**Cerdika: Jurnal Ilmiah Indonesia, Mei 2022, 2 (5), 579-586**
p-ISSN: 2774-6291 e-ISSN: 2774-6534

Available online at http://cerdika.publikasiindonesia.id/index.php/cerdika/index

# Chronic Pulmonary Aspergillosis in a Post-treated Tuberculosis Patient

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Received: 03-05-2022
Revised : 05-05-2022
Accepted: 25-05-2022

**Abstract**

Chronic Pulmonary Aspergillosis (CPA) is a progressive respiratory syndrome of severe fungal infection typically found in immunocompetent or slightly immunocompromised patients with an underlying pulmonary disease. The underlying pulmonary disease typically includes active or post-tuberculosis, chronic obstructive pulmonary disease, or a history of surgery for lung cancer, for which tuberculosis remains the most common underlying condition. A 60 years old woman came with worsening dyspnea for the last 1 week, with hemoptysis and weight loss for the last 3 months, she has a history of pulmonary tuberculosis for 39 years, which was fully treated and she had completed the treatment regimen. A computed tomography (CT) scan was conducted, which showed solid fibroxanthoma with an air bronchogram in the upper left lung area. Transthoracic lung biopsy showed hyphae and fungal spores of Aspergillosis, which was supported by a positive Galactomannan test. Eventually, she was diagnosed with pulmonary aspergillosis and was advised to undergo surgical treatment with left pneumonectomy, but the patient refused surgical treatment. Chronic pulmonary aspergillosis is a progressive respiratory condition of severe fungal infection and is mostly found in post-tuberculosis patients. The symptoms may be similar to other chronic pulmonary diseases, making the diagnosis difficult. There are several reports that said pulmonary aspergillosis was misdiagnosed and only diagnosed only on autopsy. The mortality rate of this condition is quite high, and it typically worsens the quality of life.

***Keywords**: opportunistic fungal infection; pulmonary mycoses; Candidiasis; aspergillosis*

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## INTRODUCTION

Chronic Pulmonary Aspergillosis (CPA) is a progressive respiratory syndrome of a severe fungal infection typically found in immunocompetent or slightly immunocompromised patients with an underlying pulmonary disease (Barac et al., 2019). CPA is characterized by slow-progressive pulmonary parenchymal destruction in the form of multiple cavities, nodules, infiltrates or fibrosis, with or without aspergilloma (Niu et al., 2020). The underlying pulmonary diseases typically include active or post-tuberculosis, chronic obstructive pulmonary disease, or a history of surgery for lung cancer (D W Denning, 2021). However, tuberculosis (TB) is the most common condition of these underlying conditions. Diagnosis may be difficult, and misdiagnosis or delayed diagnosis may occur due to the similarities with other chronic respiratory diseases; furthermore, no

single diagnostic test is able to diagnose the disease precisely. Therefore, CPA may cause severe morbidity and mortality.

Global epidemiological data estimated 3 million people are suffering from CPA and 1.2 million people with CPA are those with sequelae of pulmonary TB, 411,000 have allergic bronchopulmonary aspergillosis complication, and 72,000 as a sarcoidosis complications (Salzer & Cornely, 2017). This shows the extent of the problems caused by CPA from a global health perspective. The burden of post-TB CPA is also estimated to be 1.2 million cases per year. The prevalence ranges from <1 case per 100,000 population in the United States, which is a low-TB-burden country, compared to 42.9 per 100,000 population in Nigeria, which is a high-TB-burden country. A study in India showed an incidence of 27,000 out of 170,000 cases. India is a country with a high TB incidence, accounting for up to 312 cases per 100,000 population in 2019. According to surveillance data in Indonesia, the total prevalence of CPA is approximately 83,000 patients, with around 17,000 new post-TB CPA cases annually. Another study stated that around 13% of patients at the end of TB treatment have CPA (Setianingrum et al., 2020). The mortality rate of CPA is considered relatively high; a study by Lowes et al. stated that the survival rate in 1 year is 86%, in 5 years 62%, and in 10 years 47%. Indonesia has a high mortality rate due to TB, which is 34 deaths per 100,000 population of HIV-negative TB (Rozaliyani et al., 2020).

Patients with CPA may present with clinical manifestations such as chronic productive cough, weight loss, hemoptysis, and nodules, cavities, or fungal ball on chest radiographs (David W Denning et al., 2018). The clinical symptoms and radiology characteristics should be present for at least 3 months at the time of diagnosis. CPA has several forms, and the most common one is chronic cavitary pulmonary aspergillosis (CCPA). If left untreated, CCPA may worsen and progress into chronic fibrotic pulmonary aspergillosis (CFPA). The milder form is simple aspergilloma and aspergillus nodule. Acute invasive aspergillosis is a locally destructive pulmonary disease, which is formerly known as chronic necrotizing pulmonary aspergillosis (Kanj et al., 2018).

The diagnostic criteria of CPA according to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Respiratory Society (ERS) and the European Confederation of Medical Mycology (ECMM) include: one or more cavities with or without fungal ball or nodule on chest radiograph for ≥3 months; a direct evidence of Aspergillus infection or immunological response against Aspergillus spp., and other alternative diagnoses have been excluded.1,2 In this study, we reported a 60-years-old woman with a history of pulmonary TB and diagnosed with chronic pulmonary aspergillosis.

## METHOD

This research is quantitative using a descriptive approach. The object of this study was a 60-year-old woman with worsening dyspnea during the past 1 week. He also complained of hemoptysis for 3 months, which had worsened in the past 1 week. She has been losing weight for the past 3 months. He had a previous 39-year history of pulmonary TB, which had been completely treated, and he had completed the treatment regimen.

## RESULTS AND DISCUSSION

A 60-years-old woman presented to our centre with worsening dyspnea for the last 1 week. She also complained of hemoptysis for 3 months, which worsened in the last 1 week. She experienced weight loss for the last 3 months. She had a history of pulmonary

TB 39 years before, which was fully treated, and she had completed the treatment regimen. After the treatment, she regularly visited the outpatient clinic for a follow-up, and the chest radiograph showed fibrosis in the left upper lung area. A computed tomography (CT) scan was conducted, which showed solid fibrogranuloma with air bronchogram in the upper left lung area (Figure 1(a) and 2(a)). Two years before, she had been admitted to the hospital with a complaint of weight loss and fever. There was no history of long-term corticosteroid usage.

Physical examinations showed no lung sounds on the left lung field, borderline IGRA test, and negative acid-fast bacilli sputum test. Sputum culture showed Streptococcus, Staphylococcus, Acinetobacter, Pseudomonas, Cryptococcus, and Klebsiella, along with Mycelia sterilia and Candida albicans. The CEA and NSE tumour markers were within the normal limit. The patient was diagnosed with TB relapse and was treated with oral antituberculosis drugs for 6 months, but she had no clinical improvements. Afterwards, she had a transthoracic lung biopsy, which showed hyphae and fungal spores of Aspergillus. CT scans (Figure 1(b), 2(b), and 3) showed heterogenous multiloculated lesions with crescent signs in the superior lobe, with the largest size of 13.8 x 14.2 x 9.8 cm. The Galactomannan test showed a positive result (0.71). CD4+ and CD8_ were within the normal limit. She was eventually diagnosed with pulmonary aspergillosis and was advised to undergo surgical treatment with left pneumonectomy, but the patient refused surgical treatment. She was then treated with itraconazole 2x200 mg for 6 months, and her clinical symptoms improved temporarily.

The patient then returned with worsening dyspnea accompanied by fever, productive cough, and hemoptysis. Her left lung revealed no lung sounds, and a plain chest radiograph showed hydropneumothorax. She was treated with water-seal-drainage (WSD) on the left chest, and she was admitted to the intensive care unit (ICU) for 5 days; however, the symptoms did not improve. The patient then had a respiratory failure and had passed away.

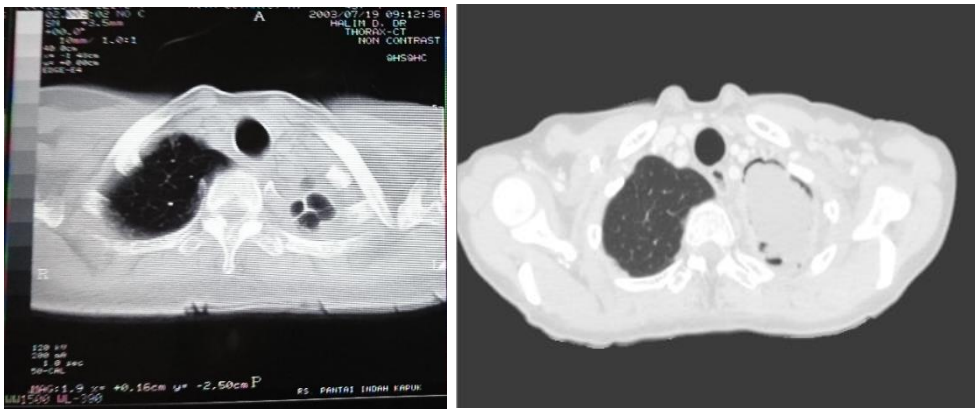


Figure 1 (a) CT scan in 2003 showing multiple cavities in the upper left lobe (black arrow) and fibrosis causing tracheal deviation. (b) CT scan in 2017 in the same section, which showed a mass pushing the trachea and crescent sign (* mark).

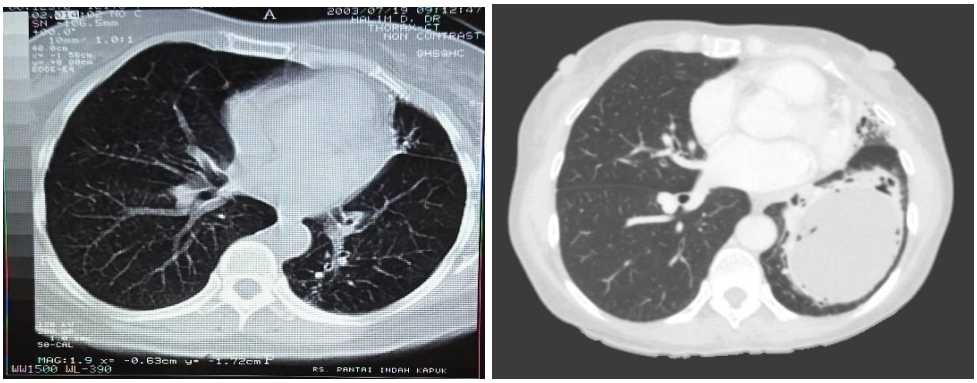

Figure 2 (a) CT scan in 2003, and (b) CT scan in 2017 on the same section, which showed disseminated lesions with thickening walls.

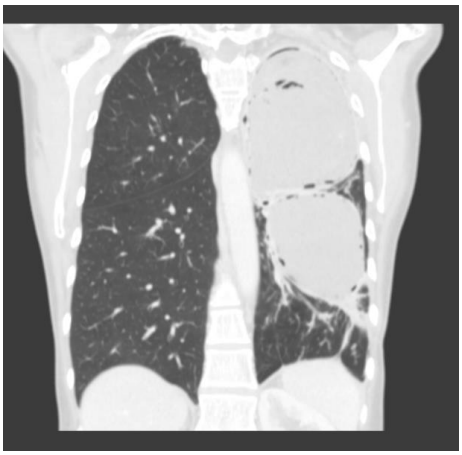

Figure 3. CT scan in 2017 showing multi-loculated lesions in the upper left lobe with thickening wall and crescent sign

Aspergillosis refers to a spectrum of infection or disease caused by fungal of the genus Aspergillus sp. The most common etiological pathogens that cause disease include Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, and Aspergillus terreus. These fungi can be found everywhere in nature. Most patients are exposed from airborne spores; hence, the lung is the primary infectious organ. Depending on the host's immune status, the inhaled spore will develop and become hyphae in the lung (Ortiz et al., 2022). The spectrum of the disease varies from invasive (allergic bronchopulmonary aspergillosis and aspergilloma) to invasive pulmonary aspergillosis, and it can also disseminate through the blood (Warris, 2014). Invasive aspergillosis is commonly found in patients with immunodeficiency conditions such as haematological malignancy, cancer chemotherapy, and AIDS. Immunocompetent patients may also suffer from aspergillosis; however, they typically have other underlying pulmonary diseases such as a history of tuberculosis with residual cavities, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and chronic alcoholism (Qiu & Su, 2019).

In patients with cavitary pulmonary diseases, repeated exposure of conidia A. fumigatus will lead to aspergillosis. A. fumigatus is the most frequent etiological pathogen of CPA; the small diameter (3-5 μm) facilitates its penetration into the alveolar space, causing saprophytic colonization of the pulmonary cavity. This will lead to local inflammation, parenchymal and/or pleural fibrosis, expansion of the colonized cavity or the formation of new cavities with or without aspergilloma or fungal ball. An aspergilloma

or fungal ball consists of Aspergillus hyphae, fibrins, and other debris that is contained in the formed cavity. This is the hallmark characteristic of CPA and can be found in all forms of CPA except the Aspergillus nodule. When the Aspergillus spores enter the lung, the cell-mediated immunity is activated, leading to leukocytosis in the patient. The pathological changes of the lung due to Aspergillus invasion into the lung parenchymal may include infarct/haemorrhage, oedema, and necrosis of the distal lung parenchyma.7,8 The findings of hemoptysis and dyspnea in our patient might be explained by the pathophysiology of these pathological changes caused by Aspergillus invasion into the lung parenchyma.

CPA occurs progressively for several months to years and is typically found in patients with an underlying pulmonary lesion (or are currently having pulmonary lesions), especially cavities. This condition is mostly found in the middle-aged and elderly with low body mass index. These findings are in line with the findings in our patient, in which the patient was 62 years old and had a history of pulmonary TB. The main symptoms of CPA include chronic productive cough, systemic symptoms such as weight loss, fatigue, fever, hemoptysis, and chest pain. These symptoms are difficult to distinguish clinically from pulmonary TB. The residual cavity may be found in 20-40% of lungs of patients who had treatment for pulmonary TB. A cohort study in Great Britain showed that out of 544 patients with persistent cavities with a size of at least 2.5 cm and negative M. tuberculosis on the sputum test, about 25% had a positive IgM and IgG for Aspergillus, and 14% had aspergilloma. With these similarities in the clinical and radiological manifestations, a more specific microbiological and serological test is required to make a definitive diagnosis. Aspergillus-specific IgG is a highly sensitive test with a positive result in over 90% of patients with CPA. The diagnosis of CPA requires a combination of clinical characteristics, including one or more cavities with or without a fungal ball or nodules in the chest radiograph, a direct evidence of Aspergillus infection (microscopic or culture from a biopsy) or immunological response against Aspergillus spp., and excluded alternative diagnoses. All these findings should be present for at least 3 months. Aspergillus IgG/IgM is the standard serological test to diagnose CPA. The sensitivity reached 91.6% and specificity 98.0%.3,8 In our case, the patient presented with dyspnea, hemoptysis, and systemic symptoms including weight loss for the last 3 months. Furthermore, the biopsy result showed Aspergillus spore; therefore, the findings and diagnosis in our patient were in line with the mentioned diagnostic criteria and theory.

The diagnostic criteria for CPA have been established by the European Society for Clinical Microbiology and Infectious Diseases, the European Respiratory Society, and the European Confederation of Medical Mycology. The Infectious Diseases Society of America (IDSA) also published a guideline in 2016. The key difference in the IDSA guideline is that they did not endorse a detection of Aspergillus spp. in sputum or serum as a part of diagnostic criteria. Besides the mentioned symptoms and diagnostic criteria, it is also stated that the symptoms should be present for at least 3 months, even though if the duration is inferred and based on the progressive or radiological abnormalities.9,10

There is an overlap in the imaging studies between the disease pattern of various CPA types. The aspergillus nodule is defined as one or more nodules with a size of <3 cm without cavities. Aspergilloma is defined as a solid oval opacity within the existing cavities. Aspergilloma typically presents in the upper lobe with a “Monod” or “air crescent” sign surrounding it since the masses are typically separated with the cavity wall, forming an air space. This air space also causes the mass to move and change its position according to the body position. Aspergilloma typically has a stable radiograph finding for months. These findings are consistent with our case, in which there was an air crescent mark on the chest radiograph, which suggested aspergilloma. Chronic cavitary pulmonary aspergillosis tends to progress with time, cavitates, eventually leading to volume loss. Therefore, it can be concluded that the hallmark features of CPA are newly formed and/or existing cavities that are expanding with various wall thicknesses in the setting of chronic pulmonary disease with or without fungal ball formation, often with pleural thickening and parenchymal

destruction and/or fibrosis. If left untreated, chronic pulmonary aspergillosis may lead to pulmonary fibrosis that involves one or more pulmonary lobes and eventually progress into chronic fibrotic pulmonary aspergillosis.

In cases where a fungal ball is found, then the confirmation of Aspergillus as the aetiology only requires a positive Aspergillus IgG (positive in >90% of cases). If the antibody test is not positive, then another evidence of Aspergillus infection is needed to establish the diagnosis. In patients with one or more cavities consistent with CPA, then any of the following criteria can be used to confirm the diagnosis, provided other diagnoses have been excluded: a positive Aspergillus IgG or precipitins, a positive Aspergillus antigen or DNA in the respiratory fluid, percutaneous of excisional biopsy showing fungal hyphae on the microscope or Aspergillus spp. growing from the cavity (David W Denning et al., 2016).

The treatment of post-TB CPA is the same as in other conditions such as COPD or sarcoidosis and depends on the radiological phenotypes. An incidental finding or asymptomatic Aspergillus nodule does not necessitate treatment; surgical treatment is best conducted in patients with simple aspergilloma on a well-circumscribed cavity without extensive destruction of the surrounding tissues; CCPA and CFPA, characterized by an enlarged old cavity or the formation of new cavities with destructive fibrotic pulmonary parenchymal changes, require long-term oral antifungal treatment. The medical treatment normally given for patients with CPA is long-term oral antifungal with itraconazole 400 mg/day or voriconazole 400 mg/day for at least 6 months; this treatment is the first-line treatment for CPA and is associated with improved quality of life, improved symptoms, and reduced disease progression. Antifungal treatment may also increase the survival rate. However, the reported survival rates are different between the published studies. The survival rate ranged from 58-93% in a follow-up of 1 year, 17.5-85% in 5 years, and 30-50% in 10 years. Another study reported that the survival rate might be as low as 47% in 10 years, depending on the severity of pulmonary damage and risk factors in the patient.3,4 In our case, the patient was treated with itraconazole 2x200 mg for 6 months, and her symptoms had improved temporarily, consistent with the theory. With the radiological findings, the patient in our case was advised to undergo surgical treatment, but she refused surgical procedures. In the 6 months of follow-up, her condition had worsened, and she eventually passed away.

The decision to treat CPA with triazole therapy depends on the clinical or disease phenotype and the patient's eligibility in receiving surgical treatment. Oral itraconazole is superior compared to conservative treatment in stabilizing clinical and radiological manifestations in patients with CCPA (Agarwal et al., 2013). Currently, oral triazole is the standard therapy for CCPA. In patients with adequate pulmonary function, the definitive treatment option is resection of the aspergilloma. Surgery is also the treatment of choice in CPA with recurrent hemoptysis despite bronchial artery embolization or azole-resistant diseases. The procedure's success depends on the ability to fully resect the aspergilloma without spillage of fungal elements into the pleural space. The decision in surgical treatment should also consider the patient's eligibility since most patients have a poor physical condition, therefore, contributing to the high risk of death and complication. The cardiopulmonary function of the patient is essential in consideration of surgery. Patients who are malnourished require supplemental feeding to improve their nutrition status before surgery, including using a nasogastric tube if necessary. The surgical procedures include bullectomy, segmentectomy, sublobar resection, wedge resection, lobectomy, pleurectomy, and pneumectomy (Takeuchi et al., 2021).

A study by Bongomin et al. in 2021 stated that the most common surgical procedure is lobectomy (in 55.3% of cases), pneumectomy (17.3%), and segmentectomy (13.1%). Post-surgery complications are common after CPA resection, which include air leak, respiratory failure, and infectious complications. Relapse occurred in 25-40% of patients following surgical interventions (Bongomin et al., 2021).

## CONCLUSION

Chronic pulmonary aspergillosis is a progressive respiratory condition of severe fungal infection and is mostly found in post-tuberculosis patients. The symptoms may be similar to other chronic pulmonary diseases, making the diagnosis difficult. The mortality rate of this condition is quite high, and it typically worsens the quality of life. The management consists of surgery and medical treatment with antifungal itraconazole. An appropriate diagnosis and treatment for the patients may improve quality of life, improve symptoms, and increase the survival rate.

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