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Case report

An unusual but unmissable link between summer-type hypersensitivity pneumonitis and asthma in an old house

Naoya Yasokawa [a,*], Kouji Kurose [a], Masaaki Abe [a], Hitomi Tanaka [a], Isao Irei [b], Shigeki Kato [a], Toru Oga [a]

[a] Department of Respiratory Medicine, Kawasaki Medical School, Kurashiki, Japan
[b] Department of Pathology, Kawasaki Medical School, Kurashiki, Japan

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ABSTRACT

While hypersensitivity pneumonitis (HP) and asthma are usually recognized as different disease entities based on their different allergic mechanisms, they may have some connections. A previously healthy 54-year-old Japanese man with no history of allergic diseases was hospitalized due to fever and breathlessness. He had lived in an old musty wooden house. He was diagnosed with acute summer-type HP induced by *Trichosporon asahii* based on bilateral ground-glass opacities on chest computed tomography (CT), a high titer of serum anti-*T. asahii* antibody, an increased number of lymphocytes and a decreased CD4/CD8 ratio in bronchoalveolar lavage fluid (BALF) and lung pathology suggestive of HP. However, untypical increased eosinophils in BALF (25.2%) and infiltrative eosinophils around bronchial walls were observed. After systemic corticosteroid treatment was started, he recovered, and was discharged with oral prednisone. However, two weeks after returning to his former house, he had fever and severe cough, and was re-hospitalized. While chest CT showed no abnormal shadows indicating a worsening of HP, pulmonary function test revealed a typical obstructive defect and eosinophilic inflammation in his sputum. He spontaneously recovered after re-hospitalization without increasing any treatments. During this second hospitalization, he was diagnosed with asthma, although it remains to be determined whether both HP and asthma were caused by *T. asahii*. Clinicians should not miss the possible overlapping presentations between HP and asthma, caused by environmental antigens.

1. Introduction

Hypersensitivity pneumonitis (HP) is an immune-mediated disease caused by the inhalation of a variety of antigens into the lungs of a host [1]. It has heterogeneous clinical presentations related to individual susceptible factors, environmental inducers, mechanisms of immune response to inducers. For example, clinical aspects of HP can differ between countries or regions within a country depending on their industry, agricultural techniques, climate and lifestyles, in addition to genetic factors of the local people [1,2]. In Japan, summer-type HP caused by the inhalation of *Trichosporon* species is common, previously accounting for 74.4% of 835 cases [3].

Thus, the pathogenesis of HP is very complex and there remain many problems to be solved. Clinical expressions of HP is broad and can include asthma or asthma-like presentations [2]. Although HP and asthma intrinsically represent allergic immune diseases, both are usually approached as separate and different pathologies [4]. However, some reports suggest a clinical relationship between these diseases, especially in farmer's lung [5–7], a well-known HP in Western countries. Similarly, we experienced a case of a middle-aged man living in an old musty house who had summer-type HP and asthma simultaneously suggesting a link between these two diseases.

2. Case report

The patient was a 54-year-old Japanese man who lived in an old musty wooden house and who had never been exposed to occupational particles. He was an ex-smoker and was previously healthy with no history of allergic diseases. From the middle of October in 2019, he had a cough, breathlessness and fever, which prompted him to visit our hospital. Chest X-ray revealed bilateral infiltrates (Fig. 1a) and respiratory failure needing oxygen therapy was observed. Therefore, he was hospitalized.

Vital signs included a heart rate of 96 beats/minute, blood pressure

* Corresponding author. Department of Respiratory Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama, 701-0192, Japan.
E-mail address: naoya.y@med.kawasaki-m.ac.jp (N. Yasokawa).

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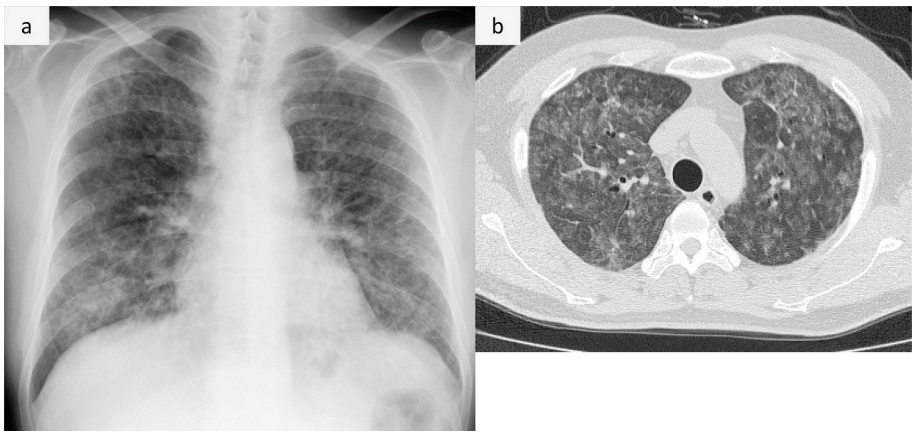

Fig. 1. (a) Chest X-ray and (b) chest CT show bilateral diffuse ground-glass opacities and infiltration shadows.

Table 1
Results of precipitation antibody reaction tests.

	Serum	BALF
Aureobasidium pullulans	+	–
Trichosporon cutaneum	–	–
Cryptococcus neoformans	3+	+
Parakeet droppings	–	–
Pigeon droppings	–	–
Cephalosporium acremonium	–	–
Aspergillus fumigatus	–	–
Aspergillus flavus	+	–
Aspergillus glaucus	±	–
Aspergillus niger	–	–
Aspergillus restrictus	–	–
Aspergillus versicolor	–	–
Penicillium digitatum	±	–
Penicillium glabrum	±	–
Penicillium luteum	–	–
Alternaria kikuchiana	–	–
Cladosporium cladosporioides	2+	–
Candida albicans	+	–

of 109/64 mmHg, SpO_2 of 92% under 4 L/minute through a nasal cannula, and body temperature of 37.2 °C. Blood examinations showed elevated white blood cell counts of 13,010/μL (84.2% neutrophils, 1.2% eosinophils), and elevated levels of lactic acid dehydrogenase (LDH) 268 U/L, C-reactive protein (CRP) 10.8 mg/dL, Krebs von den Lungen-6 (KL-6) 835 U/mL and surfactant protein-D (SP-D) 145 ng/mL. Serum anti-*T. asahii* antibody was significantly increased to >5.00 CAI. Total serum level of IgE level was normal at 65 IU/mL.

Chest computed tomography (CT) revealed bilateral diffuse ground-glass opacities (Fig. 1b). Bronchoalveolar lavage fluid (BALF) had an increased total cell count of 11.6 × 10^5/mL, a high percentage of lymphocytes (51.0%), eosinophils (25.2%) and neutrophils (15.8%), and a decreased ratio of CD4/CD8 (0.74). Subsequently, precipitation antibody reaction tests were performed using patient's serum and BALF, and revealed positive reactions for *Cryptococcus neoformans* (3+), *Cladosporium cladosporioides* (2+), *Candida albicans* (+), *Aspergillus flavus* (+) and *Aureobasidium pullulans* (+) in serum, and for *Cryptococcus neoformans* (+) alone in BALF (Table 1). It is known that *Trichosporon* species often cross-react with *Cryptococcus neoformans* [8–10], and positive findings for *Cryptococcus neoformans* both in serum and BALF are inconsistently considered to indicate cross-reactivity with *T. asahii*. Conversely, negative results for *T. cutaneum* in the present study were considered to be due to the difference in serotype of *T. asahii* (Table 1).

Histologic examination of transbronchial lung biopsy specimens revealed patchy infiltration of inflammatory cells and alveolar infiltration associated with lymphocytes (Fig. 2a). Masson bodies were also detected. Thus, summer-type HP induced by *T. asahii* was diagnosed, although other antigens might also be involved in the pathogenesis based on the results of precipitation antibody reaction tests. However, there was an infiltration of abundant eosinophils around the central bronchial walls (Fig. 2b and c), which is untypical of HP.

Systemic corticosteroid treatment was started with methylprednisone 500 mg/day, and then tapered. The patient's symptoms and chest X-ray improved. On day 19 from admission, pulmonary function test was performed. Although vital capacity (VC) and forced expiratory volume in 1 s (FEV_1) were already normal, carbon monoxide diffusing capacity per alveolar volume was low at 3.57 mL/min/mmHg/L (73.2 % predicted), possibly due to remaining alveolitis related to HP. In November, he left the hospital with oral prednisone 15 mg/day and had no choice but to go back to his former house.

Within a week after discharge, he had fever and severe cough, and was re-hospitalized. However, chest X-ray and CT showed no abnormal shadows indicating a worsening of HP. Serum KL-6 and SP-D were 740 U/mL and 34.5 ng/mL, which did not worsen. However, his pulmonary function test showed that VC and FEV_1 were 4.45 L (100.2 %predicted) and 2.93 L (80.0 %predicted), respectively, showing an apparent obstructive defect. Sputum cytology showed an elevated eosinophil score of 1+. His symptoms spontaneously improved after re-hospitalization without increasing any treatments. Eleven days later, a pulmonary function test showed the FEV_1 had improved to 3.57 L (97.5 %predicted), indicating the airflow limitation was normalized. This second hospitalization was thought to be due to asthma induced by re-exposure to *T. asahii* or other environmental antigens at his house. He left the hospital with oral prednisone 10mg/day and went back to a new house. Thereafter, his HP and asthma remained stable.

3. Discussion

We reported a case in which the patient was first hospitalized due to summer-type HP, and then re-hospitalized due to asthma after exposure to some environmental antigens in an old house. An association between HP and asthma is unusual; however, we should keep it in mind. For example, patients with farmer's lung have an increased risk of developing asthma, which tends to occur relatively shortly after a diagnosis of farmer's lung [6,7]. One study reported the coexistence of HP and asthma, caused by *T. asahii* [11]. Similarly, the patient in the present case initially presented with symptoms typical of summer-type HP, which were subsequently replaced by typical asthmatic symptoms.

During the first hospitalization, the patient resembled a summer-type HP case. However, the high percentage of eosinophils in the BALF (25.2%) without blood eosinophilia and their main localization in the airways, not in the alveoli area, suggested latent asthma rather than HP or eosinophilic pneumonia, although asthmatic symptoms were not manifest at this point.

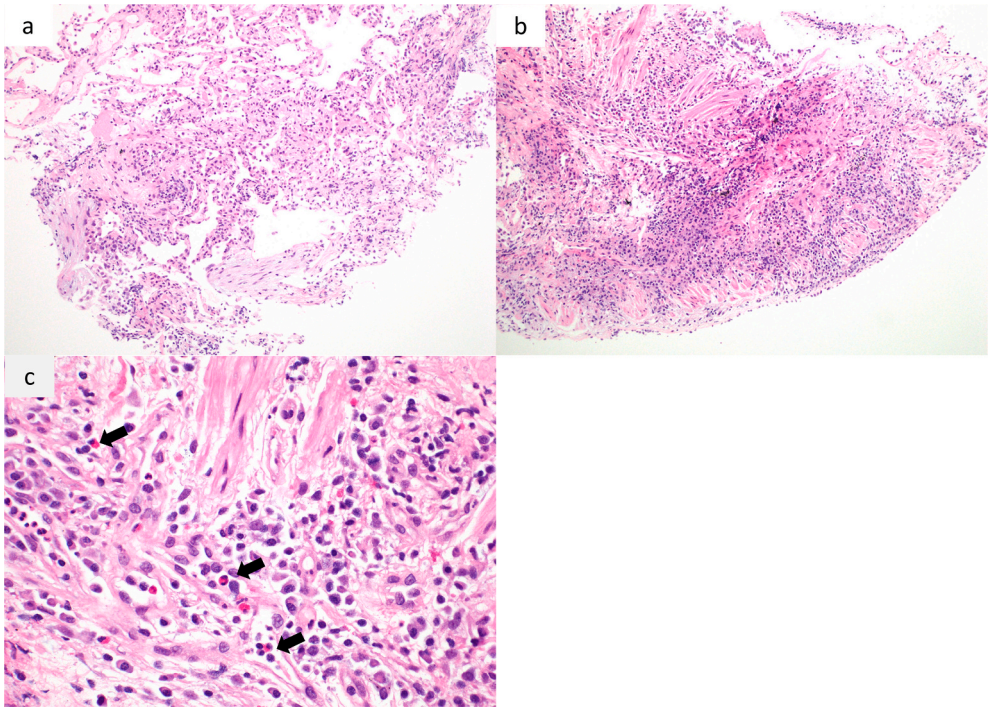

Fig. 2. (a) The alveoli area shows patchy infiltration of inflammatory cells and alveolitis associated with lymphocytes (H&E staining, low-power field). The area around the central bronchial walls shows the infiltration of abundant eosinophils (H&E staining, (b) low-power field and (c) high-power field). *Arrows* indicate eosinophils.

Within two weeks of returning to his former house with oral prednisone, the patient showed different symptoms and data from the first hospitalization. His main symptom was severe cough. Pulmonary function tests revealed an obstructive defect with reduced FEV_1 and normal VC. Mild eosinophilic inflammation was observed in his sputum. However, chest CT showed no significant worsening. After the second hospitalization, the patient gradually improved without any additional treatment and his obstructive defect returned to normal. Thus, this clinical course indicates that he had asthma stimulated by his environment without exacerbation of HP.

T. asahii may be the same causative antigen for asthma and HP. First, the patients had no history of asthma or associated allergic disorder. The nearly simultaneous development of summer-type HP and asthma may suggest the same underlying cause or trigger. Second, our case was similar to a past report by Hirataka et al. [11] in that asthma worsened while summer-type HP was stable. They showed a direct association of *T. asahii* with asthma via a provocation test by inhalation of *T. asahii* antigen. In addition, they also showed an immediate skin allergic reaction with *T. asahii* antigen. There are some similar points between this case and our present case including; 1) no history of asthma; 2) positive provocation test when returning home; 3) obstructive defect; 4) no typical finding of HP on chest X-ray and CT; 5) high percentage of eosinophils in BALF; and 6) high positive serum anti-*T. asahii* antibody. Thus, these findings suggest a similar disease course can be seen in our case.

However, the worsening of asthma might be associated with environmental antigens other than *T. asahii*. Unfortunately, we did not perform cultures with indoor samples or directly confirm allergic reactions such as airway hyperresponsiveness or perform a skin prick test using *T. asahii* antigen. Interestingly, Katayama et al. [12] reported a case of hypersensitivity pneumonitis caused by *Bjerkandera adusta* and asthma attacks caused by *B. adusta* and *Aspergillus fumigatus*, indicating the possibility of multiple causative antigens for asthma. We searched the literature using PubMed regarding coexistent asthma and HP cases and summarized the results in Table 2 [11–24]. Although many cases had the same causative antigens, others were different or related to undetermined antigens.

Table 2
Examples of coexistent asthma and hypersensitivity pneumonitis (HP).

	Antigens for asthma	Antigens for HP
Buick et al. [13]	Triphenylmethane triisocyanate	Triphenylmethane triisocyanate
Halpin et al. [14]	*Trichoderma koningii*	*Trichoderma koningii*
Hirakata et al. [11]	*Trichosporon asahii*	*Trichosporon asahii*
Katayama et al. [12]	*Bjerkandera adusta* *Aspergillus fumigatus*	*Bjerkandera adusta*
Lander et al. [15]	*Scopulariopsis brevicaulis*	*Scopulariopsis brevicaulis*
Miedinger et al. [16]	Malt	Malt
Malo et al. [17]	Hexamethylene diisocyanate	Hexamethylene diisocyanate
Matsushima et al. [18]	Methylene diphenyl diisocyanate	Methylene diphenyl diisocyanate
Ruiz-Hornillos et al. [19]	*Aspergillus fumigatus*	*Aspergillus fumigatus*
Rosenman [20].	Metalworking fluids	Metalworking fluids
Robertson et al. [21]	Metalworking fluids	Metalworking fluids
Solana et al. [22]	Corn flour	Turtledove
Vandenplas et al. [23]	Isocyanates	Isocyanates
Mapp et al. [24]	Diphenylmethane diisocyanate	Diphenylmethane diisocyanate

Increased airway inflammation or hypersensitivity is indicated in patients with HP [25,26], and it might not be surprising this patient developed asthma after HP, because asthma can occur after an episode of farmer's lung. Conversely, Jacobs et al. warned that asthmatic symptoms or presentations during the clinical course of HP should not be confused with asthma [2]. The pathogenesis of HP is heterogeneous and it remains unknown whether asthma might be considered within the extended range of HP beyond its classic concept. A specific subgroup of HP patients was reported to show more severe functional impact, BALF eosinophilia and high levels of the alpha subunit of interleukin 4 receptor [27], which might be related to asthma following HP. Further

studies are needed.

Here, we reported a case of summer-type HP and asthma, exposed to environmental antigens in an old house. Although they are usually recognized as different disease entities based on different allergic mechanisms, they may have common connections related to environmental antigens. Clinicians should not miss the possible overlap between their clinical presentations.

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