Chronic Hypersensitivity Pneumonitis Caused by *Aspergillus* Complicated with Pulmonary Aspergilloma

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Abstract

A 57-year-old man consulted our hospital with a history of the gradual onset of dyspnea and a productive cough. Chest computed tomographic (CT) scans showed a nodular shadow in a cavity lesion, and reticulonodular, cystic, and ground-grass opacities in the bilateral lung fields with honeycombing. He was diagnosed as having pulmonary aspergilloma and idiopathic pulmonary fibrosis (IPF). As an outpatient, he suffered from dyspnea upon physical exertion with exacerbation of the high-resolution CT (HRCT) opacities. An inhalation provocation test for *Aspergillosis fumigatus* was positive and chronic hypersensitivity pneumonitis (CHP) caused by *Aspergillus* was finally diagnosed. Insidious CHP is sometimes misdiagnosed as IPF. The diagnosis of insidious CHP should be made on the basis of a detailed history, specific HRCT findings, and lymphocyte-dominant bronchoalveolar lavage fluid cell findings.
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Key words: chronic hypersensitivity pneumonitis, pulmonary aspergilloma, idiopathic pulmonary fibrosis, inhalation provocation test, insidious type

Introduction

Hypersensitivity pneumonitis (HP) is an immunologically mediated inflammatory disease of the lungs. Many different antigens in organic dusts have been implicated in triggering HP. The clinical features of HP are classically divided into three subtypes; acute, subacute, and chronic (1). Chronic HP (CHP) is further divided into two groups; recurrent acute onset type and insidious type (2, 3). The clinical features, radiological findings, pulmonary functions, and prognosis of the insidious type strongly resemble those of idiopathic pulmonary fibrosis (IPF) (2, 4). CHP develops pulmonary fibrosis after a prolonged period of repeated exposure and persistent inflammation (3, 5, 6).

On the other hand, aspergillosis refers to any of the illnesses caused by fungi that are members of the genus *Aspergillus*. The disease ranges from allergic responses that occur in the absence of fungal growth, to colonization with or without an allergic component, to invasion and destruction of lung parenchyma (7). A complication of CHP and fungal growth has, to the best of our knowledge, never been reported before. We hereby describe a rare case of CHP caused by *Aspergillus* with a complication of fungal growth.

For editorial comment, see p 896.

Case Report

A previously healthy 57-year-old man consulted our hospital with a 15-month history of the gradual onset of dyspnea upon physical exertion and a 4-month history of productive cough. He had a past history of tobacco use, approximately 100 pack-years. He had a remote occupational history of engineering work, making cardboard boxes, confectionery, and in the food sample manufacturing industry. He lived in a 15-year-old wooden home and had kept a cat for three years. He denied any significant exposure to birds.

On physical examination, late inspiratory fine crackles were audible in the bilateral lower lung fields of his back. No clubbing of fingers was noted. Laboratory findings on admission in January 2001 showed a WBC count of 7,000 cells/μl with a normal differential, C-reactive protein (CRP) of 0.5 mg/dl, erythrocyte sedimentation rate of 24 mm/hour, and β-D-glucan of 5.5 pg/ml (normal range <20 pg/ml), surfac-

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tant protein D of 286.0 ng/ml (normal range <110 ng/ml), and KL-6 of 10,044 U/ml (normal range <500 U/ml). Precipitating antibody in the serum for *Aspergillus* that was examined by the Ouchterlony method was positive, while *Aspergillus* antigen in the serum that was examined by an enzyme-linked immunosorbent assay was negative. Precipitating antibodies in the serum for *Candida* and *Trichosporon asahii* were negative. Arterial blood gas at room air showed a pH value of 7.392, $PaCO_2$ of 45.4 Torr, and PaO_2 of 88.3 Torr. Pulmonary function tests showed an FVC of 3.51 *l* (99% of predicted), an FEV_1 of 2.57 *l* (90% of predicted), an FEV_1/FVC of 73%, and a diffusion capacity of the lung for carbon monoxide of 12.44 ml/min/mmHg (48% of predicted). A chest roentgenogram showed reticulonodular shadows in the bilateral lung field, predominantly in the lower lung fields, with a cavity lesion in the right upper peripheral lung field. Chest high-resolution computed tomographic (HRCT) scans showed a nodular shadow in the cavity lesion in the right S3, and reticulonodular, cystic, and ground-grass opacities in the bilateral lung fields, predominantly in the subpleural areas with honeycombing in the bilateral lower zones (Fig. 1A).

We considered the nodular shadow in the cavity as an air crescent sign. We were unable to diagnose the shadow by trans-bronchial lung biopsy or CT-guided percutaneous lung biopsy. Bronchoalveolar lavage fluid (BALF) analysis from the right B4 showed a total cell count of 11.8×10^5 cells/ml in the following proportion: pulmonary alveolar macrophage level of 41%, lymphocytes of 48%, neutrophils of 11%, and eosinophils of 0% with a CD4/CD8 ratio of 2.6. For a definitive diagnosis of the nodular shadow in the cavity, right upper lobectomy was undertaken. Histopathologic analysis showed a lump of fungi that was suspected of being *Aspergillus* (Fig. 2A). Lung tissue around the cavity showed a fibrotic change (Fig. 2B). He was diagnosed as having pulmonary aspergilloma, and treated with itraconazole. He was also diagnosed as having IPF and continued treatment as an outpatient.

In mid 2002, he suffered from dyspnea upon physical exertion and a persistent dry cough with exacerbation of the HRCT opacities (Fig. 1B). Surfactant protein D increased to 334.0 ng/ml and KL-6 to 14,290 U/ml. Precipitating antibody in serum for *Aspergillus* was positive even after the

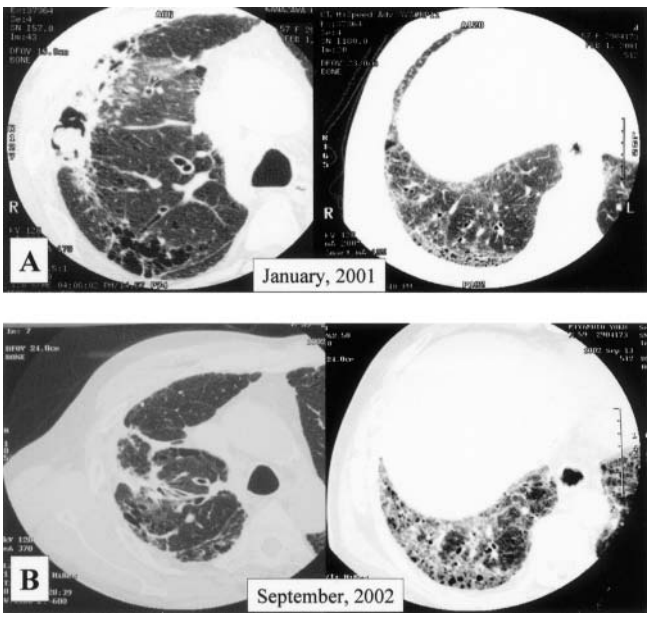


Figure 1. A: Chest HRCT scan in January 2001, showing a nodular shadow in the cavity lesion in the right S3, and reticulonodular, cystic, and ground-grass opacities in the bilateral lung fields, predominantly in the subpleural areas with honeycombing in the bilateral lower zones. B: Chest HRCT scan in September 2002, showing exacerbation of the opacities.

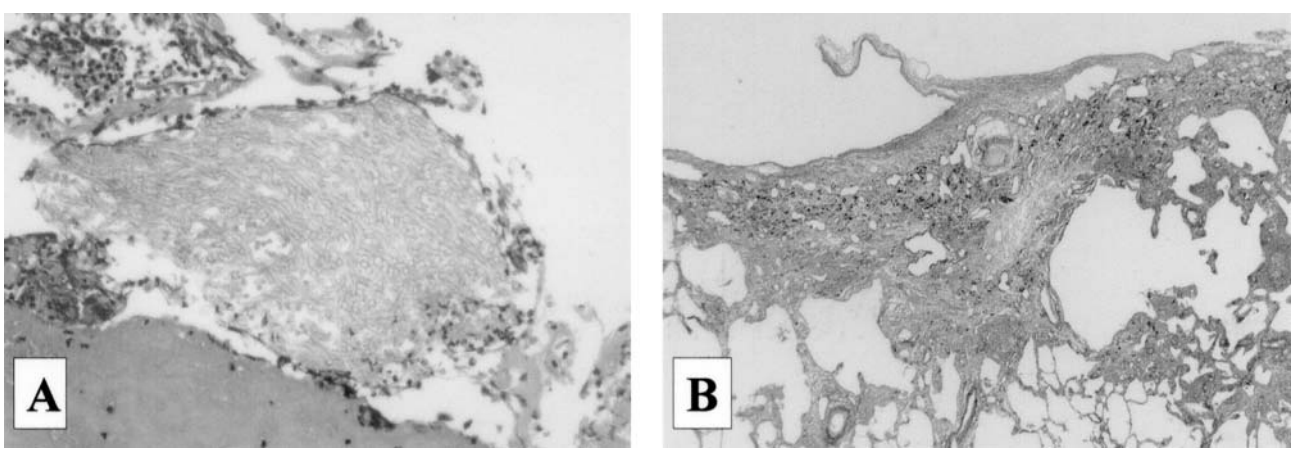
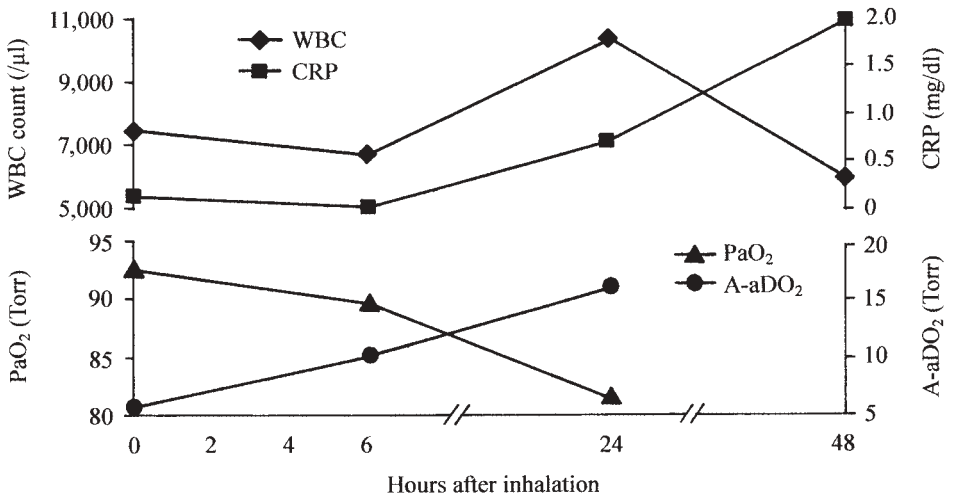


Figure 2. A: Histopathologic analysis showing a lump of fungi that was suspected of being *Aspergillus* (HE stain, ×20). B: Lung tissue around the cavity showing a fibrotic change (HE stain, ×100).



Cough	(+)	(+)	(++)	(++)
Body temperature, ℃	35.8	35.9	36.6	36.8
FVC (*l*)	3.08	3.08	3.04	3.10
FEV_1 (*l*)	2.41	2.48	2.41	2.44

Figure 3. An inhalation provocation challenge test for *Aspergillosis fumigatus*.

right upper lobectomy. For further examination, he was admitted in September 2002. BALF was performed again from the left B4 and showed a total cell count of 7.4×10^5 cells/ml in the following proportion: a pulmonary alveolar macrophage level of 24%, lymphocytes of 59%, neutrophils of 17%, and eosinophils of 0% with a CD4/CD8 ratio of 2.7. From the BALF cell findings, we suspected CHP caused by *Aspergillus*. For the final diagnosis, we undertook an inhalation provocation test for *Aspergillosis fumigatus*. He inhaled 2 ml of a 100-fold dilution of an *Aspergillus fumigatus* antigen extract (allergen scratch test, Torii pharmaceuticals, Tokyo, Japan) through a nebulizer for 2 minutes. The development of respiratory symptoms, including an increase in coughing, an increase in the peripheral WBC count by 40.5%, an increase in the alveolar-arterial oxygen pressure difference by 10.8 Torr, and an increase of CRP by 1.9 mg/dl (48 hours later), were all observed (Fig. 3). The inhalation provocation test was judged as positive according to the criteria by Ohtani et al (8), although the environmental exposure test was negative. From these results, he was diagnosed as having CHP caused by *Aspergillus* according to the current criteria for CHP (3). The environmental mycological study for *Aspergillus* was negative. Furthermore, cultures for *Aspergillus* from BALF and sputum were also negative. He was treated with 20 mg of oral prednisolone daily, and his dry cough symptom disappeared.

Discussion

The current diagnostic criteria for CHP is 3 or more of the following (including 5, either 2 or 3, and either 1 or 6): 1) a reproduction of the symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; 2) evidence of pulmonary fibrosis; 3) honeycombing on CT; 4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; 5) over 6 months in duration of respiratory symptoms related to HP; or 6) antibodies and/or lymphocyte proliferation to the presumed antigen (3). The present patient met all the aforementioned criteria for CHP from 1 to 6.

In Japan, home-related CHP is seen more often than in the Western world (3). The antigen for home-related CHP is generally unknown because a low-dose exposure to a specific antigen brings about insidious CHP. Ohtani et al reported that the insidious type of chronic bird fancier's lung is likely due to exposure to smaller birds and is more likely to be positive for specific antibodies than the recurrent type (2). The diagnosis of insidious CHP is obviously more difficult than recurrent CHP. But, the inhalation provocation test is useful for the diagnosis of chronic bird fancier's lung including the recurrent and insidious types (2, 8). In home-related HP, the identification of a particular antigen may be difficult, so the inhalation provocation test is seldom performed.

CT findings of CHP have shown ground-grass opacities, nodular shadows, air space consolidation, traction bronchiectasis, and honeycombing (3, 9–11). Adler et al reported that on HRCT scan, the fibrosis in cases of CHP was situated predominantly in the middle lung zones or showed no zonal predominance, so they concluded that the distribution of fibrosis could allow the distinction of CHP from other causes

of fibrosis in many cases (11). Lynch et al reported that patients with IPF were more likely to have honeycombing and peripheral or lower lung zone predominance of the disease, and less likely to have micronodules, than were patients with CHP (9). They concluded that CT can be used to distinguish IPF from CHP in most but not all cases and lung biopsy should still be considered the golden standard (9). The present patient had fibrosis situated predominantly in the lower lobe, but fibrosis was also found in the upper and middle lung zones. As for cases like our patient, it is difficult to distinguish IPF from CHP by HRCT findings.

Pathological findings by surgical lung biopsy indicated that many cases of CHP patients predominantly showed interstitial fibrosis with a usual interstitial pneumonia (UIP) pattern (2, 12). The present patient underwent right upper lobectomy, which showed a fibrotic change. Pathological findings of our patient were expected to show a UIP pattern, but that was not incompatible with CHP.

The development of lung aspergillosis depends on the interaction between three factors: the characteristics of the fungus, the status of the host defense mechanism, and the type of exposure (7). In CHP, *Aspergillus* deposits in the distal air spaces and produces an immune-mediated inflammatory response in sensitized individuals, although in pulmonary aspergilloma, *Aspergillus* deposits in cysts or cavities. In the present patient, because an environmental mycological study for *Aspergillus* was negative, we surmised that aspergilloma deposited in a cystic lesion first, and CHP developed from this infection thereafter. Aspergilloma stimuli were surmised to be more important than environmental *Aspergillus* stimuli in our patient.

The antigen is not completely removed by only cleaning in home-related CHP. Avoidance of continuous antigen exposure has been the mainstay of treatment, often at great cost to the affected patient with a home-related antigen who is forced to choose between removal or health. Treatment with steroid administration may be effective against CHP (3). But, insidious CHP is sometimes associated with the development of pulmonary fibrosis even when avoidance of any exposure is complete. Furthermore, in spite of steroid administration, in some patients CHP does progress.

Insidious CHP is sometimes misdiagnosed as IPF because most physicians are unacquainted with this disease. The diagnosis of insidious CHP should be carried out on the basis of a detailed history, specific HRCT findings, and lymphocyte dominant BALF cell findings; furthermore, physicians should suspect this disease.

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