Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7124-21
Intern Med 61: 379-383, 2022
http://internmed.jp

【 CASE REPORT 】

Pulmonary Aspergilloma and Allergic Bronchopulmonary Aspergillosis Following the 2018 Heavy Rain Event in Western Japan

Eri Ando[1,2], Takamasa Nakasuka[3], Toshio Kubo[4], Akihiko Taniguchi[3], Kiichiro Ninomiya[5], Yuka Kato[3,6], Eiki Ichihara[3], Kadoaki Ohashi[3], Kammei Rai[3,7], Katsuyuki Hotta[3,6], Masaomi Yamane[8], Nobuaki Miyahara[3,9], Masahiro Tabata[4], Yoshinobu Maeda[5] and Katsuyuki Kiura[3]

Abstract:

A 16-year-old boy with asthma participated in recovery volunteer work following the 2018 heavy rains in Japan. One month later, he experienced chest pain and dyspnea. Chest computed tomography revealed a cavity with a fungal ball, and *Aspergillus fumigatus* was detected in his bronchoalveolar lavage fluid. He was treated with voriconazole, but new consolidations appeared rapidly. He also experienced allergic bronchopulmonary aspergillosis. After prednisolone prescription, the consolidations improved; however, his asthma worsened. He underwent partial lung resection to avoid allergens, and his symptoms improved. We must recognize cases of infection after a disaster, especially in patients with chronic respiratory diseases.

Key words: pulmonary aspergilloma, allergic bronchopulmonary aspergillosis, disaster

(Intern Med 61: 379-383, 2022)
(DOI: 10.2169/internalmedicine.7124-21)

Introduction

Complications of pulmonary aspergilloma and allergic bronchopulmonary aspergillosis (ABPA) have been reported in some case reports (1-3). The standard treatment for ABPA is corticosteroids, although extended corticosteroid therapy may worsen the infection. Therefore, it is difficult to treat cases with coexisting aspergillosis and ABPA. Some reports have indicated that fungal infection can be related to natural disasters (4-7). Japan experienced a heavy rainfall and subsequent flooding in 2018.

We herein report a case of combined pulmonary aspergilloma with ABPA in a volunteer who worked in a flooded area after this heavy rain event.

Case Report

A 16-year-old boy with asthma had been undergoing treatment since childhood. His symptoms were well-controlled with corticosteroid inhalation (100 μg salmeterol and 500 μg fluticasone daily), and he had not experienced an asthmatic attack for several years. One year before this event, his eosinophil count in peripheral blood was almost normal at 496 cells/μL. At the beginning of July 2018, he participated in recovery volunteer work in a flooded area after heavy rains in western Japan. During a routine hospital visit in early August of 2018, he was found to have an in-

[1]Center for Graduate Medical Education, Okayama University Hospital, Japan, [2]General Internal Medicine, Okayama Medical Center, Japan, [3]Allergy and Respiratory Medicine, Okayama University Hospital, Japan, [4]Center for Clinical Oncology, Okayama University Hospital, Japan, [5]Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan, [6]Center for Innovative Clinical Medicine, Okayama University Hospital, Japan, [7]Hospital-based Cancer registry division, Okayama University Hospital, Japan, [8]Departments of General Thoracic Surgery and Breast and Endocrinological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan and [9]Department of Medical Technology, Okayama University Graduate School of Health Sciences, Japan
Received: January 19, 2021; Accepted: May 23, 2021; Advance Publication by J-STAGE: August 6, 2021
Correspondence to Dr. Toshio Kubo, t-kubo@cc.okayama-u.ac.jp

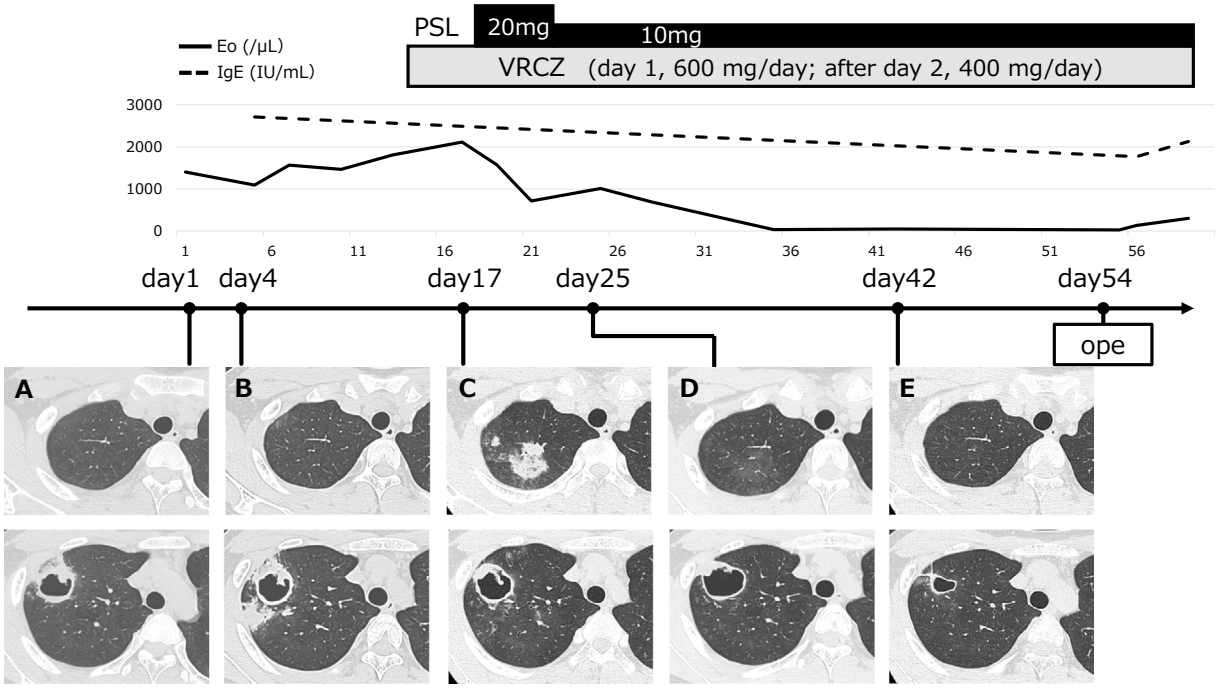

Figure 1. **Computed tomography revealed a cavity with a fungal ball (A). Three days later, new consolidations appeared around the cavity (B). After the administration of voriconazole, the consolidations around the cavity improved, although new consolidations appeared (C). After the administration of prednisolone, the consolidations disappeared (D). One month later, the cavity shadows had shrunk further (E). VRCZ: voriconazole, PSL: prednisolone, Eo: eosinophil count, ope: operation**

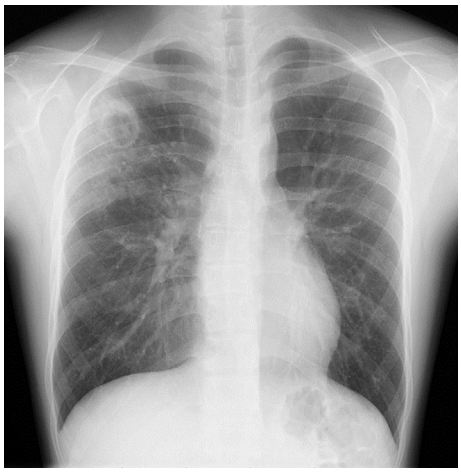

Figure 2. **Chest X-ray (day 5) showed a cavity with consolidation in the right upper lung field.**

creased eosinophil count (1,064 cells/μL) in his peripheral blood, although his forced expiratory volume (FEV) in 1 second (FEV1)/FEV ratio was within normal limits (78.4%). At the end of August, he developed a slight fever, chest pain with deep inhalation, cough, sputum, and dyspnea. He visited a hospital, and chest computed tomography (CT) revealed a cavity with a fungal ball in the right upper lobe of his lung (Fig. 1A). Treatment was started with amoxicillin and clavulanic acid. Despite antibiotic therapy, his chest pain worsened after three days, and chest CT revealed consolidation around the cavity (Fig. 1B). He was then transferred to our hospital on day 5.

At our hospital, chest radiography was conducted, showing a cavity with consolidation in the right upper lung field (Fig. 2). Laboratory tests revealed increased levels of eosinophils (1,092 cells/μL) and C-reactive protein (2.29 mg/dL). The total IgE level was remarkably elevated to 2,711 IU/mL. A serum *Aspergillus*-precipitated antibody test was positive, and an *Aspergillus*-specific IgE test was also positive. His skin reaction for *Aspergillus* was positive in both immediate and delayed types. *Aspergillus fumigatus* was detected in his sputum cultures. He also underwent a bronchoscopy examination. His eosinophil levels were increased (52%) in bronchoalveolar lavage fluid (BALF), and *A. fumigatus* was also detected in the BALF cultures.

Based on the detection of *A. fumigatus* in BALF and sputum cultures and the results of his CT, he was diagnosed with pulmonary aspergilloma. Voriconazole (day 1, 600 mg/day; after day 2, 400 mg/day) was started on day 14, which partially improved the consolidations around the cavity; however, other consolidations appeared in the same right upper lobe. A new consolidation was observed in S3, the dorsal and caudal area of the cavity (Fig. 1C).

Because of the mild worsening of asthma symptoms, we suspected a complication of ABPA. This case met six of the major diagnostic criteria postulated by Rosenberg et al. (8) (asthma, peripheral blood eosinophilia, immediate cutaneous reactivity to *Aspergillus*, precipitating antibodies against *Aspergillus*, elevated serum IgE, and presence of transient pulmonary infiltrates) except for central/proximal bronchiectasis

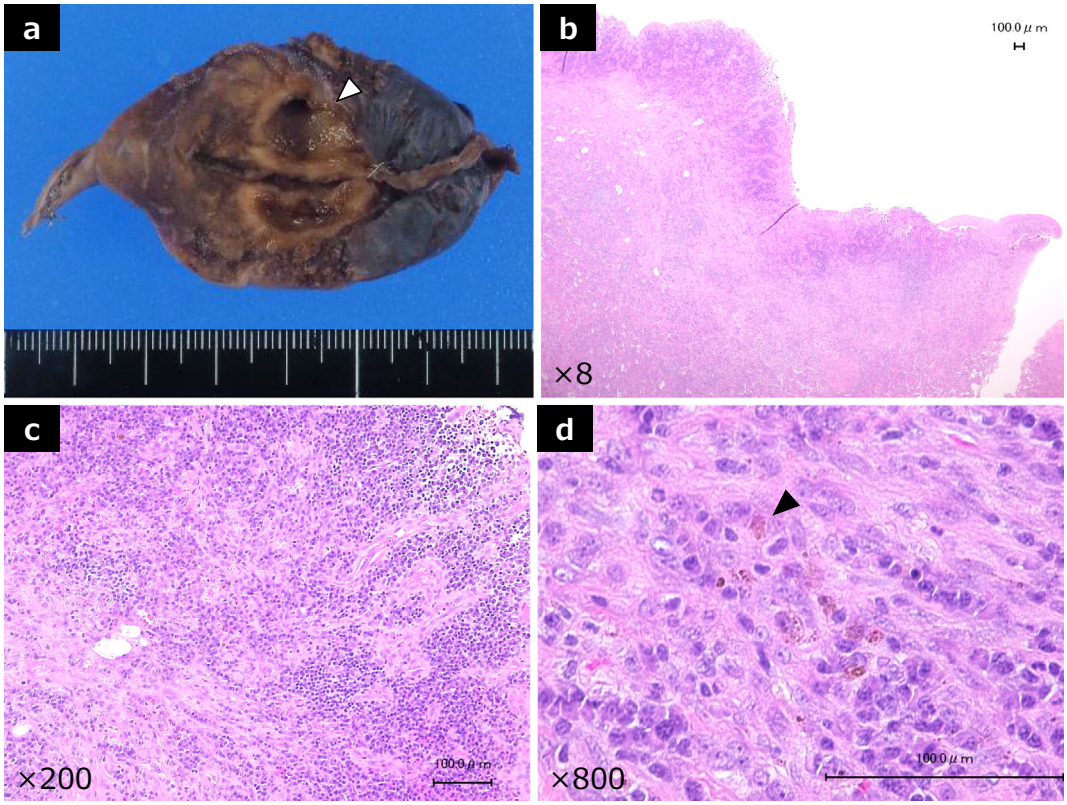

Figure 3. **Gross specimen of the lung showing a cavity (white arrowhead) (a). Microphotographs of the lung revealed inflammatory cells with fibrosis and lymphoid follicular formation around the cavity (b, c). Many histiocytes with phagocytosed brown pigment containing iron (black arrowhead) were observed (d).**

with normal tapering of the distal bronchi. Two minor criteria were met [positive sputum culture for *Aspergillus*, late (Arthus-type) skin reactivity to *Aspergillus*], except for the expectoration of golden-brownish sputum plugs. Due to the lack of apparent central bronchiectasis, we were unable to determine whether or not this was a case of ABPA. Regarding the consolidation around the cavity, there was a possibility of drug-induced pneumonia or organizing pneumonia, although the number of eosinophils in the BALF was increased, and most of the diagnostic criteria for ABPA were met. Therefore, we strongly suspected this consolidation to be due to ABPA and started prednisolone (20 mg/day) from day 19 to manage this condition. The consolidations immediately disappeared (Fig. 1D).

Subsequently, the cavity shadows decreased (Fig. 1E), although cough and respiratory distress continued. The dose of prednisolone was reduced at day 23 to 10 mg and continued. On day 54, he underwent partial resection of the right upper lobe where the lesion with the allergen was present. This was performed to avoid exposure to the allergen at the time when the infiltration shadow around the cavity lesion was disappearing, about a month after steroid administration. A cavity was found in the resected lung, and inflammatory cells with fibrosis and lymphoid follicular formation were found around it. In addition, many histiocytes with phagocytosed brown pigment containing iron were observed. *Aspergillus* was not identified by Grocotto or periodic acid-Schiff staining (Fig. 3). His symptoms improved immediately, and prednisolone was discontinued on day 102. Total IgE levels decreased to 409 IU/mL 3 months after surgery. Voriconazole was discontinued after eight months. He has not relapsed for two years and eight months since the onset.

Written informed consent to publish this report was obtained from the patient and his family.

Discussion

We encountered a case complicated by pulmonary aspergilloma and ABPA after the patient had performed volunteer work in a flooded area following a heavy rain event in western Japan. ABPA is reported to occur in 4.8-11.7% of pulmonary aspergilloma cases (1, 3, 9), and more cases may exist that are not yet diagnosed. Many of these cases had chronic changes in the lungs, such as a history of pulmonary tuberculosis. This is a rare case in which aspergilloma and ABPA coexisted despite the absence of complications such as pulmonary tuberculosis or chronic obstructive pulmonary disease (COPD). The key treatment for ABPA is corticosteroids, but extended corticosteroid therapy may worsen the infection (1). In this case, the consolidation gradually improved following the administration of antifungal treatment and corticosteroids. In addition, dyspnea re-

lated to ABPA improved after resection. Therefore, resection may be a good choice for the treatment of complications of pulmonary aspergilloma and ABPA.

Although the findings were consistent with chronic cavity aspergillosis on CT, we diagnosed him with aspergilloma because his clinical course was subacute. In general, chronic cavity aspergillosis is a type of chronic aspergillosis that does not develop rapidly, unlike in our patient. It is common for chronic cavity aspergillosis to infect existing cavity lesions, which may be present due to a history of pulmonary tuberculosis or COPD, and create fungal balls, but we found no cavitary lesions in other lobes of the lung, suggesting that this infection was the cause of the cavity formation. It was considered to be similar to subacute invasive pulmonary aspergillosis. In this case, inhaled corticosteroid treatment for asthma was found to be a risk factor for invasive fungal infection (10). We speculated that his high dose of steroid inhalation and the large amount of *Aspergillus* he had inhaled when he volunteered might have induced his atypical clinical course.

Regarding ABPA, central bronchiectasis was not recognized in this case; therefore, we diagnosed this patient with probable ABPA according to the diagnostic criteria by Rosenberg et al. (8). In some cases of ABPA, there is a previous stage in which central bronchiectasis is not visible. For the early diagnosis, Greenberger proposed seropositive ABPA, which excludes central bronchiectasis from the criteria (11). Agrawal et al. (12, 13) also proposed diagnostic criteria without central bronchiectasis. This case met the new diagnostic criteria for ABPA proposed by Asano et al. (14) and satisfied 7 out of 10 items other than diagnostic imaging. This case might have also been a previous stage of ABPA.

Treatment for the coexistence of aspergilloma and ABPA has varied in previous reports. In some cases, patients were treated with antifungal agents and inhalable steroids (1), systemic steroids (2), or additional surgical resection (15). In the present case, systemic administration of antifungal drugs and steroids followed by additional surgical resection resulted in a good outcome. Since the patient was only 16 years old, the long-term administration of steroids for ABPA was undesirable. Therefore, by removing the allergen from his body, his allergic reaction to *Aspergillus* was suppressed, and he was able to discontinue the systemic steroids. In cases where surgical resection is difficult, long-term steroid therapy is necessary, and there is concern that aspergilloma may worsen. There has been one case of improvement in ABPA with the administration of benralizumab (anti-IL-5 receptor antibody) to avoid systemic steroid administration (16). In addition, there was a report suggesting that mepolizumab (anti-IL-5 antibody) may be effective in refractory ABPA cases (17). The use of these antibodies instead of the systemic administration of steroids may help control the disease when surgical resection is difficult.

One case report details that, after the Great East Japan Earthquake, all houses in the Fukushima Daiichi Nuclear Power Plant evacuation zone contained airborne fungal levels that were higher than the environmental standard levels for residential houses published by the Architectural Institute of Japan (4). The development of allergic bronchopulmonary mycosis was also reported (5). In July 2018, heavy rain events occurred mainly in western Japan. Okayama experienced great floods and mudslides, as 8 embankments broke, 1,950 hectares were flooded, and about 9,300 buildings were completely or partially destroyed. Our patient participated in restoration efforts as a volunteer four days after the disaster and scraped mud, cleaned houses, and carried out household goods; he then subsequently developed pulmonary aspergilloma and ABPA. Considering the potential presence of *Aspergillus* in the soil and collapsed houses, it is important to explain to volunteer workers the importance of wearing masks and gloves, washing their hands, and avoiding touching their faces with dirty hands in order to minimize the risk of infection. During the same disaster, cases of *Legionella* pneumonia were also reported (18). Thus, we should be aware of the risk of not only fungal infections but also other infectious diseases after a disaster.

In conclusion, we recommend paying attention to infections (including fungus) after disasters, especially when patients have pre-existing chronic respiratory diseases, such as asthma.

Author's disclosure of potential Conflicts of Interest (COI).
Katsuyuki Hotta: Honoraria, Pfizer. Yoshinobu Maeda: Honoraria, Pfizer.

References

1. Kusumoto S, Tanaka A, Ohta S, et al. A case of pulmonary aspergilloma concomitant with allergic bronchopulmonary aspergillosis. Nihon Kokyuki Gakkai Zasshi (J Jpn Resp Soc) **49**: 377-382, 2011(in Japanese, Abstract in English) .

2. Niimi T, Maeda H, Hattori N, et al. A case of pulmonary aspergilloma suspected to overlapping allergic bronchopulmonary aspergillosis. J Jpn Soc Resp Endosc **26**: 649-653, 2004 (in Japanese, Abstract in English).

3. Sehgal IS, Choudhary H, Dhooria S, et al. Is there an overlap in immune response between allergic bronchopulmonary and chronic pulmonary aspergillosis?. J Allergy Clin Immunol Pract **7**: 969-974, 2019.

4. Shinohara N, Tokumura M, Hashimoto K, Asano K, Kawakami Y. Fungal levels in houses in the Fukushima Daiichi Nuclear Power Plant evacuation zone after the Great East Japan Earthquake. J Air Waste Manag Assoc **67**: 1106-1114, 2017.

5. Oshikata C, Watanabe M, Saito A, et al. Allergic bronchopulmonary mycosis due to exposure to *Eurotium herbariorum* after the Great East Japan Earthquake. Prehosp Disaster Med **32**: 688-690, 2017.

6. Robinson B, Alatas MF, Robertson A, Steer H. Natural disasters and the lung. Respirology **16**: 386-395, 2011.

7. Benedict K, Park BJ. Invasive fungal infections after natural disasters. Emerg Infect Dis **20**: 349-355, 2014.

8. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med **86**: 405-414, 1977.

9. Jewkes J, Kay PH, Citron KM. Pulmonary aspergilloma: analysis of prognosis in relation to haemoptysis and survey of treatment. Thorax **38**: 572-578, 1983.
10. Ader F, Nseir S, Le Berre R, et al. Invasive pulmonary aspergillosis in chronic obstructive pulmonary disease: an emerging fungal pathogen. Clin Microbiol Infect **11**: 427-429, 2005.
11. Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol **110**: 685-692, 2002.
12. Agrawal R, Maskey D, Aggarwal AN, et al. Diagnostic performance of various tests and criteria employed in allergic bronchopulmonary aspergillosis: a latent class analysis. PLoS One **8**: e61105, 2013.
13. Agarwal R, Chakrabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy **43**: 850-873, 2013.
14. Asano K, Hebisawa A, Ishiguro T, et al. New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation. J Allergy Clin Immunol **147**: 1261-1268, 2021.
15. Tomiyama K. A case of pulmonary aspergilloma treated by multimodality therapy. J Jpn Soc Respir Endoscopy **38**: 96-100, 2016 (in Japanese).
16. Matsuura H, Fujiwara K, Omori H, et al. Successful treatment with benralizumab for allergic bronchopulmonary aspergillosis that developed after disastrous heavy rainfall in Western Japan. Intern Med **60**: 1443-1450, 2021.
17. Oda N, Miyahara N, Senoo S, et al. Severe asthma concomitant with allergic bronchopulmonary aspergillosis successfully treated with mepolizumab. Allergol Int **67**: 521-523, 2018.
18. Oda N, Hirahara T, Fujioka Y, Mitani R, Takata I. *Legionella* pneumonia following the heavy rain event of July 2018 in Japan. Intern Med **58**: 2831-2834, 2019.