CASE REPORT

Pulmonary Aspergilloma Co-Existing with Pulmonary Tuberculosis: A Case Report in Type 1 Diabetes Mellitus (T1DM) Patient

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ABSTRACT

Introduction: Pulmonary aspergilloma is a disease frequently found in immunocompromised patients. In Indonesia, around 18% of diabetes mellitus (DM) patients suffer from chronic pulmonary aspergilloma. However, data on type 1 DM (T1DM) are still limited.
Case: We presented the case of a 22-year-old male admitted to the emergency room due to hemoptysis of approximately 200 ml within six hours before admission, nonspecific chest pain during cough, fever, night sweats, and weight loss of 3 kg over the last months. The patient had a history of T1DM and no prior history of respiratory diseases. Physical examination showed tachycardia, tachypnoea, subfebrile, normal body mass index, and rhonchi on the left thorax. Routine laboratory tests revealed increased blood sugar level (503 mg/dL) and HbA1c 16.4%. Chest X-ray and high-resolution computed tomography (HRCT) showed a cavity with an opaque lesion, crescent sign, consolidation, and reticulonodular infiltrate on the left lung. Rapid molecular tests, tuberculosis (TB), and serum galactomannan (GM) were negative. The patient was diagnosed with pulmonary aspergilloma, T1DM, and clinical TB. He was treated with fluconazole, insulin, and a fixed-dose combination of anti-TB. The patient refused the surgery procedure. Immediately, the hemoptysis stopped, blood glucose level was normal, and concomitant with weight gain.
Conclusion: Due to innate and acquired immunity impairment, T1DM is a risk factor for pulmonary infections, including TB and pulmonary aspergilloma. Chest HRCT may help diagnose fungal balls. Though the patient refused to undergo surgery, administering antifungal, anti-TB drugs, and glucose control as initial treatment presented a good prognosis in the patient.

INTRODUCTION

Pulmonary mycosis is a lung disorder caused by fungal infection, colonization, and hypersensitivity reactions to mold.[1] It is also caused by primary or secondary lung mycosis. Primary infections are due to pathogenic fungi that cause inflammations in the bronchial or lung. The fungal infection can easily lead to immunocompromised individuals, such as neutropenia, hematologic malignancy, hematologic cell or solid organ transplant recipient, or ongoing chemotherapy.[2]

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One of the opportunistic fungi, including *Aspergillus,* is the main sources of fungal infections in the human lungs. *Aspergillus* is a saprophytic and ubiquitous fungus in the air. Twenty of 200 species of *Aspergillus* are classified as human pathogens. The most common *Aspergillus* is *A. fumigatus* which causes aspergillosis. Pulmonary mycosis is often difficult to distinguish from other lung diseases. The diagnosis of pulmonary mycosis may be delayed due to similarity of symptoms or radiography findings to tuberculosis (TB). Patients with underlying lung pathology or immunocompromised are more likely to have fungal infection, especially in those who do not respond to typical antibacterial antimicrobial drugs.[3,4]

As one of the countries with endemic TB, pulmonary TB in Indonesia is the most common disorder that precedes pulmonary aspergillosis (PA).[4] Aspergillosis coinfection among patients with pulmonary TB is 15.4%.[5] Other intermediate risk patients include those on long-term use of high dose corticosteroid or antibiotics, human immunodeficiency virus (HIV), chronic renal insufficiency, liver cirrhosis, or diabetes mellitus (DM). Significantly, there is increased risk of DM due to impaired innate and adaptive immunity.[3] Hyperglycemia makes the individual becomes more susceptible to *Mycobacterium tuberculosis* (MTB) infection.[4]

In Indonesia, around 18% of DM patients suffer from chronic pulmonary aspergillosis (CPA). However, specific data on diabetes mellitus type 1 (T1DM) are still limited. Patients with T1DM may develop lung infection depending on the degree of immune compromise of the host or underlying lung pathology. As T1DM usually affects the younger age group, it could be overlooked as the underlying disease of pulmonary infection, including TB.[6] The awareness among clinicians and health workers to detect pulmonary infection in this group of patients is important for better outcome. Here we reported a T1DM patient with pulmonary mycosis coinfection with lung TB.

CASE

A 22-year-old male was admitted to the emergency room due to hemoptysis of approximately 200 ml within six hours before admission. He complained of left chest pain during cough, fever, night sweats, and weight loss of 3 kg over the last months. The patient had a history of T1DM since 18 years old without taking any routine medication. The patient had no prior history of other respiratory diseases. The patient had a normal body mass index (BMI). Vital signs on admission showed fever, normal blood pressure, and respiratory rate. Physical examination found rhonchi on the left lung auscultation.

Laboratory test on admission revealed normal hemoglobin (15.3 gr/dL), compensated acidosis metabolic on blood gas analysis, slight increase of leucocyte (10.300 gr/dL), normal neutrophil (75.1%), normal lymphocyte (12.9%), high blood sugar level (503 mg/dL), and an increase of HbA1c (16.4%). Chest X-ray on admission showed a cavity with opaque lesion in the left perihilar lung (Figure 1A). Thoracic high-resolution computed tomography (HRCT) examination on day 2 of admission revealed multiple cavities with crescent sign, consolidation, and reticulonodular infiltrate on apicobasal left lung (Figure 1B). Sputum GeneXpert (MTB) and serum galactomannan (GM) were both negative. The patient refused to undergo surgery or bronchoscopy.

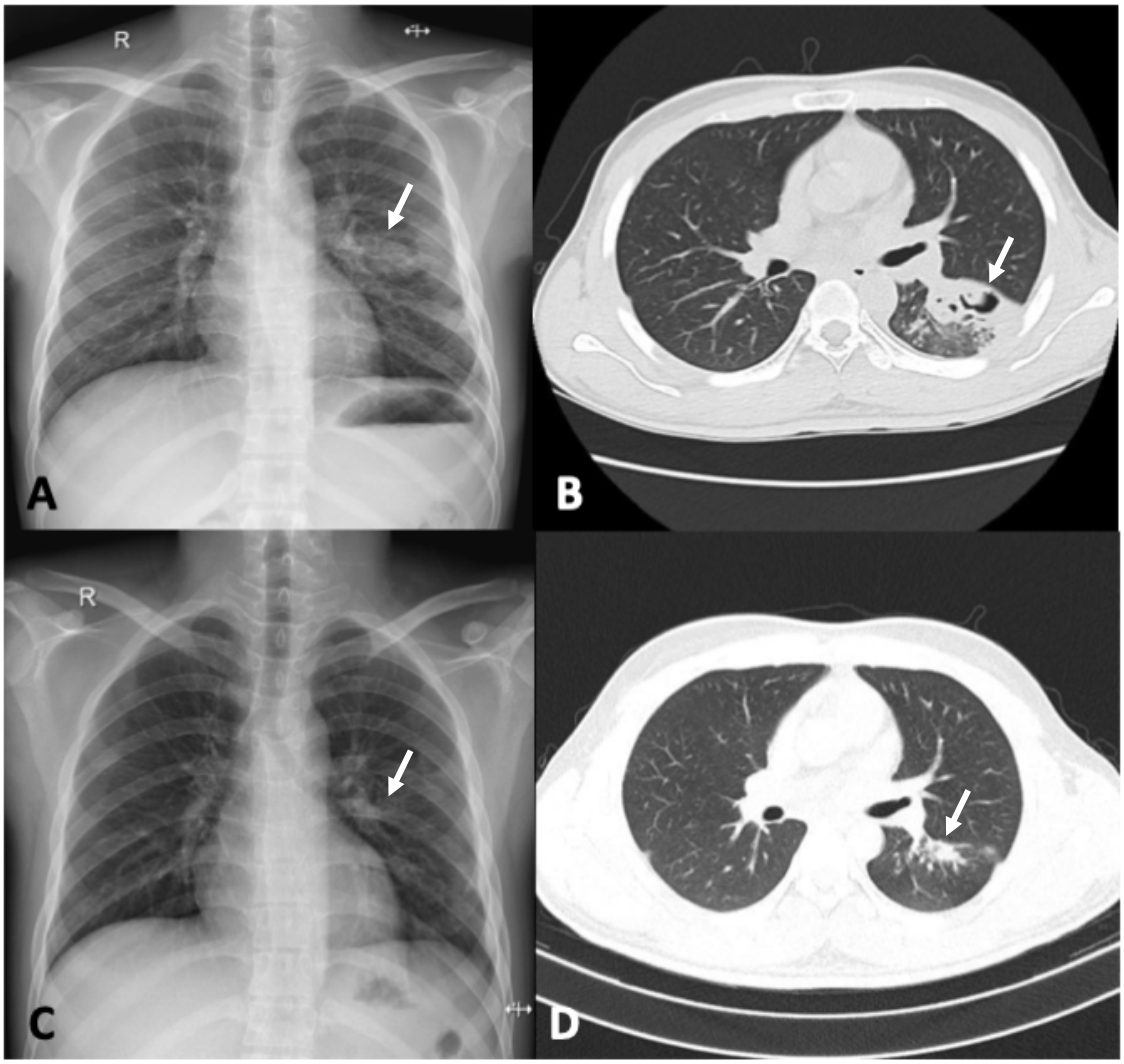

Figure 1. A. Chest X-ray on day of admission showed cavity with opaque lesion in the left perihilar lung (white arrow); B. HRCT on day 2 of admission showed multiple cavities with crescent sign, consolidation, and reticulonodular infiltrate on apicobasal left lung (white arrow); C. Chest X-ray two months after therapy showed improvement of consolidation (white arrow); D. HRCT five months after therapy showed resolution of crescent sign and stable condition of infiltrate on apicobasal left lung (white arrow).

The patient was diagnosed with possible CPA, T1DM, and clinical pulmonary TB. Fluconazole 1x200 mg, insulin short acting 3x20 unit and insulin long acting 1x20 unit, and a fixed-dose combination of anti-TB 4FDC 1x4 tablets were administered. Anti-TB drugs were given in intensive phase for two months (4FDC 1x4 tables) and continuation phases for seven months (2FDC 1x4 tablets). Following the nine months of anti-TB therapy and antifungal drug, the patient was clinically improved, the hemoptysis stopped, blood glucose was controlled, and concomitant with weight gain.

Two months after anti-T medication, the patient agreed to have bronchoscopy procedure. The bronchial branches were within normal limits. Bronchial washing of polymerase chain reaction (PCR) MTB and acid-fast bacilli revealed no MTB detected. Both microorganism and potassium hydroxide of fungi in bronchial washing were negative. Chest radiography showed ground glass opacity in the middle and lower left lung (Figure 1C). Five months after anti-TB medication, HRCT was performed and showed consolidation, fibrosis, and centrilobular nodule in segment 6 and 8 of the left lung (Figure 1D). Fluconazole was given for two months and discontinued since no fungi were detected on bronchial washing specimen. Anti-TB medication was given for nine months and later discontinued due to clinically improved symptoms and no hemoptysis recurrence. The patient still received insulin therapy.

DISCUSSION

The prevalence of pulmonary mycosis in recent years has increased along with the increasing number of HIV infections, malignancy, organ transplantation, chronic systemic disease, and other risk factors such as long-term use of antibiotics, steroids, and invasive medical devices. One of the common pulmonary mycosis is aspergillosis.[7] *A. fumigatus* is a common causal agent in chronic CPA, a fungal infection of the lungs. Among the other types are *A. flavus*, *A. niger*, and *A. terreus*. The lung parenchyma is slowly but steadily destroyed by aspergillosis. Patients with pre-existing pulmonary conditions, including TB, chronic obstructive pulmonary disease (COPD), lung cancer, bronchogenic carcinoma, non-tuberculous mycobacterial (NTM) infection, bullae or lung cysts, lung abscess, or healed abscess cavities, are disproportionately affected. Daily inhalation of *Aspergillus* spores is common because *Aspergillus* releases airborne conidia.[8,9] Nevertheless, the illness will occur in patients with underlying lung pathology or immunocompromised.[8]

CPA involves a spectrum of diseases with similar risk factors and clinical presentation.[8] Different forms of CPA are a simple aspergilloma, a single fungal ball in a single pulmonary cavity with no progression over months of observation, and few pulmonary or systemic symptoms.[9] The distinguishing difference between CPA and simple aspergilloma is period of disease progression. Meanwhile in CPA, the presence of symptoms and abnormalities on imaging around 1-6 months, usually occurs for three months.[10] The patient had symptoms over three months including chest pain during cough, hemoptysis, fever, night sweats, and weight loss. However, there were limited data of radiographic imaging. Hence, the cavitation on serial chest radiographs could not be observed.

Clinicians must consider PA with different diagnosis such as persistent lung infiltrates, with or without mediastinal lymph adenopathy, which does not respond to the antibacterial agents.[3] As one of the countries with endemic TB, pulmonary TB in Indonesia is the most common disorder that precedes PA. It is thought that PA is most often develops in pre-existing cavities in the lungs, commonly in 20% of TB patients.[5] Coinfection of active pulmonary TB and CPA may occur. Proven and probable cases of CPA rose from 7.9% at baseline to 13.3% at the conclusion of TB treatment, according to Setianingrum, *et al*. (2021).[5] CPA resolved on its own in many of the research participants.[5]

Conidia, or asexual spores of *Aspergillus*, are readily disseminated in the air, both indoors and outdoors. The advancement of cavities and parenchymal opacities is difficult to distinguish from the failure of TB therapy or recurrent infection.[11] Inhalation of small diameter conidia of *Aspergillus* (2-3 mm) causes deposition of conidia in the bronchioles or alveolar spaces. The fungal surface is comprised of polysaccharide components or glycans which are considered by host cells as pathogen-associated molecular patterns (PAMPs) structure. Neutrophil and macrophage as a first line immune cells are recruited to inflammatory sites, bind the structure of conidia PAMPs through specific pattern recognition receptors (PRRs). TNF-α, IL-1, IL-6, IL-8, macrophage inflammatory protein 1, and monocytes chemoattractant proteins are all produced by PRR in response to the presence of the *A. fumigatus* ligand, which triggers a pro-inflammatory response.[4]

In immunocompetent individuals, conidia are eliminated by alveolar macrophage and killed by phagocyte. Adaptive mechanisms, such as natural killer cells, can directly kill fungal pathogens by cytotoxicity, and adaptive T lymphocytes are important to restrain fungal expansion. Otherwise, conidia can avoid host elimination system in immunocompromised condition. Escaped conidia grow into mature germ tubes and germinate into hyphae. Hyphae invade the tissue that continues over a period of time.[4] This process may lead to inflammation and expansion of the colonized cavity with or without aspergilloma or fungus ball.[12]

DM is a risk factor that predisposes to aspergilloma and other pulmonary infections. Based on a retrospective study in Pakistan, DM was the most commonly comorbid-associated in CPA (28.4%).[13] The patients who suffered from DM had impaired of innate and adaptive immunity. It causes patients with DM to be prone to develop *Aspergillus* infection and relapse in TB cases.[14] The intracellular level of cytokines (IFN-γ, IL-2, TNF-α, and IL-17) was found to be diminished.[4] Deficiency of surfactants A4 and toll-like receptor-4 (TLR-4) impairs immune function naturally, reduces the production of cytokines, as well as resulting in progressive destruction of lung tissue.[1] Consequently, hyperglycemia makes the patient more susceptible to MTB infection and inadequate killing of inhaled fungal conidia.[4] The patient had high level of serum glucose and HbA1c, meaning that he had a persistent hyperglycemia condition within at least three months. Due to the fact that the patient had uncontrolled T1DM since younger age, in addition to the clinical and radiographical findings, this supported the diagnosis of possible pulmonary mycosis.

CPA is diagnosed based on symptoms, abnormalities of radiological examination, direct evidence of *Aspergillus* infection or an immune reaction to *Aspergillus spp*., and all other possible causes have been eliminated.[9] Based on the modification version by

Denning, *et al*. (2018), CPA was classified as proven, probable, and possible.[14] Symptoms of persistent *Aspergillus* infection for more than three months and confirmation by chest radiograph evaluation define CPA in a resource-constrained settings country.[14] The symptoms of CPA may occur for at least three months and include respiratory and or constitutional symptoms. Patients usually have one of the following symptoms, namely cough, hemoptysis, chest pain, dyspnea, fatigue, weight loss, fever, fatigue, and night sweats.[13]

Fever is uncommon in CPA. It may indicate a subacute invasive aspergillosis. Frequently, the diagnosis of a pulmonary mycosis may be delayed as a result of its overlapping symptoms with other respiratory diseases.[9] The patient came to the hospital with the main symptoms of hemoptysis, which may be resulted from endotoxins and injury to the fungal ball with the high vascularization of the bronchial artery surrounding the involved area.[14,15] Hemoptysis is the most common symptom in CPA (75%) and varies from blood streaking to massive hemoptysis. This symptom might be caused by other respiratory infections and coincide with pre-existing lung diseases. Hemoptysis in TB is not severe, and is as a result of erosion of the pulmonary capillaries or adjacent bronchial arteries in necrosis of pulmonary parenchyma.[12,15]

Compared to a chest X-ray, thoracic computed tomography (CT) scan displays superior sensitivity and specificity. Radiologic imaging of CPA includes progressive cavitation, intracavitary fungal ball, and pleural thickening or pericavitary fibrosis of infiltrates surrounding the cavities.[15] A cavity is a gas-filled space seen as a low attenuation area or lucency within pulmonary consolidation, mass, or a nodule. Benign lesion is indicated when the degree of contrast is less than 10 HU, smooth walls, and wall thickness of <7 mm.[16] The cavities are a slow progression over months or years.[8] One possible disease predictor is lesion location. Thin-walled cavities in the upper lung zone are a common early sign of PA, which can be mistaken for TB.[8] In immunocompetent of TB patients, a hollow is often located between the apical and posterior portions of the upper lobes.[17] The cavity may be located in any lung zone in patients with NTM infection and endemic fungal disease.[14] The cavity is often surrounded by satellite nodules. The cavity wall shows rim enhancement on CT with variation of thickness.[17]

The fungus ball develops in the cavity to form the Monod's sign, an air surrounding a fungal ball in pre-existing cavities caused by soft tissue attenuation material separated from the cavity wall. The presence of a fungal ball is highly suggestive of an aspergilloma. It consists of *Aspergillus* hyphae, inflammatory cells, fibrin, mucus, and tissue debris that arise in pulmonary cavities.[14,18] Other *Aspergillus spp.* may also be manifested as a fungal ball.[19] The differential diagnosis of fungal ball in the lung are acute or subacute invasive fungal infection, lung abscess, cavitating hematoma, necrotizing bronchogenic carcinoma, or echinococcal cyst.[14] Pleural thickening is a presage of aspergillosis, characterized by adjacent to the areas of consolidation or cavitation.[11] Pleural thickening is a useful diagnosis rarely seen in pulmonary TB.[14] Thoracic HRCT of the patient showed consolidation and multiple cavities with fungal ball in the apicobasal segment that is highly suggestive of aspergilloma. Reticulonodular infiltrate and subpleural nodules surrounding the consolidation in the lower lobes. The location showed predilection for TB.

The diagnosis of CPA must be supported by microbiological or immunologic evidence. *Aspergillus* must be confirmed by a positive result in either the *Aspergillus* IgG or precipitin test, or by the detection of *Aspergillus* antigen or DNA in respiratory fluids. Bronchoscopy or transthoracic aspiration might be used to collect the tissue sample for the biopsy.[9] Sputum microscopy for hyphae or fungal culture should be conducted if the *Aspergillus* IgG test cannot be obtained.[14] Unfortunately, we were unable to get a sample for the *Aspergillus* IgG test since no sputum specimens were available.

The non-culture examination for aspergillosis is GM. GM is a carbohydrate antigen component of *Aspergillus spp.* cell wall that is specific for all *Aspergillus* species. It has been widely used as a tool for diagnosing invasive pulmonary aspergillosis. In a study by Shin, *et al*. (2014), sensitivity of GM serum antigen was 23%, specificity was 85%, the area under the receiver operating characteristic curve was 0.538, and overall accuracy of the test was 54%.[20] Another study from Sehgal, *et al*. (2019) showed that GM in bronchoalveolar lavage (BAL) fluid specimens performs better than serum in diagnosing CPA.[21] Sensitivity and specificity BAL fluid in simple aspergilloma was 86% and 81% with a best cut-off value of 1.[21] The normal level of serum GM in the patient may exclude the diagnosis of invasive aspergillosis.[22] The limitation of this case was, we could not get a specimen from BAL fluid due to lack of consent to perform bronchoscopy in the early treatment. We used serum as a non-invasive method to check GM. The negative results of GeneXpert may indicate clinical diagnosis of pulmonary TB.

An asymptomatic aspergilloma could be observed conservatively without giving any antifungal treatment with close monitoring.[22] For patients with life-threatening aspergilloma symptoms, such as hemoptysis, or patients who failed antifungal therapy, surgical resection is considered as a gold standard of aspergilloma. The management of surgical resection is

either by conventional lobectomy of a video-assisted thoracic surgical (VATS) procedure. Surgical resection can eradicate the fungus ball, underlying cavity, and surrounding unhealthy parenchyma.[23] Bronchial artery embolization (BAE) is another less invasive alternative treatment for short-term control of hemoptysis. Recurrence of hemoptysis occurred in 10-50% of post BAE cases.[23]

Since the patient refused the surgery procedure, we decided to give conservative treatment by administering azole antifungal. Antifungal treatment is indicated for patients who are symptomatic. Oral triazole is considered to have good activity against *A. fumigatus* by interfering with cell membrane synthesis and inhibiting biosynthesis of ergosterol.[24] Itraconazole is a well-tolerated drug as first line treatment for pulmonary aspergillosis. The other choices are voriconazole, posaconazole, and isavuconazole.[23] The response to antifungal therapy is generally slow. It is suggested a minimum of 4–6 months of treatment.[9] Nevertheless, some patients with a mild immunosuppression may need more than six months of treatment. The role of medical therapy in the treatment of aspergilloma is uncertain because of penetration into pre-existing cavities.[21] Patients with single aspergilloma or *Aspergillus* nodules often not respond to antifungal. Otherwise, antifungal treatment can prevent disease progression, improve symptoms, and quality of life.[22] The Indonesian Society of Respirology (PDPI) in its mycosis guideline advises to give antifungal therapy for another two weeks after the clinical improvement.[7]

Unfortunately, the availability of antifungal drugs covered by the National Health Insurance (JKN) in the hospital is only fluconazole and itraconazole. Due to negative mycological examination results, patients with a diagnosis of probable or possible CPA can be given fluconazole. The successful treatment of CPA and pulmonary TB is influenced by blood sugar regulation. This will increase the immune response against invading pathogens in diabetic patient. The patient in this case report showed a favorable outcome and reduced hemoptysis after receiving antifungal therapy, a fixed-dose ant-TB, insulin, and tranexamic acid. Since the symptoms were clinically improved, surgical resection was not considered.

CONCLUSION

This case report highlights the incidence of possible CPA co-existing with pulmonary TB in T1DM patient. Although the overlapping clinical and radiological characteristics made a distinct diagnosis of CPA and TB difficult, it is necessary to consider coincidence of CPA in immunocompromised patients such as T1DM. Inadequate blood glucose control is a risk factor for pulmonary infection in T1DM. In resource-limited settings, CPA is diagnosed based on symptoms more than three months, radiologic imaging (preferably CT scan), microbiological evidence of *Aspergillus* infection and mycobacterial infection eliminated with smear, GenExpert, and/or mycobacterial culture. The treatment includes antifungal drugs, anti-TB drugs, and insulin. Therefore, raising awareness as well as regular monitoring are important to ensure that patients receive adequate therapy and comply with the treatment.

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

Conception: HKPF, FY. Data collection: WTK, GS. Data analysis: HKPF, HK. Writing the manuscript: WTK, HKPF. Review and revision: WTK, HKPF, HK, GS, FY. All authors contributed and approved the final version of the manuscript.

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