Respiratory Medicine Case Reports 39 (2022) 101738

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Pulmonary aspergilloma coexisting with hamartoma in post pulmonary tuberculosis: A case report

Kristin Purnama Dewi [a, d, *], Ivana Purnama Dewi [b, d], Iswanto [d], Yovita Citra Eka Dewi Djatioetomo [a], Lyndon Darwin [c], Ariani Permatasari [a]

[a] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Airlangga University - Dr. Soetomo General Hospital, Surabaya, Indonesia
[b] Department of Cardiology and Vascular, Faculty of Medicine, Airlangga University - Dr. Soetomo General Hospital, Surabaya, Indonesia
[c] Department of Thoracic and Cardiovascular Surgery, Faculty of Medicine, Airlangga University - Dr. Soetomo General Hospital, Surabaya, Indonesia
[d] Faculty of Medicine, Duta Wacana Christian University, Yogyakarta, Indonesia

ARTICLE INFO

Keywords:
Aspergilloma
Pulmonary tuberculosis
Hamartoma
Diagnosis
Management

ABSTRACT

Introduction: Aspergillosis is a fungal disease caused by the *Aspergillus fumigatus*. Until now, the management of aspergilloma is still controversial, and there is no consensus among experts. Hamartoma is a benign tumor that can be found in the lung. We report a case of pulmonary aspergilloma coincidentally with hamartoma in pulmonary tuberculosis (TB) patients. Aspergilloma and hamartoma diagnoses are challenging because of various clinical symptoms.

Case report: A 46 years old man came to emergency unit with complaints shortness of breath, cough, and chest tightness. He also has a red-black blood streak and terrible odor sputum. He had a history of two episodes of pulmonary TB. Holistic physical and additional examinations were done. Patient was diagnosed with aspergillosis infection in post pulmonary TB. The patient was then undergoing surgery. From the pathology of lung tissue, we found hamartoma features. Antifungal, antibiotic, and supported therapy were given, and his condition improved after a month of hospitalization.

Conclusion: Pulmonary aspergilloma and hamartoma coincidence are rare diseases. Aspergilloma diagnosis is made based on clinical symptoms, radiological, and serological examination. Pulmonary hamartoma is generally asymptomatic. In this case, hamartoma was incidentally found in pathology examination. Prompt and precise diagnosis with good therapeutic management yield favorable outcomes.

1. Introduction

Pulmonary aspergilloma is a disease caused by aspergillus infection [1,2]. About three million people are estimated to have chronic pulmonary aspergillosis (CPA) worldwide. The CPA incidence in developed countries such as Europe and the United States is less than 1 per 100,000. In contrast, in developing countries such as Congo and Nigeria, the prevalence of CPA is 42.9 per 100,000 population [3]. The incidence of pulmonary tuberculosis (TB) can influence CPA prevalence. The prevalence of CPA is increasing in post-pulmonary TB patients.

Pulmonary hamartoma is a rare disease with an incidence rate of 0.025–0.032% in adults [4]. Hamartoma is a benign lung tumor often obtained from all solitary nodules in the lung. Hamartomas are more common in men than women, with a ratio of 2:1. It usually

* Corresponding author. Jalan Mayjen Prof. Dr. Moestopo No.6-8, Surabaya, 60286, Indonesia.
E-mail address: kristin_purnama_d@yahoo.co.id (K.P. Dewi).

https://doi.org/10.1016/j.rmcr.2022.101738
Received 25 May 2022; Received in revised form 30 August 2022; Accepted 8 September 2022
Available online 16 September 2022

grows in adults in their fifth or sixth decade. The incidence peaks at 60 years and rarely occurs under 30 years [4,5]. The location is commonly in the peripheral lung [6,7].

2. Case report

A 46 years old man came to emergency unit with a chief complaint of shortness of breath for eight months that was getting worse in the last two months. This condition was getting worse, especially when he had vigorous activity. He also had cough with a red-black blood streak and foul odor sputum for three months. He had a history of two episodes of pulmonary TB that was cured after six months of therapy. He was diagnosed with a cerebral abscess and underwent cerebral surgery one year before. The patient works in textile fabric with dusty environment, but he rarely used masks. The patient also smoked ten cigarettes per day since he was 18 years old, but stopped when he was diagnosed with pulmonary TB.

On physical examination, the patient was alert with increased respiratory rate and decreased oxygen saturation. Head and neck examination showed dyspnea and slight conjunctiva anemic. Chest examination showed decreased right lung movement and vesicular breath sounds in the two-thirds superior right hemithorax.

Chest X-ray showed an air crescent with consolidation leading to an impression of lung mass and fibroinfiltrates in the superior and medius lobe of the right lung (Fig. 1). A contrast CT scan showed a consolidation (40 HU), cavities, air crescent signs, fungus ball, and pulmonary inflammatory process in the anterior segment superior lobe of the right lung (Fig. 2). Laboratory examination showed anemia (Hb 6.6 g/dL), leucocytosis (WBC 11.15 x 10^3/μL), neutropenia (neutrophils 54.1%) and low tumor marker (AFP 5.7 ng/mL, CEA of 2.12 ng/mL). Blood gas analysis showed fully compensated respiratory acidosis with mild hypoxemia. *Mycobacterium tuberculosis* (MTB) was not detected in the GeneXpert MTB/RIF sputum examination. We also did a sputum culture that grew fungal hyphae of *Aspergillus fumigatus*.

Spirometry examination showed moderate restrictions with no obstruction results. Cytology examination from left and right bronchoalveolar lavage revealed no malignant cells. Fine needle aspiration biopsy (FNAB) guiding CT examination found suppurative inflammation with atypical epithelial cells (reactive cell change) and cavity lesion.

Based on clinical symptoms, radiology imaging, and sputum culture, we manage the patient with a working diagnosis of aspergillosis. The patient was then consulted to thoracic and cardiovascular surgeons. Superior and medius lobectomy (bilobectomy) and adhesiolysis were performed (Fig. 3). During the surgical procedure, we accidently found an endobronchial nodule. Histopathology of lung tissue, fungal ball, and endobronchial nodule found aspergillus colonies and hamartoma features, as seen in Fig. 4. Meanwhile, the left lung lymph nodes cytology showed no tumor cell metastasis.

The patient has been treated with antifungal micafungin 200 mg intravenously once a day for one month and other supportive therapy. The patient's condition gradually improved after medication. He was discharged after thirty-day hospitalization with oral antifungal therapy of 100 mg/day fluconazole for 14 days.

3. Discussion

The healing process in TB patients can make scars in the lung parenchyma. A cavity in pulmonary TB is a suitable place for various organisms, including fungi, where aspergillus colonization grows [8]. The Research Committee of the British Tuberculosis Association states that post-pulmonary TB patients have a higher risk of fungal colonization [2]. Pulmonary aspergillosis can grow in lung tis-

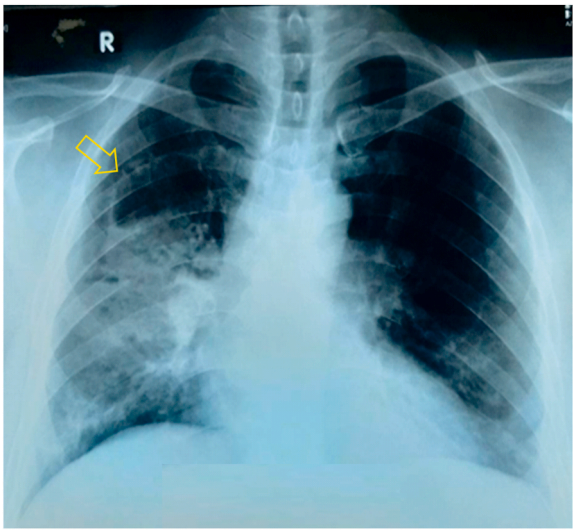

Fig. 1. Chest X-ray showed a fungus ball (yellow arrow), an air crescent with consolidation, an impression of a lung mass, and fibroinfiltrates in the superior and medius lobe of the right lung. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

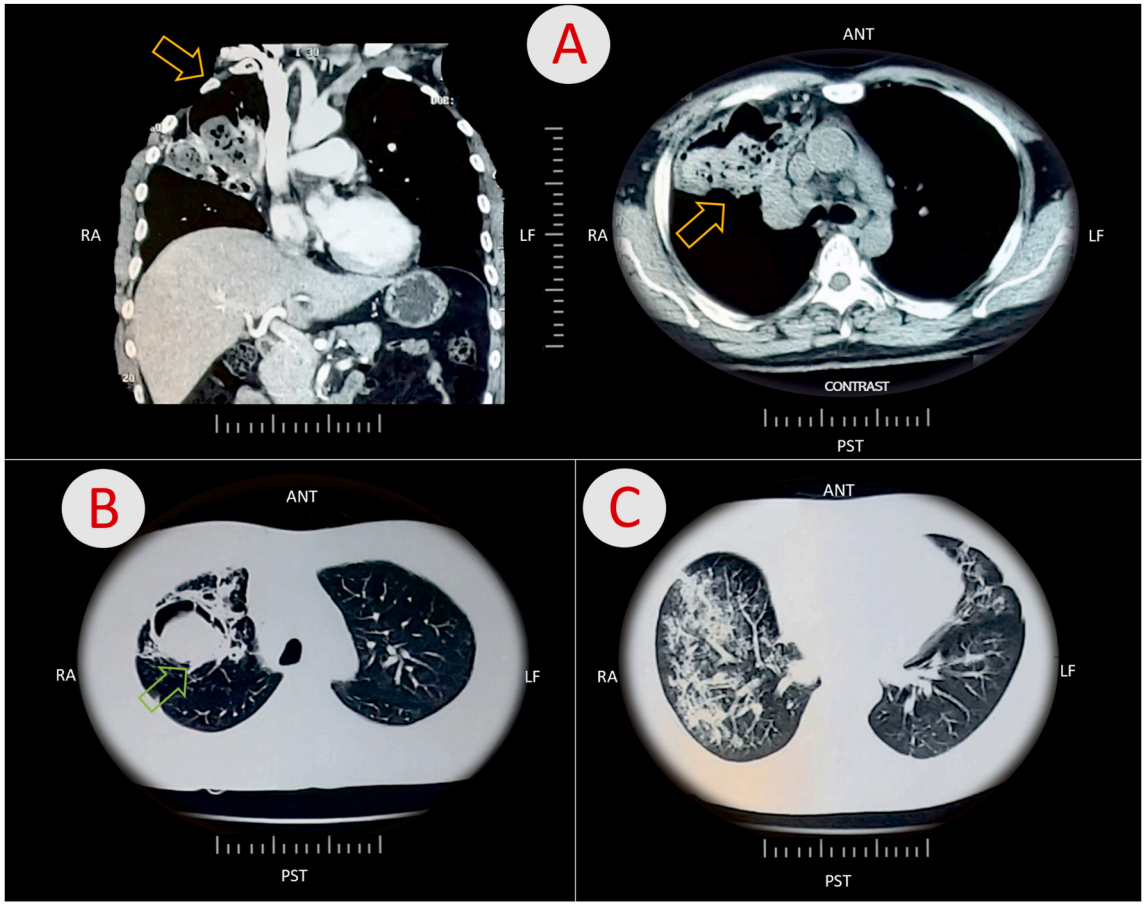

Fig. 2. (A) The mediastinum window shows a cavity with a relatively firm border, a rounded mass in the center (fungus ball), and an air crescent sign (yellow arrow). (B) Lung window: Mass in the right superior lobe with an air crescent sign (green arrow). (C) Fibroinfiltrates in the inferior lobe of the right lung and the anterior segment of the inferior lobe of the left lung. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

sue that already has abnormalities, such as pulmonary TB cavities [8–10]. CPA that is easily recognized and commonly associated with pulmonary TB is aspergilloma [3].

Hamartomas are one of the most common benign pulmonary tumors [11]. Hamartoma comprises cartilage, connective tissue, muscle, fat, and bone [5]. Hamartoma can be located in central, endobronchial, or peripheral lung tissue. Approximately 90% of lung hamartomas grow in peripheral, and 10% develop in endobronchial [5,6]. The relation between hamartoma origin and the development of TB seems to be obvious. We presented a case of aspergilloma coexisting with pulmonary hamartoma in post-pulmonary TB patients.

3.1. Diagnosis

Aspergilloma diagnosis is based on clinical symptoms, radiological, histopathology, culture, and cytology examinations.

3.1.1. Clinical symptoms

Patients with aspergilloma present a variety of clinical symptoms, ranging from asymptomatic to life-threatening conditions. The most important symptom is hemoptysis and cough with foul odor sputum. Chamilos et al. reported that hemoptysis happened in 74% of Aspegilloma cases [12]. Hemoptysis occurs through several mechanisms, such as vascular erosion, mechanical vascular irritation, also endotoxin and trypsin-like proteolytic release by fungi [12,13].

Pulmonary hamartoma is generally asymptomatic. Even though it is rare, hamartoma can also cause hemoptysis [6]. Kitamura et al. reported hemoptysis from non-adjacent bronchus in peripheral pulmonary hamartoma [11]. Active TB can also have hemoptysis presentation. So, in this case, we also suspect TB relapse. However, GeneXpert MTB/RIF sputum was done, and MTB was not detected.

In this case, we found an endobronchial nodule that was revealed as a hamartoma from the cytology examination. Endobronchial pulmonary hamartoma can cause obstructive bronchial complications. Hamartoma with bronchial obstruction can be accompanied by cough, phlegm, and chest pain [11,14].

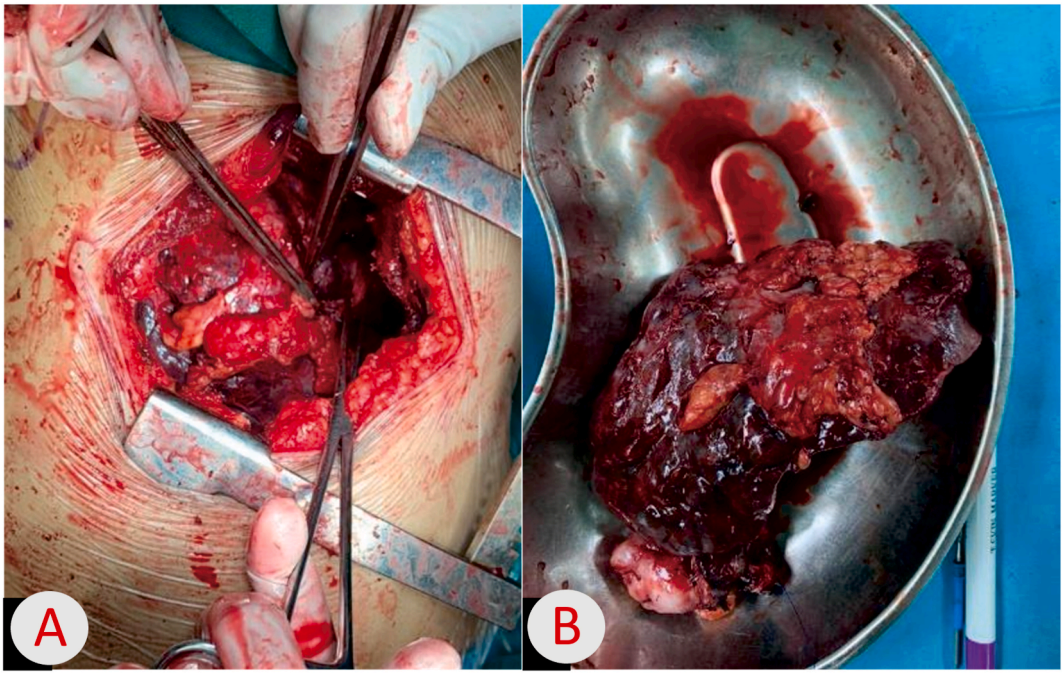

Fig. 3. (A) Durante surgery found that the superior and middle lobe was attached. There is mass in the middle lobe with severe adhesion; B) Atelectasis of the superior and middle lobes of the right lung.

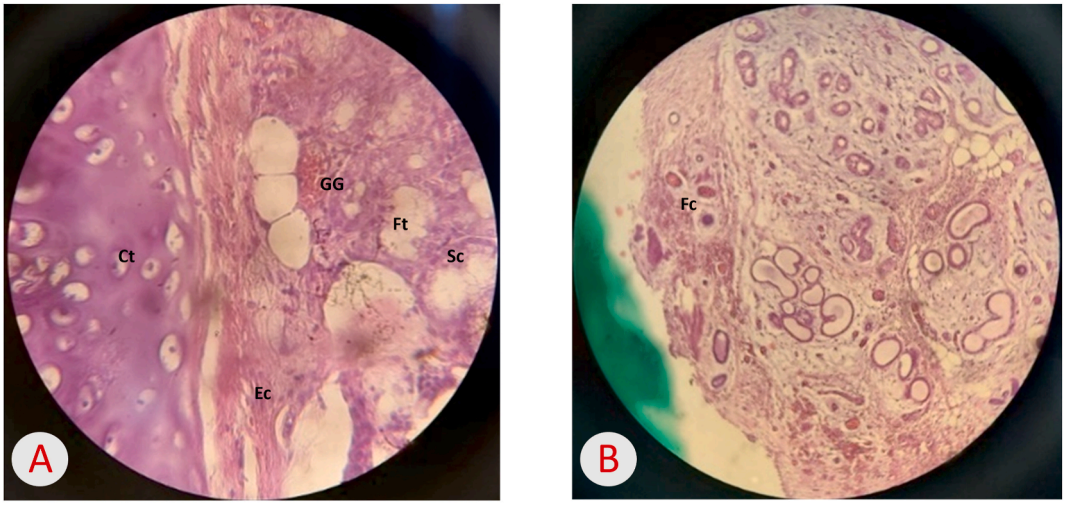

Fig. 4. (A) Histopathology of endobronchial tissue shows hamartoma features; respiratory epithelial cells (Ec): squamous epithelium (Sc), goblet gland epithelium (GG), fatty tissue (Ft), and cartilage tissue (Ct). (B) Histopathology shows inflammatory cells such as lymphocytes, eosinophils, neutrophils, plasma cells, and foci of aspergillus fungal colonies (Fc).

3.1.2. Radiological examination

Aspergilloma radiological examinations include chest X-rays and CT scans [1,12]. Fungus ball (Monod's sign) is a pathognomonic feature in aspergilloma chest X-ray. It forms a radiolucent image and air crescent with irregular edges in superior segment [8,10,15]. Pulmonary aspergilloma is found in the superior segment of the superior lobes because it mainly occurs in post-pulmonary TB patients [10,15]. In this case, we find a fungus ball sign and the intracavitary ball with a compact configuration in chest X-rays (Fig. 1). The air crescent is also seen in tuberculosis, lung abscess, bronchogenic carcinoma, and hamartoma [12,17].

CT scan demonstrates a mass within cavity better than plain chest X-ray. It also provides an early diagnosis that is crucial in life-saving conditions. CT scan offers a quick, non-invasive procedure that is beneficial in diagnosing aspergilloma when a cytology examination is difficult and fungal cultures may be time-consuming and unpredictable. CT scan feature is invasive aspergillosis is a well-circumscribed lesion(s) with or without a surrounding "halo" of ground-glass grey attenuation, fungus ball, air-crescent sign, and cavity formation [16].

Hamartoma nodule has several millimeters to centimeters size with round, sharp, and well-defined edges. Hamartoma has a typical appearance of solitary nodule that contains fatty tissue and calcification [6,14]. Small patches of calcification, also called Popcorn calcification, are a pathognomonic hamartoma feature found in CT scans [14].

3.1.3. Culture and histopathology examinations

In a tropical climate, lung sputum cultures can be contaminated with Aspergillus, leading to false diagnoses. Sometimes we need to repeat the culture and if the result remains positive, it indicates aspergillus infection [1,12]. From the microscopic examination, we can see hyphae of *Aspergillus fumigatus* surrounded by inflammatory cells.

Transbronchial or transthoracic lung biopsy is necessary to diagnose aspergillosis. Histologically, we can find aspergillus colonies [1,18]. At the same time, 85% of hamartoma diagnoses are confirmed by biopsy and pathological examination. Microscopically it is composed of fibromyxoid tissue, fat, or cartilage associated with benign reactive epithelial cells [7].

3.1.4. Immunological examinations

Several pulmonary disorders may have similar features with CPA, including tuberculous or non-tuberculous pulmonary mycobacterial infection, lung abscess, and lung malignancy. These disorders should be excluded before the diagnosis of CPA. Immunological examination methods using *Aspergillus fumigatus* - specific IgG is one of the most useful tests. Study Sehgal et al., stated a cut-off value of 27 mgA/L provides the highest sensitivity and specificity for CPA diagnosis [19].

3.2. Management

Management of aspergilloma patients is still controversial, and there is no consensus among experts until now. Most of the therapy data are based on cohort studies or case reports. Oral antifungals such as itraconazole can prevent the infection spreading to the lung tissue. Denning et al., stated oral itraconazole could improve clinical and radiological conditions [20]. The recommended dose is 200–400mg/day for 6–18 months. Another antifungal is voriconazole, 150–200mg twice a day, or posaconazole with a dose of 300mg once a day. Micafungin and Amphotericin B can be used as alternative therapy (Table 1) [12,20,21].

Because of limited resources, treating pulmonary aspergilloma and hamartoma in developing countries is challenging. In this case, we gave intravenous micafungin 200mg once a day for one month and oral fluconazole 100mg once a day for 14 days, resulting in a good outcome. Micafungin is a member of the echinocandin antifungal agents alongside caspofungin and anidulafungin. Micafungin has fungistatic activity against *Aspergillus* spp. that targets the fungal cell wall. Micafungin also has minimal drug interactions. In vitro and in vivo data showed good efficacy of micafungin against *Aspergillus* spp. Current available studies indicate that micafungin can be used for aspergillus infections, monotherapy or combination therapy, with non inferior success rates to other antifungals [22]. A multicenter study by Yu Ji et al., suggests that micafungin is effective and well-tolerated in patients with proven or probable IA in China. Micafungin success rates were higher than those treated with amphotericin B. Current international guidelines for the diagnosis and management of invasive aspergillosis recommend echinocandins such as micafungin as the management strategy[23].

Surgery is now recommended for managing aspergilloma [12,13]. Hamartoma rarely transforms into malignancy, and recurrence is rare when complete resection was done. Therefore, surgery is the definitive therapy for hamartoma [4,7]. In complex cases, surgery is needed to establish the diagnosis besides curative surgery. Complications that can occur after aspergilloma surgery are hemorrhage, secondary bacterial infection, bronchopleural fistula, empyema, and respiratory failure [2].

4. Conclusion

Aspergilloma is still an important health issue in developing countries with tropical climates. Pulmonary aspergilloma is caused by aspergillus infection that often preceded by pulmonary TB. Aspergilloma and hamartoma diagnoses are challenging because of various clinical symptoms. CT scan benefits making the early diagnosis, especially in life-saving conditions. Treatment of pulmonary aspergilloma and hamartoma is still challenging, and the definitive therapy is surgery. Complications of surgery are still high. However, recurrence is rare.

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Table 1
Antifungal therapy for aspergillosis [20,21].

Antifungal agent	Dose	Strength of Recommendation	Quality of evidence
Itraconazole	200 mg twice daily	A	II
Voriconazole	150–200 mg twice daily	A	II
Posaconazole	400 mg twice daily (intravena); 300 mg once daily (tablet)	B	II
Micafungin	150 mg/day	B	II
Amphotericin B	0.7–1.0 mg/kg/day	C	III

Authors' contributions

KPD, YCEDD, and LD have substantially contributed to the manuscript's conception or design. KPD and IPD were major contributors in writing the manuscript. IPD editing the manuscript for publication. All authors have participated in drafting the manuscript, I and AP revised it critically. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Acknowledgements

not applicable. Consent for publication: Written informed consent was taken from the patient to use medical data for academic and research purposes, including publication.

References

[1] D.W. Denning, Aspergillosis, in: Harrison's Principle of Internal Medicine 19th Edition, 2015, pp. 1345–1349.
[2] E. Passera, A. Rizzi, M. Robustellini, et al., Pulmonary aspergilloma clinical aspects and surgical treatment outcome, Thorac Surg Clin NA 22 (3) (2012) 345–361.
[3] G.E. Hayes, L. Novak-Frazer, Chronic pulmonary aspergillosis — where are we? and where are we going? J Fungi 18 (2) (2016) 1–34.
[4] K.S. Lundeen, M.S. Raj, D. Ludhwani, Pulmonary hamartoma, in: Pulmonary Hamartoma, StatPearls Publishing, 2019.
[5] R.S. Fraser, J.A.P. Pare, Neoplastic disease of the lungs, in: Synopsis of Diseases of the Chest, second ed., Saunders, 1994, pp. 518–520.
[6] K. Minegishi, S. Endo, H. Tsuboi, T. Nakano, Y. Kanai, Peripherally located endobronchial hamartoma mimicking aspergilloma : a case report, Ann. Transl. Med. 4 (2) (2016) 3–5.
[7] D. Ost, Approach to the patient with pulmonary nodules, in: Fishman's Pulmonary Disease and Disorders, fifth ed., 2015, pp. 1684–1686.
[8] Y. Park, T.S. Kim, C.A. Yi, E.Y. Cho, H. Kim, Y.S. Choi, Pulmonary cavitary mass containing a mural nodule : differential diagnosis between intracavitary aspergilloma and cavitating lung cancer on contrast-enhanced computed tomography, Clin. Radiol. 62 (2007) 227–232.
[9] T. Hirano, M. Yamada, R. Igusa, et al., Two cases of endobronchial aspergilloma complicated with primary and metastatic lung cancer : a case report and literature review, Respir. Investig 54 (3) (2016) 211–215.
[10] M. Yasuda, A. Nagashima, A. Haro, G. Saitoh, Aspergilloma mimicking lung cancer, Int. J. Surg. Case Rep. 4 (8) (2020) 690–692.
[11] N. Kitamura, T. Ojima, Peripheral pulmonary hamartoma with haemoptysis from the non-adjacent bronchus, Respirology Case Reports 8 (4) (2020) e00553.
[12] G. Chamilos, D.P. Kontoyiannis, Aspergillus, candida, and other opportunistic mold infections of the lung, in: Fishman's Pulmonary Disease and Disorders, fifth ed., 2015, pp. 2039–2057.
[13] L. Moodley, J. Pillay, K. Dheda, Aspergilloma and the surgeon, J. Thorac. Dis. 6 (3) (2014) 202–209.
[14] R.A. Matthay, L.T. Tanoue, D.C. Carter, Lung neoplasm, in: Chest Medicine Essential of Pulmonary and Critical Care Medicine, Lippincott Williams and Walkins, 2008, pp. 356–357.
[15] P.D. Barnes, K.A. Marr, Aspergillosis : spectrum of disease, diagnosis, and treatment, Infect. Dis. Clin. 20 (2006) 545–561.
[16] A. Prasad, K. Agarwal, D. Deepak, et al., Pulmonary aspergillosis: what CT scan can offer before it is too late, J. Clin. Diagnosis Res. 10 (4) (2016) TE01–TE5.
[17] F. Spycher, G.J. Kocher, M. Gugger, T. Geiser, S.R. Ott, Pulmonary aspergilloma : a rare differential diagnosisofo lung cancer after a positive FDG PET scan, Respir. Med. Case Reports 12 (2014) 1–3.
[18] M.J.E.G.W. Vanfleteren, A.-M.C. Dingemans, V.F. Surmont, et al., Invasive aspergillosis mimicking metastatic lung cancer, Front. Oncol. 8 (2018) 1–7.
[19] I.S. Sehgal, S. Dhooria, V. Muthu, K.T. Prasad, R. Agarwal, An overview of the available treatments for chronic cavitary pulmonary aspergillosis, Expet Rev. Respir. Med. 14 (7) (2020 Jul) 715–727, https://doi.org/10.1080/17476348.2020.1750956.
[20] D.W. Denning, J. Cadranel, C. Beigelman-Aubry, et al., Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management, Eur. Respir. J. 47 (2016) 45–68.
[21] K.C. Patterson, M.E. Strek, Diagnosis and treatment of pulmonary aspergillosis syndromes, Chest 146 (5) (2014) 1358–1368.
[22] D.A. Enoch, S.F. Idris, S.H. Aliyu, C. Micallef, O. Sule, J.A. Karas, Micafungin for the treatment of invasive aspegillosis, J. Inf. 68 (2014) 507e526.
[23] Y. Ji, Y. Song, F. Zhou, T. Liu, M. Jiang, X. Zhao, X. Huang, Efficacy and safety of micafungin for the treatment of patients with proven or probable invasive aspergillosis, Medicine 96 (2017) 52.