Successful Embolization in Recurrent Hemoptysis Caused by Pulmonary Aspergilloma: A Case Report

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Abstract

Background: Aspergilloma is a fungal infection that can cause recurrent hemoptysis. One of the treatment modalities is embolization, which has a success rate of 85% to 100%, although the recurrence rate may reach 10% to 33%.

Case Illustration: A 29-year-old female came to the emergency ward with recurrent hemoptysis. She had a history of tuberculosis with completed treatment 7 years ago. Chest radiography showed left lung tuberculosis with emphysematous lung. Chest CT with contrast revealed an air-crescent sign, and culture from bronchoalveolar lavage (BAL) showed Aspergillus spp. Then, she was diagnosed with pulmonary aspergilloma. Embolization was performed in the left internal mammary artery, and the blushing was decreased by 80%. However, the hemoptysis was still recurrent; a second embolization was performed in the left supreme intercostal artery, costocervical trunk artery, and bronchial artery, resulting in no blushing. The patient had no further episodes of hemoptysis, and her antifungal therapy was changed from fluconazole to voriconazole.

Discussion: Recurrent hemoptysis can be caused by pulmonary aspergilloma. Embolization is usually done to reduce bleeding before surgery. The patient had performed embolization 2 times with no further episodes of hemoptysis. Surgical resection as a definitive treatment was recommended in this case, but the patient refused. Therefore, the patient's management was optimized using voriconazole and embolization for the hemoptysis.

Conclusion: Management of recurrent hemoptysis in patients with aspergilloma may include embolization and antifungal treatment which give improved clinical outcomes.

Keywords: recurrent hemoptysis, embolization, aspergilloma, tuberculosis

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1. Introduction

Aspergilloma is a type of noninvasive chronic pulmonary aspergillosis. Aspergilloma manifests as a fungal ball or mycetoma consisting of *Aspergillus spp.* hyphae, cellular debris, and mucus.[1,2] The prevalence of chronic pulmonary aspergillosis (CPA) varies from 1 case per 100.000 people in developed countries such as the United States and may reach 42.9 cases per 100.000 people in some developing countries in Africa. The incidence of aspergilloma in patients with

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chronic pulmonary aspergillosis is approximately 25%. The global burden is estimated at 1.2 million patients with a higher incidence and prevalence in Africa, the western Pacific, and Southeast Asia. The incident is far less frequent in patients without previous parenchymal disease which is only 0.13%.[3] Invasive aspergillosis commonly occurs in immunocompromised populations, such as patients with AIDS, neutropenia, long-term corticosteroid users, and transplant recipients. Patients with chronic obstructive pulmonary disease, tuberculosis, asthma, lung cancer, and sarcoidosis are also at increased risk of developing chronic aspergillosis. Globally, it is estimated that more than 3 million people suffer from CPA and around 1.2 million cases of which are thought to be caused by previously treated pulmonary tuberculosis (PTB).[2] CPA generally affects patients aged 34-65 years and is more common in men.[4]

Aspergillus spp infection into the lungs begins with the exposure of fungal spores which are ubiquitous in the air into the airways. *Aspergillus fumigatus* and *Aspergillus nigger* are the most common etiology. Spores must pass through the body's defenses including mucosal lining and ciliary action (compromised in diseases such as cystic fibrosis, asthma, and Kartagener) to reach the lungs.[1,5] Nearly 60% of aspergillomas thrive in poorly drained, avascular cavities where they attach to the wall with their conidia, germinate, and cause an inflammatory reaction.[6] Macrophages recognize key fungal cell wall components such as beta-D-glucan and secrete inflammatory mediators attracting neutrophils to initiate cellular immunity. Many Aspergillus species produce toxic metabolites (aflatoxin, mycotoxin 3-nitro propionic acid, and ochratoxin A) that inhibit the phagocytic action of macrophages and neutrophils. Immunosuppression as well as chronic steroid treatment can lead to the dysfunction of neutrophils and macrophages and a decrease in neutrophils which exacerbates the disease.[1,5] The organisms, along with inflammatory debris, form an amorphous mass identified as an aspergilloma.[6] Vascular invasion may occur when surface components of the fungal cell bind to components of the vascular wall which eventually results in necrosis, infarction, or bleeding.[1,5]

The initial symptoms of aspergillosis are sometimes non-specific, such as a dry cough, fever, and chest pain. Immunocompromised patients often don't even have any fever.[6,7,8] Hemoptysis is the most common clinical manifestation, which indicates a pulmonary infarction and can be recurrent, may occur massively, is difficult to control, and is often fatal.[2] The diagnosis of CPA is a multi-

factorial process involving a combination of clinical presentation, radiological findings, positive culture growth, and serological tests. The disease must be present for at least 3 months and with little/no immune compromise. A definitive diagnosis can be achieved by sampling sputum or bronchoalveolar lavage and trying to grow the fungus in the culture, although this has a negligible success rate, with studies citing positive rates as low as 26% and, therefore, this cannot be used to rule out disease.[9,10] Only about 7%-10% of aspergilloma cases resolve spontaneously without treatment.[3,6] Difficulties in diagnosing aspergillosis often result in delayed and inadequate therapy. One of the treatment modalities is embolization, which has a success rate of 85% to 100%, although the recurrence rate may reach 10% to 33%.[10] Those with persistent symptoms, such as hemoptysis, require further treatment, for which surgery is the gold standard.[3,6] Patients with contraindications or refusing surgery should be treated conservatively with systemic or intracavitary anti-fungal agents although it has limited efficacy.[2]

We present a case of post-tuberculous aspergilloma in a 29-year-old woman with recurrent hemoptysis. We hope this case report may provide insight and understanding about the risk factors, clinical manifestations, diagnosis, various therapeutic options, and complications of aspergilloma.

2. Case

A 29-year-old female came to the emergency ward with recurrent hemoptysis from 2017 up to August 2021. She was diagnosed with Lung Tuberculosis in 2012 and only took her medicine for 28 days. In 2014 she was diagnosed with Lung Tuberculosis which was confirmed by acid-fast bacilli and chest radiography (CXR) and had completed her 9-month treatment. Currently, the patient has been declared cured with far advanced lesions accompanied by multiple cavities.

Her chest radiography on October 26th, 2021, showed a cavity with opacity in it, forming an air-crescent sign (Figure 1). Chest Computed Tomography (CT) angiography with contrast on October 21st, 2021, showed dilatation and tortuosity in several branches of the artery in the left superior thoracic artery, left apical segmental artery, left bronchial artery at the levels T4 and T6, left posterior segmental artery, and left intercostal artery III and IV (Figure 2).

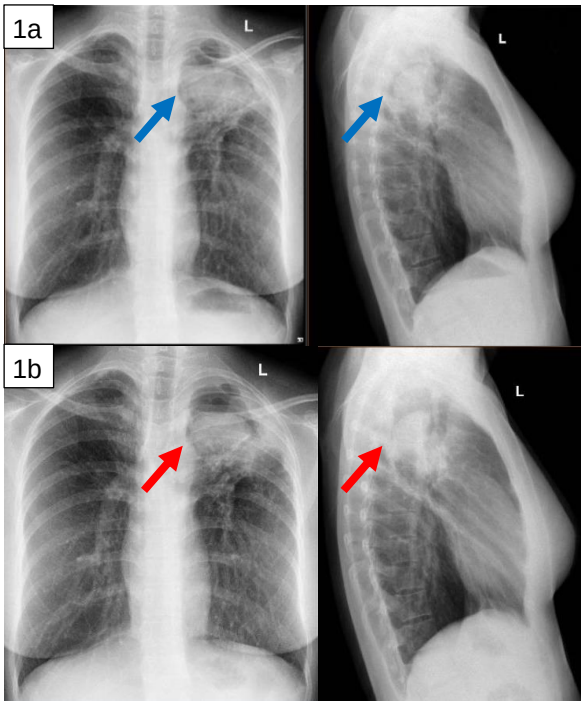

Figure 1. A comparison of CXR taken in Saiful Anwar General Hospital on October 26th, 2021 (1a, blue arrows) and December 21st, 2021 (1b, red arrows) showed an air-crescent sign at the apex of the left lung which had improved.

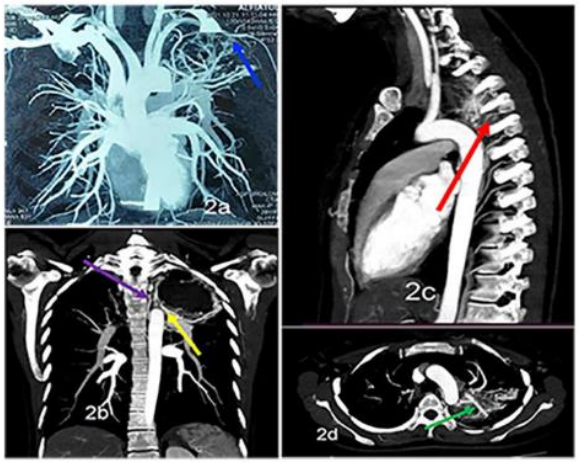

Figure 2. Chest CT Angiography with contrast on October 21st, 2021, showed dilatation and tortuosity in several branches of the artery in the left superior thoracic artery, left apical segmental artery, left bronchial artery at the levels T4 and T6, left posterior segmental artery, and left intercostal artery III and IV.

Culture taken from bronchoalveolar lavage (BAL) performed on October 15th, 2021, showed *Aspergillus spp* (Figure 3). Xpert Mtb Rif sputum was already done on July 3rd, 2021, and October 27th, 2021, showing negative results in both tests.

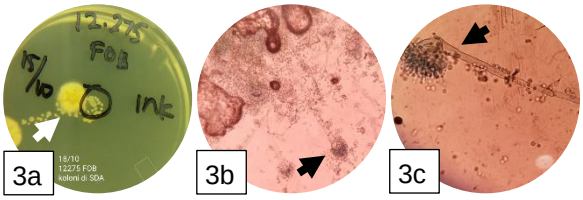

Figure 3. BAL culture in the macroscopic examinations showed growth of fungal colony (3a, white arrow). Microscopic examination of specimen from BAL culture (3b) and sputum (3c) with KOH staining showing septate hyphae with long conidiophores carrying many spores (black arrow).

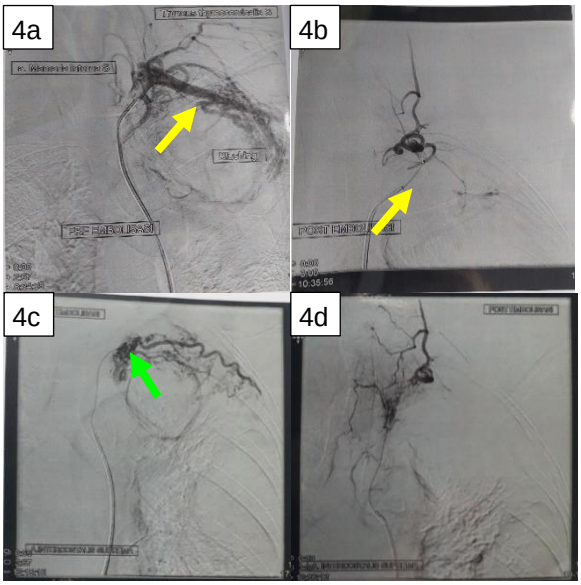

Figure 4. Angiography on the left internal mammary artery before (4a) and after (4b) the first embolization on October 13th, 2021. Angiography on the left supreme intercostal artery before (4c) and after (4d) the second embolization on November 2nd, 2021.

The patient was then diagnosed with pulmonary aspergilloma. Embolization was performed on October 13th, 2021, using polyvinyl alcohol (PVA) and gelfoam in the left internal mammary artery, resulting in decreased blushing by 80%. However, the hemoptysis still recurred, therefore the second embolization was performed on November 2nd, 2021, in the left supreme intercostal artery, costocervical trunk artery, and bronchial artery, resulting in no blushing (Figure 4).

The patient had no further episodes of hemoptysis, and her antifungal therapy was switched from Fluconazole to Voriconazole.

The patient was informed about the plan to consult Cardiothoracic Surgery Department for left lung lobectomy but the patient refused it.

3. Discussion

In this case, it was reported that a 29-year-old woman came with recurrent hemoptysis. In theory, the initial symptoms of aspergillosis can be non-specific, including dry cough and fever, and pleuritic or non-specific chest pain.[11] Hemoptysis is the most common clinical manifestation in symptomatic patients, reported in 54-87.5% of cases, and may turn into massive fatal bleeding in 30% of patients.[2] The source of bleeding is usually bronchial vessels and can be secondary to direct invasion of the lining of the capillary walls, release of endotoxins from organisms, and mechanical irritation of open vessels in the cavity. In rare cases the rapidly growing cavity can erode the pleural surface and intercostal arteries, causing massive and often fatal hemoptysis which is very difficult to control.[1]

In addition, this patient has had a history of lung tuberculosis (TB) in 2012. Currently, the patient has been declared cured with far advanced lesions accompanied by multiple cavities. Aspergillosis is closely related to TB. Research from The Research Committee of the British Tuberculosis Association shows that patients with post-TB cavities have a high risk of experiencing fungal colonization, where more than 17% of patients with post-TB cavities have radiological mycetoma. Fungi grow well in cavities formed post-TB because these places contain plenty of oxygen and necrotic tissue that supports their growth.[7,12]

Culture taken from bronchoalveolar lavage (BAL) in this patient showed *Aspergillus spp.* Theoretically, the diagnosis of aspergilloma is a multi-factorial process involving a combination of clinical presentation, radiological findings, positive culture growth, and serological tests. A definitive diagnosis can be achieved by sampling sputum or bronchoalveolar lavage and attempting to grow

the fungus in culture. However, this has a negligible success rate, with studies citing positive rates as low as 26% and, therefore, these tests cannot be used to rule out the disease.[10]

Meanwhile, other sources state that the gold standard for the diagnosis of invasive pulmonary aspergillosis is a histopathological examination of lung tissue taken by thoracoscopic technique or open-lung biopsy. The presence of septate, acute, and branching hyphae that invade the lung tissue along with positive culture results for Aspergillus at the same site, can diagnose IPA. Histopathological examination also has the advantage of being able to rule out differential diagnoses such as malignancy or other non-fungal infectious diseases.[13]

The patient was also examined by chest radiography showing an air crescent sign or fungus ball appearance. Chest radiography is often the first diagnostic test ordered in a symptomatic patient. This examination shows predominantly the left upper lobe cavity with opacity in it, forming an air crescent sign. Chest CT scan may assist in determining cavity wall thickness, architectural distortion and inflammation of the surrounding parenchyma and pleura, the relationship of the mycetoma to the surrounding vessels as well as the nature of neovascularization in both the pulmonary parenchyma and parietal pleura. In the clinically relevant setting, characteristic chest CT findings combined with the presence of microbes in sputum culture and serological evidence (serum antibodies) confirm the diagnosis.[10,14]

One of the treatment modalities is embolization. Embolization was performed twice in this patient. Embolization was performed using PVA (Polyvinyl Alcohol) and Gelfoam in the Left internal mammary artery, and the blushing was decreased by 80%. But, the hemoptysis was still recurrent; a second embolization was performed with no blushing. Bronchial artery embolization is the preferred approach for patients with massive hemoptysis both as first-line treatment and as a bridge to more definitive surgical resection. However, in advanced disease, architectural distortions, neovascularization, and multiple vascular sources often make identification and control a challenging task.[10]

The source of hemoptysis is the bronchial circulation in 90% of cases, although various branches of the thoracic and abdominal aorta can provide collateral supply to the interstitial and bronchi rarely in 10%. Identification and differentiation of ectopic or orthotopic bronchial arteries can be challenging even on a bronchial arteriogram. Bronchial artery branches tend to follow a

vertical or horizontal path before joining the bronchial tree, unlike non-bronchial collaterals which follow trans-pleural pathways not following the bronchial tree. In 70% of cases, the bronchial arteries arise from the descending thoracic aorta at segments T5-T6, with variants arising from the aortic arch or ascending aorta and occasionally from other aortic branches in the thorax or abdomen. Important, in the same context, are the pathways of the anterior spinal arteries which receive collateral from up to eight segmental medullary arteries, ventral to the lower thoracic and upper lumbar spinal cord. In addition to supplying the pulmonary interstitium and bronchi, the bronchial arteries also provide blood flow to the visceral pleura, the middle third of the esophagus, the vasa vasorum of the aorta and pulmonary arteries, and the mediastinum. Therefore, complications and adverse events are associated with nontarget embolization and transient vascular obstruction of other mediastinal structures. Transient chest pain and dysphagia are the most frequently reported side effects and are usually self-limited.[10]

This patient was previously taking fluconazole 150 mg once a day for 21 days. When admitted to our hospital, after BAL culture was taken and confirmed *Aspergillus Spp*, the anti-fungal agent was switched to Voriconazole inj 2x300 mg on the first day, continued 2x200 mg (D2-D9) in first admission, stopped because of increasing of Liver Enzyme > 5x. On the second admission on December 15th, 2021, the patient got treated with Voriconazole inj 2x200 mg until the 8th day, stopped again because of increasing of liver enzyme >5x, after 5 days, the liver enzyme already getting normal, and peroral Voriconazole 1x200 mg was given until 14th day. Voriconazole is an alternative oral agent to itraconazole and is indicated to treat resistant strains of *Aspergillus fumigatus*. It has demonstrated efficacy against invasive pulmonary aspergillosis in a landmark 2002 study in which 144 and 133 patients with invasive pulmonary aspergillosis were treated with voriconazole and amphotericin B, respectively, in a large unblinded randomized trial. As many as 52.8% of the voriconazole group had complete or partial resolution of clinical signs and symptoms at 12 weeks, compared with 31.6% in the amphotericin B group. Furthermore, the 12-week survival rate was 70.8% and 57.9% for the voriconazole and amphotericin B groups, respectively. Meanwhile, the use of voriconazole to treat aspergilloma was only reported in three case reports in which only 2 of 3 patients eventually recovered. IDSA recommends voriconazole for pulmonary aspergilloma at a

dose of 6 mg/kg IV every 12 hours for one day, and 4 mg/kg IV every 12 hours thereafter; Oral therapy can be given in a dose of 200-300 mg every 12 hours. Azoles have several drawbacks that preclude their use as a primary treatment for aspergilloma. The overall efficacy of itraconazole is below 70% and has not been established for voriconazole. Furthermore, an extended duration of treatment, often more than six months, is required to clear up the infection and there have been cases of recurrence of aspergilloma after discontinuation of antifungals. Finally, because of delayed response, azoles do not help treat patients with life-threatening hemoptysis.[10,15]

The patient was scheduled to have a lobectomy performed by the Cardiothoracic Surgery Department, but the patient's family refused. Surgical resection is the definitive treatment for aspergilloma if the patient has good lung function. Surgery should be considered in massive and recurrent coughing up of blood. Segmental resection or just the lesion is sufficient, but to completely eradicate the disease a lobectomy is needed.[12]

4. Conclusion

Aspergilloma is a fairly rare type of non-invasive chronic pulmonary aspergillosis. Invasive aspergillosis commonly occurs in the immunocompromised population and those with a history of chronic obstructive pulmonary disease. Patients with post-tuberculous cavities are at high risk for fungal colonization. Having a history of TB in aspergillosis can increase patient morbidity and mortality. Hemoptysis is the most common clinical manifestation.

The diagnosis of aspergillosis is considered difficult because pulmonary mycosis rarely causes sudden death, atypical clinical symptoms and examination results, and overlooked risk factors. Patients diagnosed as proven aspergillosis if they meet the criteria for host factors, and clinical features and found *Aspergillus spp* from the mycological examination.

In this patient, there were risk factors in the form of a history of Lung TB, clinical symptoms such as recurrent hemoptysis, chest radiography, and Chest CT scan with contrast showed air crescent sign or fungus ball appearance, and BAL culture results showing the presence of *Aspergillus spp*. Therefore, the diagnosis of aspergilloma can be enforced in this patient.

Recurrent hemoptysis can be caused by pulmonary aspergilloma. Embolization is usually done to reduce bleeding before surgery. The patient has been embolized 2 times with no episodes of hemoptysis. Management of recurrent hemoptysis in patients with

aspergilloma includes embolization and anti-fungal therapy which provides clinical improvement.

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