Respiratory Medicine Case Reports 22 (2017) 220–223

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

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

Case report

A young immunocompetent patient with spontaneous *Aspergillus* empyema who developed severe eosinophilia

Fumiaki Kudo [a], Hiromitsu Ohta [a, *], Yoshiaki Nagai [a], Kentaro Minegishi [b], Shinichiro Koyama [a]

[a] Department of Pulmonary Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan
[b] Department of General Thoracic Surgery, Jichi Medical University Saitama Medical Center, Saitama, Japan

ARTICLE INFO

Article history:
Received 3 August 2017
Received in revised form
25 August 2017
Accepted 27 August 2017

Keywords:
Aspergillus empyema
Eosinophilia
Fungus

ABSTRACT

Aspergillus empyema is usually reported as a complication of surgical procedures, and spontaneous cases are quite rare. Here, we describe the case of a 16-year-old man who suddenly developed dyspnea despite previously being healthy. Chest computed tomography showed multiple mass-containing cavity lesions, pneumothorax, and pleural effusion in the left thorax. Within 2 weeks, *Aspergillus fumigatus* grew from his pleural effusion, thus he was diagnosed with *Aspergillus* empyema. He also developed severe eosinophilia after admission, and was treated with anti-fungal drugs. Although there are many factors that can cause eosinophilia, we suspect that infection with *Aspergillus fumigatus* was the major cause of the eosinophilia in this patient. The lack of bronchial symptoms and lesions were not consistent with a diagnosis of allergic bronchopulmonary aspergillosis. As far as we know, this is the first case of spontaneous *Aspergillus* empyema resulting in severe eosinophilia.

1. Introduction

Aspergillus species are ubiquitous airborne saprophytic fungi that cause a variety of lung diseases. These lung infections, including simple pulmonary aspergilloma (SPA), chronic cavity pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CFPA), chronic necrotizing pulmonary aspergillosis (CNPA), invasive pulmonary aspergillosis (IPA), and allergic bronchopulmonary aspergillosis (ABPA), may manifest with clinically and radiologically distinct patterns. However, the lung disease, *Aspergillus* empyema is rare, and most cases occur as a surgery-related complication. Only a few spontaneous cases of *Aspergillus* empyema have been reported [1].

Aspergillus infections sometimes cause eosinophilia, most cases of which are ABPA. ABPA is a pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus*, and it is associated with chronic asthma or cystic fibrosis. ABPA is classified as sero-positive ABPA (ABPA without bronchial lesions), ABPA with central bronchiectasis, ABPA with high attenuation mucus, and ABPA with chronic pleuropulmonary fibrosis, according to the radiological findings [2]. Although numerous radiological findings are observed in ABPA, pleural effusion is an extremely uncommon manifestation [3].

Here, we describe the quite rare case of a previously healthy patient who developed spontaneous *Aspergillus* empyema and severe eosinophilia without bronchial symptoms.

2. Case presentation

A 16-year old man visited the emergency department at the local hospital owing to dyspnea. His medical history revealed that he had developed appendicitis at 9 years old and migraines at 16 years old, but he did not have bronchial asthma. A cavity was identified in his left lung during a chest X-ray that was performed at his annual medical check-up at his high school (Fig. 1). However, he did not complain of any symptoms; thus, no additional examinations were performed. Three months before visiting the hospital, he presented with yellow purulent sputum, and 1 day before his visit, he suddenly experienced left chest pain and developed dyspnea.

Chest radiographs revealed left pneumothorax and pleural effusion (Fig. 2). An intercostal drain was inserted and purulent

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ANCA, anti-neutrophil cytoplasmic antibodies; CRP, C-reactive protein; CT, computed tomography; IgE, immunoglobulin E; WBC, white blood cell.

* Corresponding author. Jichi Medical University Saitama Medical Center, Amanuma 1-847, Oomiya, Saitama, Japan.
E-mail address: hootatky@jichi.ac.jp (H. Ohta).

http://dx.doi.org/10.1016/j.rmcr.2017.08.022

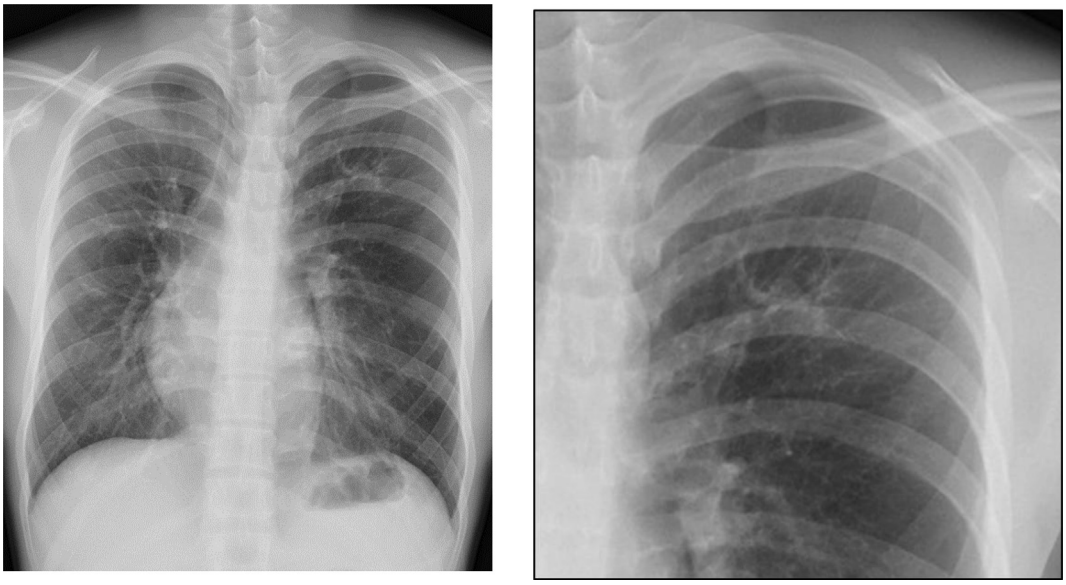

Fig. 1. A chest X-ray acquired 1 year before admission at the patient's annual medical check-up at his high school. The image reveals transparency of the left lung and deviation of the mediastinum. A cavity is also visible in the left upper lung field.

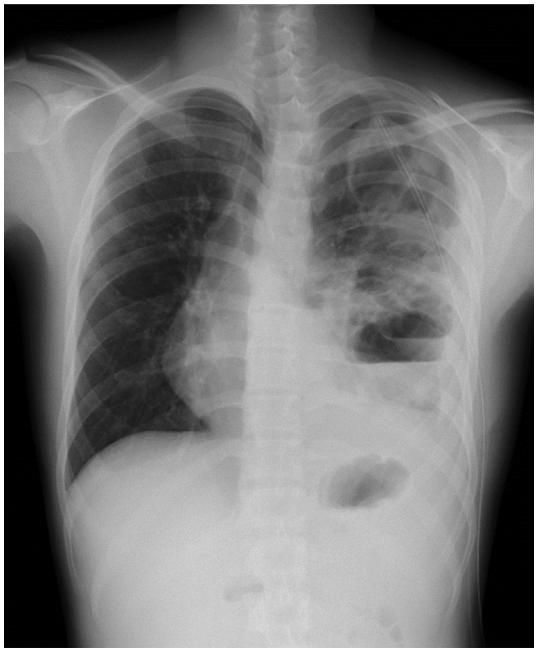

Fig. 2. A chest X-ray obtained upon admission to the local hospital. The image shows left pneumothorax, pleural effusion, and multiple cavities.

fluid was drained from the left thoracic cavity on the day he was admitted to the local hospital. Bacterial empyema was suspected and empirical antibiotic therapy with amoxicillin/sulbactam (3 g, three times daily, intravenously) was initiated. However, 3 days after, the patient developed a skin rash, and thus, amoxicillin/sulbactam was discontinued. A constant air leak from the left lung continued for a week, and he was transferred to our hospital.

He had low grade fever (37.2 °C), however blood pressure (106/58 mmHg) and pulse rate (92 beats/min) were normal. Physical examinations performed on admission showed that the patient had no gross lesions in the chest wall and he denied experiencing any trauma. Moreover, auscultation of the lungs revealed decreased breath sounds in the left lung but no abnormal sounds. Laboratory analyses indicated that most values were within the normal ranges, although his white blood cell (WBC) count was elevated (8460 with eosinophilia [22% of the WBCs]), as was his C-reactive protein (CRP) level (5.80 mg/dl). Microscopic examinations of the drained fluid did not reveal any bacteria or fungus. A chest computed tomography (CT) scan on the day of admission demonstrated mass-containing cavity lesions, which were surrounded by consolidation (Fig. 3A). Levofloxacin (500 mg, once daily, oral) was administered, however, 8 days after admission, it was discontinued due to the emergence of a spiked fever and deterioration of eosinophilia (WBC count: 12650, eosinophil count: 6578 [52% of the WBCs]). Ten days after admission, laboratory analyses showed that the number of WBCs and eosinophils in the peripheral blood had increased (WBC count: 21560, eosinophil count: 16170 [75% of the WBCs]), as had the CRP level (10.14 mg/dl). Analysis of the pleural effusion revealed an exudate and elevation of the eosinophil count (7200 [81.8% of the total number of cells]). His serum immunoglobulin E (IgE) level was 3900 KU/L. Repeated analyses performed for detecting *Aspergillus* antigens yielded negative results, and an analysis performed for detecting *Aspergillus*-specific IgE yielded a positive result (6.59 UA/ml, classIII; normal value $\leq$ 0.34 UA/ml). Analyses for perinuclear anti-neutrophil cytoplasmic antibodies (ANCA) and cytoplasmic ANCA were negative. The patient did not complain of dyspnea and wheezing was not heard over the lung fields. A chest CT scan acquired 15 days after admission showed the emergence of multiple bronchiolar nodules in the right lung field (Fig. 3B). Two weeks after admission, *Aspergillus fumigatus* was detected in the initially cultured sputum and pleural effusion.

The systemic administration of voriconazole (620 mg for the first dose, followed by 230 mg twice daily, intravenous) was initiated 15 days after admission. Afterwards, the patient's fever and peripheral eosinophilia decreased to within the normal range. Although the opacity on his chest CT scans also improved, the pleural effusion drainage and air leak continued. At 63 days after admission, an open window thoracostomy and debridement of the focus in the parietal pleura were performed (Fig. 4). Pathological examinations demonstrated that numerous hyphae had infiltrated

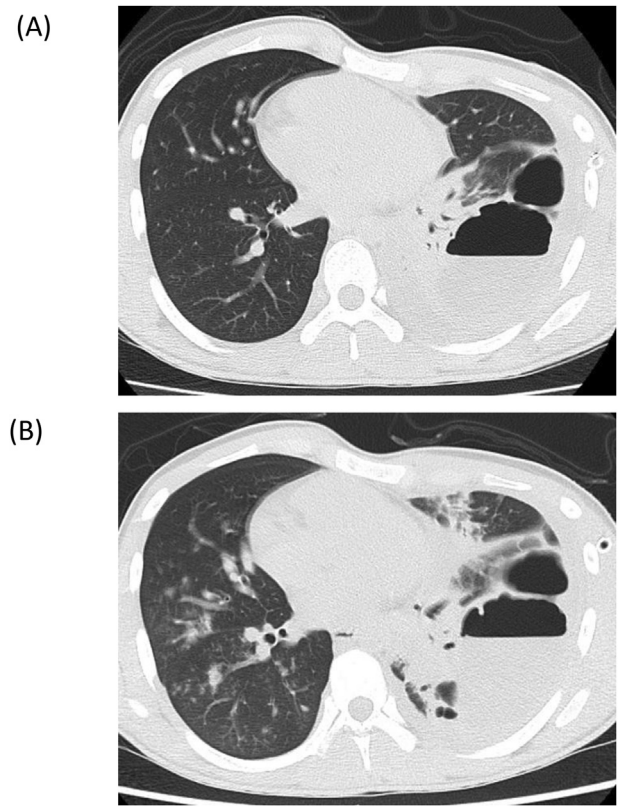

Fig. 3. Chest computed tomography (CT) images. (A) Chest CT scan acquired after the insertion of a drainage tube shows mass-containing cavity lesions surrounded by consolidations. (B) Chest CT scan acquired 15 days after admission shows multiple bronchiolar nodules in the right lung field.

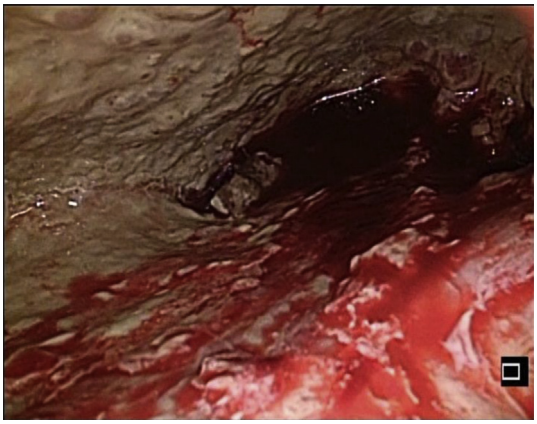

Fig. 4. Intraoperative findings during the open window thoracostomy and debridement. The parietal pleura was entirely covered with xanthochromic pus, suggesting fungal proliferation.

the pleura. Following the operation, the administration route of voriconazole was changed from intravenous to oral. The general status was good, and the membrane and necrotic tissue covering the pleura disappeared. At day 81 after admission, the patient was discharged from our hospital. Since then, he has visited our hospital regularly for ~1 year, with the thoracostomy window remaining open. At his last follow-up examination, the peripheral eosinophil count was within the normal range.

3. Discussion

Spontaneous empyema owing to *Aspergillus fumigatus* is very rare, especially in an immunocompetent patient like ours. Furthermore, our patient developed severe eosinophilia without asthmatic symptoms.

Recently, the incidence of fungal empyema has been increasing. The most common pathogens in fungal empyema are from the *Candida* species, with pathogens from the *Aspergillus* species being rare [1]. Moreover, as mentioned above, most cases of *Aspergillus* empyema reportedly occur as a complication of surgical operations or chest drainage [4], with only a few reports describing spontaneous cases [5–7]. Spontaneous *Aspergillus* empyema may develop when an aspergilloma ruptures or as a complication of preexisting chronic empyema [8]. Pulmonary aspergilloma is the colonization of preexisting lung cavities with the *Aspergillus* species. It is further divided into simple pulmonary aspergilloma (SPA) and chronic cavitary pulmonary aspergillosis (CCPA). SPA is associated with a single fungus ball in a single cavity, whereas CCPA is characterized by multiple aspergillomas in multiple thick-walled cavities. In our patient, it was difficult to determine whether the *Aspergillus* empyema was a result of a ruptured aspergilloma or was a secondary infection related to preexisting empyema. Chest X-ray performed at the patient's annual medical check-up showed a cavity in the left lung and deviation of the mediastinum, indicating that the patient might have cystic lesions, such as congenital pulmonary airway malformations, bronchogenic cysts, and/or congenital bullae [9]. Chest CT performed after admission showed multiple thick-walled cavities. Additionally, cultures of the pleural effusion did not reveal any other pathogens except for *Aspergillus fumigatus*. Considering these facts, we speculated that our patient had CCPA, and ruptured *Aspergillus*-infected cavities caused the *Aspergillus* empyema.

Eosinophilia has various causes. Although there are many factors that can cause eosinophilia, we suspect that the major cause of this patient's severe eosinophilia was an *Aspergillus* infection. The most frequent causes of severe eosinophilia are neoplastic disorders, including primary hypereosinophilic syndrome, acute eosinophilic leukemia, chronic eosinophilic leukemia, and some solid tumors. Other causes such as adrenal insufficiency, parasite infection, drug allergies, and connective tissue disease should also be considered in all patients with eosinophilia. Eosinophilic granulomatosis with polyangiitis is the major vasculitis associated with eosinophilia. Some fungi can also cause eosinophilia, and the *Aspergillus* species is the most commonly implicated fungus in cases of ABPA [10]. Regarding our patient, systematic examinations did not reveal any evidence of neoplastic disease. The patient's eosinophilia did not improve after the antibiotics were discontinued, and these were the only medications he was taking. He did not have any symptoms leading us to suspect adrenal insufficiency, connective tissue disease, or eosinophilic granulomatosis with polyangiitis. His serum was negative for cytoplasmic ANCA, perinuclear ANCA, and other autoantibodies. Although pleural diseases, like pneumothorax or trauma, can sometimes cause eosinophilia, the eosinophil count of our patient returned to within the normal range after administering the anti-fungal drug voriconazole. Moreover, the air leak and drainage from the chest tube continued. Collectively, the severe eosinophilia, elevated IgE level, and presence of the specific IgE to the *Aspergillus* species implied that he had hypersensitivity to the *Aspergillus* species; however, the lack of asthmatic symptoms or bronchial lesions on chest CT images was inconsistent with a diagnosis of ABPA.

Predisposing conditions of asthma or cystic fibrosis are thought to be essential for the diagnosis of ABPA. Glancy et al. reported on 11 patients who did not have a history of asthma and had negative bronchodilator responsiveness, among 42 patients who had

allergies to fungi. Some of these patients subsequently developed asthma, suggesting that they might be in a preclinical phase of ABPA [11]. We speculated that, in our patient, acute or subacute infection by *Aspergillus fumigatus* might have caused hypersensitivity to the *Aspergillus* species, and that he might have developed asthma if he was not treated properly.

In conclusion, we reported a case of spontaneous *Aspergillus* empyema that occurred in a young patient who had otherwise appeared healthy. We speculated one of the causes to be congenital cysts, and that he might have had CCPA. He had developed severe eosinophilia, which was normalized after administration of an antifungal medication. As far as we know, this was the first report of a patient with *Aspergillus* spontaneous empyema who developed severe eosinophilia. We suspected that the primary cause of his severe eosinophilia was an *Aspergillus* infection, although he had several conditions that could cause eosinophilia. Our case showed acute or subacute infection of *Aspergillus* species could cause severe eosinophilia without asthmatic symptoms.

Conflicts of interest

Patient consent was obtained.

References

[1] S.C. Ko, K.Y. Chen, P.R. Hsueh, K.T. Luh, P.C. Yang, Fungal empyema thoracis: an emerging clinical entity, Chest 117 (2000) 1672–1678.
[2] R. Agarwal, A. Chakrabarti, A. Shah, D. Gupta, J.F. Meis, R. Guleria, R. Moss, D.W. Denning, ABPA complicating asthma ISHAM working group, Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria, Clin. Exp. Allergy 43 (2013) 850–873.
[3] K. Madan, A. Bal, R. Agarwal, Pleural effusion in a patient with allergic bronchopulmonary aspergillosis, Respir. Care 57 (2012) 1509–1513.
[4] N. Ashizawa, S. Nakamura, S. Ide, M. Tashiro, T. Takazono, Y. Imamura, T. Miyazaki, K. Izumikawa, Y. Yamamoto, K. Yanagihara, Y. Miyazaki, S. Kohno, Successful treatment of aspergillus empyema using open window thoracostomy salvage treatment and the local administration of an antifungal agent, Intern. Med. 55 (2016) 2093–2099.
[5] C.H. Chen, C. Ho, H.C. Liu, T.T. Tsung, T.T. Hung, Spontaneous empyema necessitatis caused by Aspergillus fumigatus in an immunocompetent patient, JRSM Short. Rep. 2 (2011) 25.
[6] T. Bhatnagar, A.K. Bhatnagar, Pleural aspergillosis in an otherwise healthy individual, Lung India 31 (2014) 155–157.
[7] H.W. Lee, Y.W. Kim, J. Cho, C.H. Lee, Empyema necessitatis due to Aspergillus fumigatus, BMJ Case Rep. 2014 (2014), http://dx.doi.org/10.1136/bcr-2014-206047.
[8] H.C. Meredith, B.M. Cogan, B. McLaulin, Pleural aspergillosis, AJR Am. J. Roentgenol. 130 (1978) 164–166.
[9] K. Oden, I. Guler, T. Altinok, S. Pekcan, A. Batur, H. Osier, Cystic and cavitary lung lesions in children: radiologic findings with pathologic correlation, J. Clin. Imaging Sci. 3 (2013) 60.
[10] A.P. Knutsen, R.K. Bush, J.G. Demain, D.W. Denning, A. Dixit, A. Fairs, P.A. Greenberger, B. Kariuki, H. Kita, V.P. Kurup, R.B. Moss, R.M. Niven, C.H. Pashley, R.G. Slavin, H.M. Vijay, A.J. Wardlaw, Fungi and allergic lower respiratory tract diseases, J. Allergy Clin. Immunol. 129 (2012) 280–291 quiz 92–93.
[11] J.J. Glancy, J.L. Elder, R. McAleer, Allergic bronchopulmonary fungal disease without clinical asthma, Thorax 36 (1981) 345–349.