CASE REPORT

Chronic Pulmonary Aspergillosis with Tracheobronchial Involvement

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ABSTRACT

Introduction: Aspergillosis is a fungal infection commonly found in human lungs and takes several forms. Chronic pulmonary aspergillosis (CPA) commonly affects individuals with underlying disease, most usually lung tuberculosis (TB). Aspergillosis can cause the formation of a fungus ball in the lung cavity and can also manifest in the tracheobronchial area, although this is rarely seen in immunocompetent patients.
Case: A 23-year-old woman came with persistent cough, hemoptysis, and shortness of breath for 4 months. The patient also had a significant weight loss and a history of lung TB 3 years ago. She had completed her lung TB medication. Physical examination showed increased respiratory rate and rhonchi on the left lung. GeneXpert showed no *Mycobacterium tuberculosis* (MTB) detected. The chest X-ray showed a cavity on the left superior lobe of the lung. Bronchoscopy showed multiple plaques along the trachea, carina, and left main bronchus. A chest computed tomography (CT) scan with contrast enhancement was performed, and a fungus ball was found inside the cavity in the left upper lobe of the lung. The patient was given intravenous fluconazole as therapy and continued with oral fluconazole when discharged. A second bronchoscopy was performed, and improvement was shown.
Conclusion: Early detection and treatment should be applied to CPA patients since some studies showed poor prognosis and low five-year survival rates.

INTRODUCTION

Aspergillosis is one of the most frequently found fungal infections in the lungs. It is caused by *Aspergillus*, a ubiquitous saprophytic mold, and can cause various symptoms and manifestations depending on the patient's immune status. The most common *Aspergillus* species that can cause infection in the lungs is *Aspergillus fumigatus*. Other species, such as *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus flavus*, are also reported as significant pathogens in immunocompromised patients.[1] Several forms of aspergillosis exist in the lungs, including allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), and invasive pulmonary aspergillosis (IPA). CPA usually affects patients with underlying diseases such as lung tuberculosis (TB), lung cancer, and bronchiectasis. Pulmonary TB is the most important risk factor for developing CPA.[2] There are many patients with pulmonary cavities due to lung TB that develop into CPA. Common manifestation of CPA is aspergilloma and aspergillus nodule. Pulmonary aspergilloma is a colonization of the fungus, creating a spherical mass in a pre-existing cavity, usually seen in post-TB patients. Untreated CPA may develop into chronic fibrosing pulmonary aspergillosis (CFPA) characterized by fibrosing of lung parenchyma. Tracheobronchial manifestation is uncommon in aspergillosis. It is generally seen in immunocompromised patients. Receivers of lung transplants are also a major risk factor for tracheobronchial manifestations. This is typically correlated to the use of aggressive immunosuppressive drugs and continuous exposure to the pathogens.[3,4] We presented a rare case of pulmonary aspergilloma with tracheobronchial manifestation.

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CASE

A 23-year-old woman came to the outpatient department with a persistent cough for the past four months. The patient has a history of hemoptysis and shortness of breath when performing heavy activity. There is no history of fever and significant weight loss. The patient had a prior history of lung TB three years before and has completed her medication. The patient has no history of diabetes or *human immunodeficiency virus* (HIV) infection, does not consume any medication, and has no history of smoking. The patient has never undergone a chest X-ray examination after completing her lung TB medication. Physical examination revealed an increase in respiratory rate and rhonchi on the upper left side of the chest. Laboratory examination showed normal results. A chest X-ray was then performed and showed a pulmonary cavity in the left superior lobe.

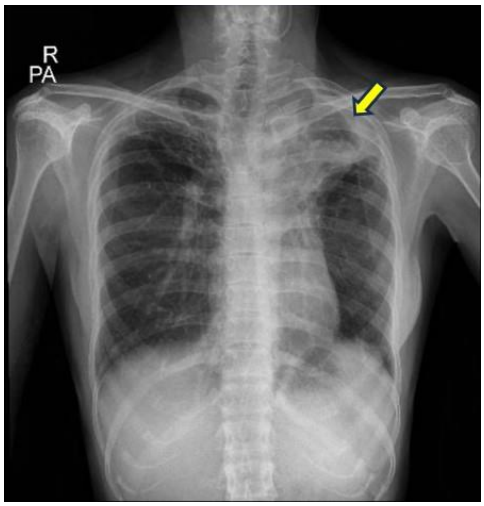

Figure 1. Chest X-ray shows pulmonary cavity in left upper lobe (arrow)

GeneXpert test was performed to rule out relapsed lung TB, and the test showed no *Mycobacterium tuberculosis* (MTB) bacteria were detected. Bronchoscopy was then performed and revealed multiple white-yellowish plaques from the proximal trachea, distal trachea, carina, and throughout the left main bronchus accompanied by hyperemic and edematous mucous. There was no sign of obstruction by the mucus plug. Biopsies were then performed, followed by brushing and washing the trachea and bronchus.

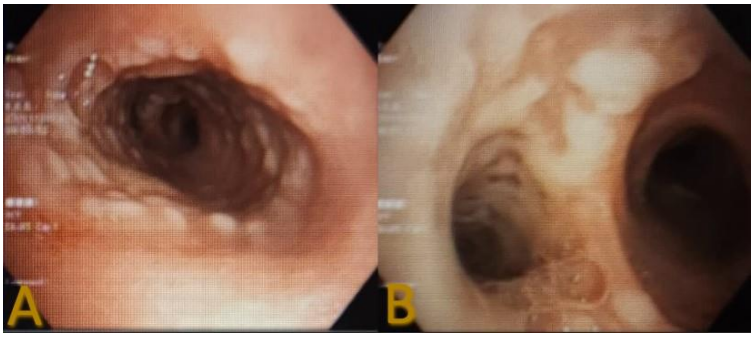

Figure 2. Multiple white-yellowish plaques in (A) distal trachea and (B) carina

A contrast-enhanced computed tomography (CT) scan was scheduled. It revealed a round mass inside the cavity with a size of 4.6 cm x 4.1 cm x 4.2 cm located in the superior lobe of the left lung, suggesting a fungus ball appearance. Pathological examination of the samples later revealed *Aspergillus spp.* and supported the diagnosis of CPA with tracheobronchial manifestations.

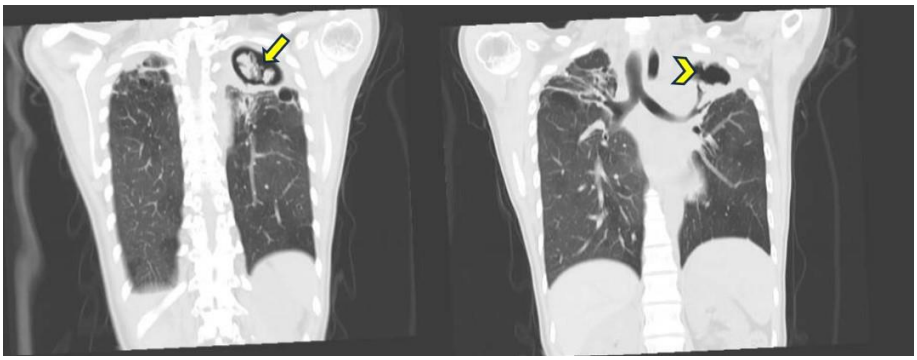

Figure 3. Contrast-enhanced CT scan reveals fungus ball (arrow) inside cavity in left superior lobe and communication between bronchus and cavity (arrow tip)

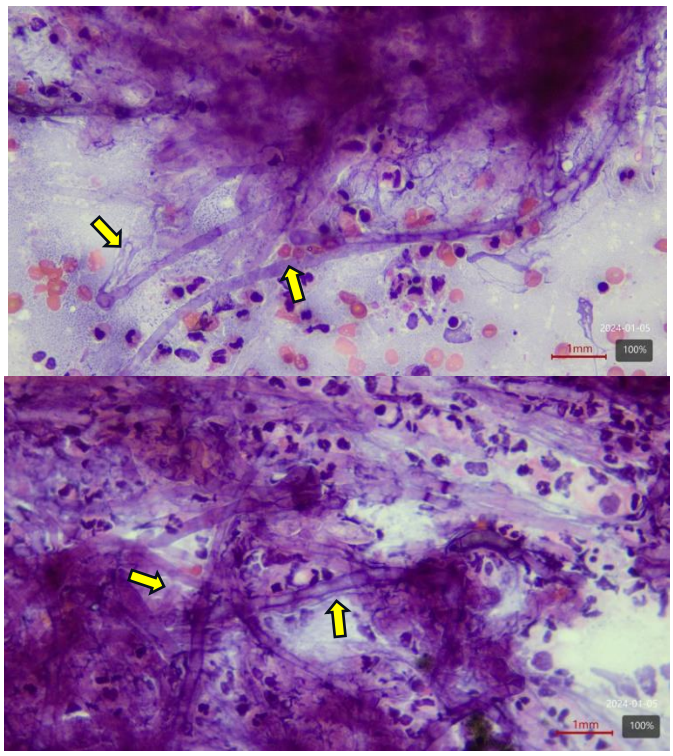

Figure 4. Pathology examination with Papaniculaou stain reveals *Aspergillus* organism with septated hyphae (arrow)

The patient was given intravenous fluconazole as therapy and other supportive medication. The fluconazole dose given was 400 mg loading dose on the first day and continued by 200 mg once daily. After seven days of intravenous fluconazole, the symptoms improved, and the therapy was switched to oral fluconazole 150 mg once daily, and the patient was discharged. After two weeks of oral fluconazole therapy, the patient visited the outpatient department for evaluation, and the symptoms were improving. The patient has not experienced another new episode of hemoptysis or shortness of breath. A second bronchoscopy was scheduled for evaluation, and it showed that the amount of plaque had decreased. Oral fluconazole was then continued, and the patient was scheduled for another chest CT scan after three months of oral anti-fungal medication to evaluate the therapy.

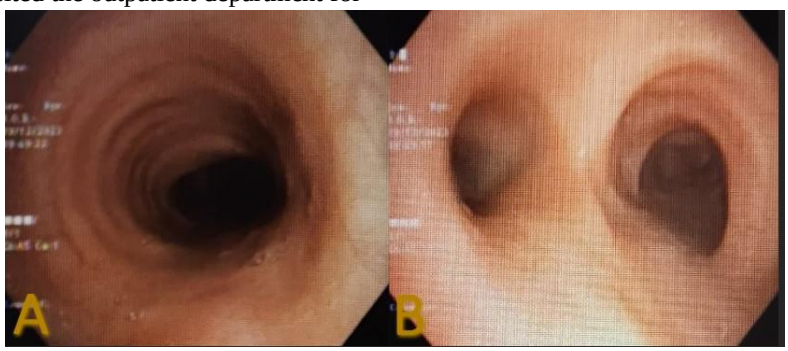

Figure 5. The second bronchoscopy shows a reduction in the amount of plaque in (A) the distal trachea and (B) the carina

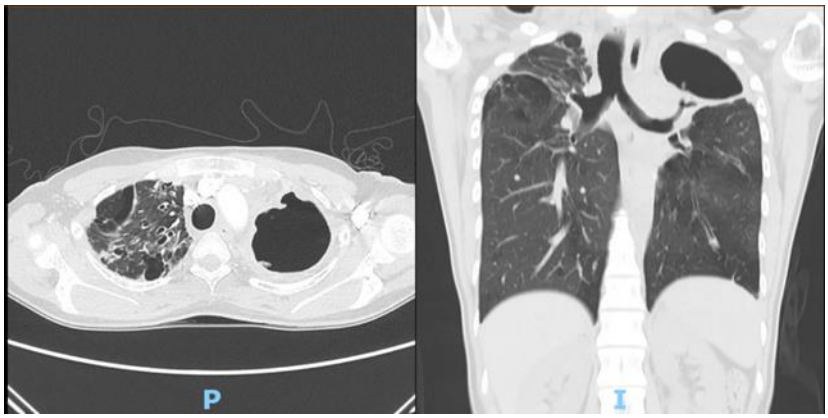

Figure 6. Contrast-enhanced chest CT scan three months after treatment with fluconazole

DISCUSSION

Pulmonary aspergillosis is a bronchial or lung disease caused by the infection of *Aspergillus*, which is a ubiquitous saprophytic mold that can release conidia in high concentrations. Conidia have a small diameter (2-3 μm) and can reach the human alveoli. Over 170 kinds of *Aspergillus* have been identified. The most common cause of pulmonary aspergillosis is *Aspergillus fumigatus*. Other microorganisms that can cause aspergillosis in humans are *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus nidulans*. There are three main categories of pulmonary aspergillosis: ABPA, CPA, and IPA. CPA is a chronic form of *Aspergillus* infection in the lung and usually affects patients with underlying disease, most commonly pulmonary TB. Other associated diseases include bronchiectasis, malignancy of lung tissue, and chronic obstructive pulmonary disease (COPD). It can produce various manifestations depending on the immune status of the patients.[1,4]

Infection of *Aspergillus* begins when the host inhales conidia into the respiratory system. The mucus layer in the pulmonary tract contains a large amount of anti-microbial factors and has an important role in preventing pulmonary aspergillosis. Immunocompetent individuals will eliminate the conidia and avoid infection. In atopic individuals, it can trigger immune reactions and develop into allergic rhinitis, asthma, hypersensitivity pneumonitis, and ABPA. When the exposure becomes constant and the host is in an immunosuppressed state, infection can occur. Alveolar macrophages will recognize conidia that reach the alveoli. The macrophages will engulf the conidia, produce chemokines, and recruit neutrophils. Neutrophils will then prevent infection through the release of reactive oxygen species (ROS) and eliminate the pathogen. Thus, any condition that causes neutropenia increases the risk of developing pulmonary aspergillosis. Conidia are also covered by hydrophobic Rod-A protein and the pigment DHN-melanin, which allows them to escape recognition by the immune system. When the infection occurs, conidia adhere to lung epithelial cells and promote the growth of hyphae that can penetrate the pneumocyte membrane and invade blood vessels. The invasion of tissue induces hypoxia and an inflammatory response. In an immunocompromised host, the hyphae can spread to another part of the body through the bloodstream and cause infection in multiple organs.[5]

The estimated prevalence of CPA in Western Europe and the United States is <1 case per 100,000 persons.[6] However, CPA is often underdiagnosed, and the incidence is suspected to be higher, especially in regions with a high incidence of TB. It also may be misdiagnosed as a relapse of TB since the clinical manifestations resemble those of TB. Most patients with CPA have a history of lung disease that results in scarring, bullae, or cavities. TB is the most important risk factor for developing CPA. The overall risk of developing CPA in the pulmonary cavity of over 2 cm in diameter is estimated to be 15-20%.[7] CPA is more common in middle-aged and elderly men, especially those with low body mass index (BMI). Defects in mucociliary clearance are associated with the development of CPA. In addition, CPA is also commonly found in patients who have undergone lung transplantation surgery and accounts for around 44% of all fungal infections.[8] The clinical manifestations are chronic productive cough, dyspnea, hemoptysis, and chest discomfort. The hemoptysis can be minor or life-threatening. The symptoms should be present for at least three months. The radiological findings can vary, such as the presence of a fungus ball, expansion of thickening of the existing cavity, parenchymal destruction, fibrosis, pleural effusion, and pleural thickening.[2,9]

Aspergilloma is one of the most common radiological findings in CPA and can be seen from a CT scan of the thorax. It is characterized by the appearance of a round and well-formed mass in the pulmonary or pleural cavity, often called a fungus ball. Aspergilloma

sometimes has calcification and may be surrounded by air. It also may be gravity-dependent and move if the patient changes position. The term aspergilloma is used if only one fungus ball has been found. If multiple cavities are seen containing one or more aspergillomas accompanied by pulmonary and systemic symptoms, it is called chronic cavitary pulmonary aspergillosis (CCPA). Patients with aspergilloma usually present with hemoptysis or chronic cough. Untreated CPA may develop into chronic fibrosing pulmonary aspergillosis marked by severe fibrotic destruction of at least two lobes of the lung. Another form of CPA that has been recorded is subacute invasive aspergillosis (SAIA). It usually occurs in immunocompromised patients and has similar manifestations with CCPA but with more rapid disease progression. Laboratory findings are typically normal in patients with simple aspergillomas.[1,4]

Tracheobronchial involvement of aspergillosis is a rare aspergillus-related manifestation. It occurs in a small number of patients, especially those with immune suppression, such as hematologic malignancy patients. Lung transplant recipients are also seen as susceptible hosts. The patient may show signs of airway obstruction, and the radiographic examination might be normal. There are three types of tracheobronchial involvement: saprophytic, allergic, and invasive tracheobronchial aspergillosis (ITBA). The saprophytic type is characterized by obstruction of the bronchi by thick mucus plugs containing *Aspergillus* hyphae. The allergic type is caused by hypersensitivity to *Aspergillus* antigens. The symptoms that arise will mimic asthma. ITBA is the more severe form of tracheobronchial manifestation of aspergillosis and is commonly associated with IPA. It is also widely seen in patients who have undergone lung transplantation. The incidence is highest in the first year after transplantation. The patients may develop serious airway obstruction, and this can result in respiratory failure.

There are three different forms of tracheobronchial invasion: tracheobronchitis, ulcerative, and pseudomembranous form. Tracheobronchitis is the least severe form, marked by excessive mucous production with signs of inflammation in the bronchial wall. Ulcer-like lesions and multiple plaques characterize the ulcerative form. Pseudomembranous is the most severe tracheobronchial manifestation, where pseudomembranes can be seen along the bronchial wall. The main treatment for ITBA is voriconazole, and alternative treatments include amphotericin B, micafungin, and itraconazole.[10,11] Tracheobronchial manifestation in immunocompetent patients resembling the patient presented in this case is not common. There have been a couple of case reports in the past ten years that have been present in such patients, although the incidence rate is unknown. The pathophysiology of tracheobronchial manifestation in immunocompetent patients is unclear. Direct communication between the cavity containing aspergilloma and the bronchi is suspected to be one of the contributing factors. However, it was not confirmed since we were unable to find similar cases (direct communication between the aspergilloma-contained cavity and bronchi).

Diagnosis of CPA should be suspected in patients with a history of lung disease, particularly pulmonary TB. The symptoms must persist for at least three months. Chest X-ray and CT scan can show cavity and air crescent signs. CT scan provides better imaging and more accurate location of the cavity. Multiple cavities can also be found in cases like CCPA. Aspergilloma is usually present in the upper lobe and has a spherical form inside a cavity. If a fungus ball is found, *Aspergillus* IgG can be tested from the patient and has a high chance of being positive (over 90% of cases).[1,2] It is recommended for diagnosis and for monitoring medication response. A bronchoscopy specimen for culture is recommended rather than sputum due to the ubiquitous nature of *Aspergillus*. Polymerase chain reaction (PCR) is more sensitive than culture, but it could be hard to use for differentiating between colonization and infection. Galactomannan examination from bronchoalveolar lavage fluid (BAL) has a sensitivity of 77.2% and specificity of 77.0%, but it is challenging in a resource-limited setting when bronchoscopy is not routinely performed. Galactomannan test in serum has poor sensitivity and is not recommended.

Biopsy of the lesions can provide a definitive distinction between invasive aspergillosis and can be used to identify the tissue invasion in subacute invasive pulmonary aspergillosis. The lung function of the patient must be carefully assessed since surgery has major postoperative complications such as bronchopleural fistulae, respiratory failure, and dissemination of the *Aspergillus*.[3,12] In this case, the patient has a previous history of lung TB. Hence, the presence of a lung cavity before *aspergillosis* infection is highly possible. The presentation of a fungus ball from the thorax CT scan and the symptoms that persist for more than three months strongly indicate the diagnosis of CPA. *Aspergillus* IgG examination is usually recommended if a fungus ball is visible, but it was not available in our hospital. The tracheobronchial involvement in the patient was suspected in the form of tracheobronchitis because no ulcerative lesions and pseudomembranes were visible. The cause of tracheobronchial manifestations is alleged to be a result of communication between the bronchus and the cavity containing the aspergilloma, as seen from the thorax CT scan.

Pulmonary aspergillosis is often underdiagnosed. Early identification will improve treatment outcomes. Aspergilloma is reported to be able to resolve spontaneously but only in less than 10% of cases. The treatment of pulmonary aspergillosis can involve a multidisciplinary approach, depending on the case. There are currently three anti-fungal drugs that can be used to treat aspergillosis: the polyenes (amphotericin B), the triazoles, and the echinocandins. Antifungal drugs using triazoles, including itraconazole, voriconazole, posaconazole, and isavuconazole, are usually the initial choice of treatment. These drugs inhibit the synthesis of ergosterol in *Aspergillus* and have a fungicidal effect. Itraconazole is one of the most tested drugs for treating pulmonary aspergillosis due to its availability and low cost. It is reported to have good efficacy against *Aspergillus fumigatus* and has good lung penetration. An international study reported that the daily administration of 50 to 400 mg of itraconazole leads to clinical improvement.[15] The recommended dose is 200 mg once daily or twice daily. An alternative antifungal drug that is frequently used is voriconazole. It is indicated for the management of *Aspergillus fumigatus* with drug-resistance traits. Voriconazole is also recommended as the first-line treatment for invasive pulmonary aspergillosis. Patients with invasive pulmonary aspergillosis with azole-resistant *Aspergillus fumigatus* have a poor prognosis.[2,3]

The recommended duration of antifungal drug administration is 4-6 months. A deteriorating patient's condition in this period indicates a change of therapy.[2,3] The most common main side-effect of triazole drugs is hepatotoxicity, which is more frequently seen in voriconazole and posaconazole but is usually reversible. Another complication that can be seen is prolonged QT interval. Amphotericin B has a fungicidal effect against *Aspergillus* except *Aspergillus terreus*. Amphotericin B is rarely used because of its side effect, which is nephrotoxicity. The usage is also limited because it is only available as an intravenous formulation.[10] Echinocandins can inhibit the synthesis of beta-glucan and cause the integrity of the cell wall to be lost. The commonly used echinocandins are caspofungin, anidulafungin, and micafungin, but they are only available in intravenous formulations.[13,14] There are currently no randomized trials comparing the efficacy of triazoles, echinocandins, and amphotericin B. Regular chest CT every three to six months is recommended to assess the response to therapy. Signs of signaling improvement include decreased substances in the cavity and smaller tissue consolidation around the cavity.[15] Fluconazole is used in this case because other recommended antifungal drugs were not available in our hospital. We could not find any tracheobronchial aspergillosis case reports that use fluconazole as its treatment of choice.

The gold standard for the management of aspergilloma is surgical resection, which is because poor vascularization makes it hard for antifungal drugs to reach the lesion.[16,17] However, surgical therapy is often less preferred because of postoperative complications such as hemorrhage, formation of fistula, and infection. Surgery is usually reserved for patients with severe hemoptysis and having good pulmonary function. It is also considered in chronic pulmonary aspergillosis patients who are unresponsive to antifungal drugs.[18,19] Treatment using antifungal drugs before surgery may be needed to prevent dissemination to the pleural region. Several non-surgical managements have been proposed, such as direct intracavitary administration of antifungal drugs with CT guidance and transbronchial removal using bronchoscopy.[2,20] Bronchial artery embolization (BAE) has also been used in cases of life-threatening hemoptysis when surgery is not possible. It is a less invasive technique for short-term control until surgery can be performed.[21] BAE is reported to be effective at treating massive hemoptysis in 84% of patients with aspergilloma.[15] Recurrence of hemoptysis occurs in 10-55% of cases.[15]

A study also recommended administering itraconazole for 6-18 months, which results in symptomatic improvements in 60% of the patients.[15] Antifungal therapy can prevent the progression of the disease in conditions when surgery is not available or possible. Itraconazole is recommended as first-line therapy because of its low cost. Voriconazole can be given in severe cases. Echinocandin can be considered if there is resistance to other antifungal drugs.[2,3] We decided to give fluconazole to the patient because other recommended antifungal drugs were not available in our hospital. Surgical resection has not yet been considered in the patient because no life-threatening hemoptysis is present, and the patient shows symptomatic improvement with the antifungal drug. The tracheobronchial manifestation also indicates a good response to the therapy, as shown from the second bronchoscopy. Evaluation of the fungal ball with a chest CT scan will be planned three months after the antifungal medication is given.

CPA has a poor prognosis. Several factors, such as older age, low albumin, low BMI, and COPD, have been correlated with increased morbidity and mortality. There is limited data on the mortality rate. The five-year survival rate for CPA in the United Kingdom (UK) was reportedly 62%, and the 10-year survival rate was 47%.[2] The prognosis is affected by the clinical manifestations and radiological phenotypes of the disease. Patients with subacute invasive aspergillosis usually have worse outcomes. A radiologically visible fungus ball indicates

an advanced stage of the disease. Thus, bilateral aspergilloma suggests a poor prognosis. Relapse of CPA is also recorded in 36% of patients who have discontinued antifungal medication.[9] The recurrence rate is often associated with younger age, multi-lobar involvement, and prolonged therapy. Some studies showed recurrence of CPA in patients who had undergone surgery with or without antifungal therapy.[22,23]

CONCLUSION

Pulmonary aspergillosis should be suspected in patients with prolonged cough and hemoptysis, especially in Indonesia, where a high number of lung TB cases are recorded. Tracheobronchial manifestation of aspergillosis, usually seen in immunocompromised patients, can also be present in immunocompetent patients, although the pathophysiology is still unclear. Diagnosis remains challenged since the symptoms can mimic other diseases like lung TB. Early diagnosis and treatment are recommended since it has a poor prognosis. Treatment with fluconazole can be considered if antifungal availability is limited, as in this case. However, we still recommend the usage of itraconazole or voriconazole if the medication is available, especially in immunocompromised patients, since it is the treatment of choice in this type of case. Relapse of CPA is common after discontinuation of treatment. Therefore, routine examination is recommended.

Consent

Written informed consent was obtained from the patient.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Data gathering, analysis, and discussion: YKH, AANSP, WWSP, IWS, NN, CRA. All authors contributed and approved the final version of the manuscript.

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