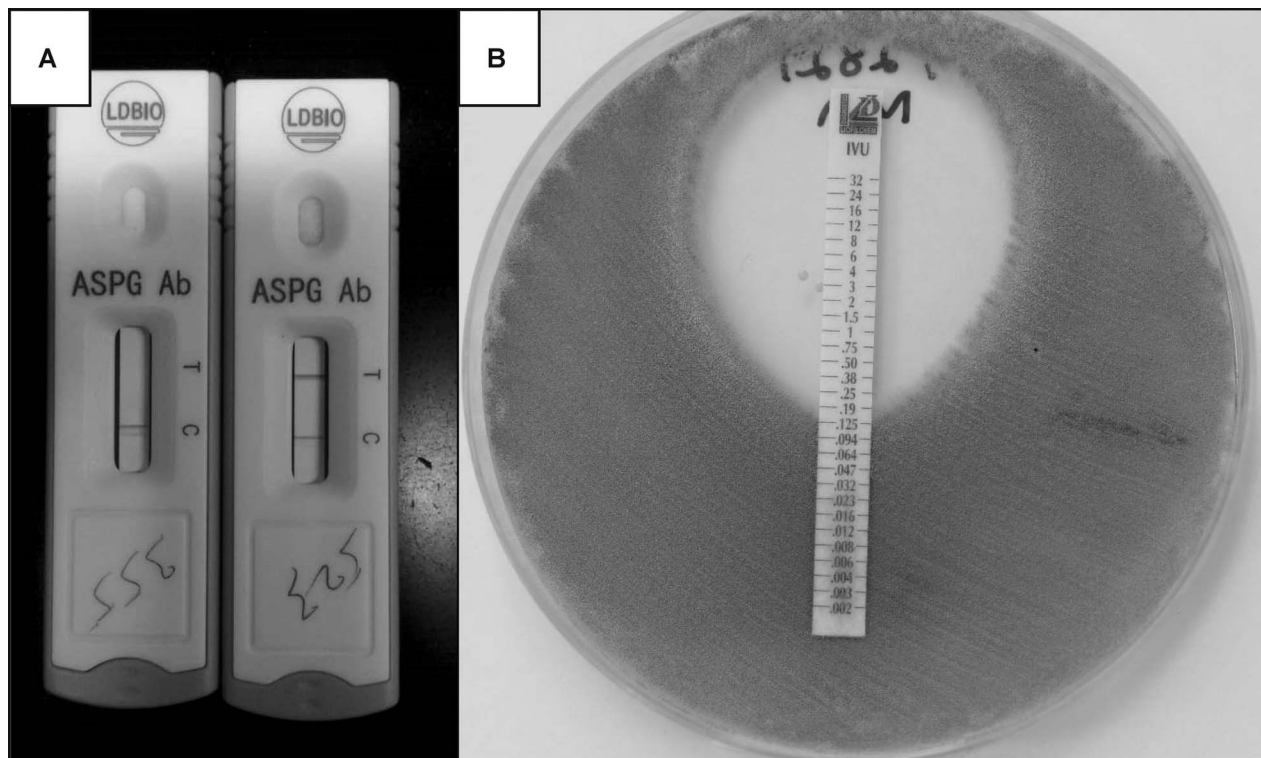


**Figure 4** Panel A) *Aspergillus*-specific IgG/IgM lateral flow device showing a negative (–) and a positive (+) tests. **Panel B** shows a confluent growth of *Aspergillus fumigatus* from a patient with chronic pulmonary aspergillosis susceptible to IVU with a minimum inhibitory concentration of 0.125 mg/L using an E-test method. IVU = isavuconazole; Ig = immunoglobulin.

which serum itraconazole levels are significantly reduced.<sup>67</sup> Doubling the dose of itraconazole should be considered where therapeutic drug monitoring is possible. While there are no studies that have evaluated appropriate anti-fungal therapy among patients with CPA and PTB co-infection, alternatives to triazoles such as cyclical short courses of the echinocandins (e.g., micafungin) or amphotericin B,<sup>68</sup> could be considered among patients with CCPA and CFPA, although a major drawback is the need for intravenous administration. Another approach would be to first complete TB treatment before initiating the triazoles, especially in patients with non-severe disease.

#### DRUG-RESISTANT TB AND CPA

There are few reports on post-drug-resistant TB (DR-TB) CPA or co-existence of CPA and DR-TB. Considering the higher incidence of thick-walled cavitary disease among patients with DR-TB, it is reasonable to expect a high prevalence and incidence of CPA in DR-TB.<sup>69</sup> However, few studies have reported the incidence/prevalence of CPA in DR-TB. In Brazil, 6.3% of DR-TB patients had CPA in a retrospective cohort of 48 patients at a referral DR-TB facility.<sup>70</sup> In Peru, of 121 DR-TB patients who underwent surgical interventions, 6 (5.0%) had aspergilloma.<sup>71</sup> Another cohort of DR-TB patients

who underwent surgery in Egypt reported that 3 (13.0%) had fungal balls as a source of haemoptysis, although the causative organism was not ascertained.<sup>72</sup> Risk factors, clinical features and outcomes of CPA among patients with current or previous DR-TB are unknown. A few available case reports on *Aspergillus* infection among individuals with DR-TB are given in Table 3.

#### CONCLUSION

In summary, there is a substantial overlap in the risk factors, and clinical and radiological findings of CPA and PTB, and both are global in distribution. Misdiagnosis, especially of CPA, is common due to the lack of essential diagnostics for *Aspergillus* infections and non-availability of skilled mycologists, particularly in low- and middle-income countries which also have a high burden of TB. CPA-PTB co-infection is common and is challenging to diagnose and treat. Accurate diagnosis is key as PTB and CPA treatments are completely different. *Aspergillus*-specific IgG serology is key in differentiating PTB and PTB relapse from CPA. It may be worthwhile developing clinical predictive scores that can be used in low-income settings to differentiate active TB, post-TB disease, and TB+CPA co-infection. The epidemiology of CPA in patients with DR-TB is of special interest and remains an area of further research.

**Table 3** Case reports on *Aspergillus* infection and DR-TB

| Study                | Aspergillus syndrome                                         | Possible risk factors for CPA                                       | Clinical features                                                                                                                                                                                     | Radiological findings                                                                               | Laboratory abnormalities                                                | Management                                                   | Outcome                          |
|----------------------|--------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------|----------------------------------|
| Kumar <sup>81</sup>  | Aspergilloma, invasive aspergillosis with co-existing MDR-TB | Diabetes, previous TB with treatment non-adherence, age >40 years   | 50-year-old female<br>Symptoms: haemoptysis<br>Signs: bronchial breathing                                                                                                                             | Thick-walled cavity in the right lung upper lobe with indwelling aspergilloma                       | Anaemia                                                                 | Lobectomy, voriconazole and DR-TB treatment                  | Improved                         |
| Katoto <sup>82</sup> | Suspected CPA with co-existing MDR-TB                        | Mining, previous TB with treatment failure, male sex, age >40 years | 44-year-old male<br>Symptoms: fever, cough, haemoptysis, mucopurulent sputum<br>Signs: pyrexia, dyspnoea, absence of tactile fremitus, dull percussion and reduced breath sounds on the affected side | Pneumothorax, pleural effusion, complete destruction of left lung with compensatory right emphysema | Leucocytosis with eosinophilia                                          | DR-TB treatment; treatment for suspected CPA is not provided | Died                             |
| Ray <sup>83</sup>    | Invasive aspergillosis with co-existing poly-resistant TB    | Previous TB with treatment completion, post-partum                  | 20-year-old, 40 days postpartum female<br>Symptoms: weight loss, anorexia, fever and shortness of breath<br>Signs: pyrexia, tachycardia, tachypnoea, low SpO <sub>2</sub>                             | Bilateral widespread cavitation                                                                     | Anaemia, leucocytosis, positive c-ANCA, and serum galactomannan antigen | Mechanical ventilation, TB treatment, amphotericin B         | 8 months hospital stay, improved |
| Takeda <sup>84</sup> | Aspergillus superinfection with concurrent MDR-TB            | Age >40, previous lung cancer and lobectomy                         | 70-year-old                                                                                                                                                                                           | Unknown                                                                                             | Not available                                                           | Pneumonectomy                                                | Died                             |

DR-TB = drug-resistant TB; CPA = chronic pulmonary aspergillosis; MDR-TB = multidrug-resistant TB; SpO<sub>2</sub> = oxygen saturation, ANCA = antineutrophil cytoplasmic antibodies.

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## RÉSUMÉ

**CONTEXTE :** La tuberculose pulmonaire (TBP) et l'aspergillose pulmonaire chronique (CPA) sont des maladies à la fois progressives et invalidante du parenchyme pulmonaire avec des facteurs de risque, une symptomatologie et des signes radiologiques chevauchants, qui aboutissent souvent à une erreur de diagnostic de l'une ou l'autre des maladies.

**MÉTHODES :** Nous avons entrepris une revue par approche narrative pour décrire les manifestations cliniques et radiologiques de CPA et de TBP et souligner les caractéristiques majeures qui différencient ces deux maladies très proches.

**RÉSULTATS :** La CPA complique fréquemment la TBP traitée. En fait, 15–90% des cas de CPA surviennent chez des patients ayant des lésions pulmonaires résiduelles suivant le traitement de la TBP. Si la CPA affecte de façon prédominante les patients plus âgés avec des maladies pulmonaires sous-jacentes, à la fois la TBP et la

CPA ont des symptômes cliniques impossibles à distinguer. Des images radiologiques de cavitation? et de fibrose sont fréquentes dans les deux maladies. Cependant, des adénopathies, une image de miliaire et un épanchement pleural prédisent une TBP active, tandis qu'un aspergillome, un épaississement pleural et une fibrose para cavitaire sont plus fréquents dans la CPA. La sérologie, par dosage des immunoglobuline G (IgG) spécifiques d'*Aspergillus*, a un rôle central dans la différenciation de la TBP (à la fois active et guérie) et de la CPA avec une sensibilité et une spécificité élevées.

**CONCLUSION :** La sérologie par IgG spécifiques d'*Aspergillus* est la clé de la différenciation entre la TBP et la rechute de TBP par rapport à la CPA. Il serait peut-être utile de développer des scores prédictifs cliniques qui peuvent être utilisés dans des contextes de faibles revenus pour différencier la TB active, la maladie post-TB et la co-infection TB-CPA.

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