Cladosporium Species-Related Hypersensitivity Pneumonitis in Household Environments

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Abstract

Home-related chronic hypersensitivity pneumonitis (HP) is sometimes difficult to discriminate because patients do not have an obvious history of antigen exposure. We report two HP cases which developed in an office area and in a home: a 47-year-old woman with acute-onset HP and a 72-year-old woman with chronic HP followed up as idiopathic pulmonary fibrosis following isolation of Cladosporium cladosporioides and Cladosporium herbarum, respectively. Lymphocyte stimulating activity and antibody titer to these fungi were increased in these patients. Since Cladosporium spp. and several other fungi are present ubiquitously in our living environment, it is difficult to eliminate the antigen from the patients’ environment to control the disease. Cladosporium spp. can be key antigens in inducing chronic HP in the home environment.

Key words: chronic hypersensitivity pneumonitis, fungal antigen

(Inter Med 48: 363-367, 2009)
(DOI: 10.2169/internalmedicine.48.1811)

Introduction

Hypersensitivity pneumonitis (HP) represents a group of interstitial inflammatory diseases of the lung induced by an immunological response to inhaled organic dust or non-organic chemicals. Many types of antigen are reported to be involved in the pathogenesis of HP. In specific subgroups of HP, such as bird fancier’s lung, farmer’s lung or summer-type HP, antigens have been identified and measures have been taken to contain the diseases. On the other hand, in HP without a specific antigen exposure such as HP in the home environment, which is increasing in importance regarding HP (1), identification and protection against pathogenic antigens have not been thoroughly performed. Household exposure to antigens tends to involve longer exposure periods and can easily be overlooked, possibly leading to occult and chronic disease that is sometimes indistinguishable from idiopathic pulmonary fibrosis (IPF).

Here, we report two HP cases with no history of specific environmental exposure and no response to commercially available antibody tests related to HP. In both cases, Cladosporium spp. represented by Cladosporium cladosporioides in case 1 and Cladosporium herbarum in case 2 were isolated from their environments as possible antigens. Cladosporium spp. have not been recognized as common antigens inducing HP, but are among the most common and thus hard-to-remove fungal antigens in our living environment (2, 3). This report shows the possibility of Cladosporium spp. as antigens inducing chronic HP, and as a tool to differentiate HP from IPF.

Case Report

Case 1.

In June 2006, a 47-year-old woman working as an assistant at a railway station kiosk and with no history of smoking was admitted to our hospital because of worsening cough and dyspnea for 2 months. Her chest X-ray and computed tomography showed a ground glass-like appearance in her middle to lower lung field, but no honeycombing or nodular shadow (Fig. 1). Mixed respiratory dysfunction (%VC 74.4%, FEV1.0 42.9%), a decrease in DLCO (%DLCO 38.4%) and mild hypoxemia were observed following a respiratory function examination. A mild increase in LDH and

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Received for publication October 24, 2008; Accepted for publication November 27, 2008
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increase in KL-6 to 3,060 IU/mL were observed in her serum. Peripheral blood WBC count and CRP in serum were not increased. After one week of observation, with no sign of improvement, we performed bronchoscopy. An increase in lymphocytes to 75% of total cells in broncho-alveolar lavage fluid was observed. The CD4/CD8 ratio of lymphocytes was 0.49. The percentages of eosinophils and macrophages in the broncho-alveolar lavage fluid were 10% and 15%, respectively. A transbronchial lung biopsy showed mild cellular infiltration to the alveolar wall, but no granulomatous change.

We isolated 5 fungal colonies from a swab taken from an air conditioner at her work place; she had complained that she felt ill while she was working under the blast of the air conditioner. Each colony was grown on a Sabouraud dextrose agar culture plate, suspended in saline, autoclaved and then subjected to a lymphocyte stimulation assay. An increase in lymphocyte stimulating activity was observed in two of the five fungi, which were identified as *Cladosporium cladosporioides* and a *Phoma* sp. Antibody titers to both fungi were measured using an immunofluorescent assay. The patient’s serum with a four-fold dilution from 10 to 163,840 times was added to the *C. cladosporioides*-mounted slide glass. Polyclonal rabbit anti-Ig Kappa Lambda/FITC (Dako Japan, Tokyo) was used as a second antibody. An increase in the antibody titer to *C. cladosporioides* to 10,240 times (normal volunteers 40 to 640, median 160, n=22) was recorded (Fig. 2), but not to the *Phoma* sp. (40 in the patient, ranging from 10 to 40, median 10 in normal volunteers, n=4). One out of two co-workers had high anti-*Cladosporium* antibody titer (2,560 times), but no sign of HP. Later, she was exposed to the *C. cladosporioides*-cultured culture plate for a few seconds, and developed an immediate cough and headache lasting several days, but no change in vital capacity (VC) 4 hours after the exposure, indicating *C. cladosporioides* as the causative antigen.

The patient’s symptoms and lung function improved rapidly after the initiation of steroid therapy. Discharge from hospital did not worsen her respiratory symptoms and lung function. But, going back to her job, one week after the discharge, worsened her symptoms and lung function even with the steroids. Moving to a new work place improved her symptoms and lung function, and steroid treatment was tapered to 5 mg of prednisone. But she possessed a high antibody titer for one year after moving to the new work place, and still has a mild malaise and a paroxysmal cough.
Case 2.

A 72-year-old house wife with a history of breast cancer at the age of 56 and no history of smoking was followed up for two years after first being diagnosed with IPF following an X-ray mass examination. A high anti-nuclear antibody titer was recorded, which was higher than 1,280 times, but there was no sign of collagen diseases or no increase in other autoimmune antibodies.

In September 2005, she visited our hospital and complained of chest tightness during deep breathing for a week. She was admitted to our hospital two months later because of worsening symptoms and a rapid decrease in lung function. Her VC was 1.89 L (89.0%) at admission. Although % VC was in the normal range, it decreased by 100 mL (5.2%) in two months and by 480 mL (20.8%) in the two years of follow-up. Her X-ray showed a reticular shadow and loss of volume for both lungs (Fig. 3). Her computed tomography showed a reticular shadow mainly in the middle lung zone, with a little honeycombing, which is not compatible to the findings of IPF (Fig. 4). A thoracoscopic lung biopsy was performed on the 4th and 9th segment of her left lung. Her lung showed inflammatory and fibrosing changes spreading from the airways. The sequence of inflammatory and fibrosing changes seemed to be different between each airway in the same lung specimen and suggested the possibility of several periods of exposure to airborne pathogens, which differs from the findings for UIP, NSIP or IP related to collagen diseases (Fig. 5).

We captured fungal spores in 10 liters of sampled air in each room of her house using an air sampler (Biotest Hycon...
Steroid therapy was started following a transbronchial lung biopsy. Three days of 500 mg of methyl prednisolone was followed by alternate-day administration of 20 mg of prednisone. We added other medications during the course of treatment, such as cyclophosphamide, inhaled steroids, inhaled N-acetyl-L-cysteine, leukotriene receptor antagonist, and anti-histaminergics. KL-6 in her serum was significantly decreased in the summer and increased in the other seasons; 945±77 IU/mL in July to September during the years 2004 to 2008, and 1,356±339 IU/mL in the other seasons of these years, (p<0.001). Trips to several countries and several domestic areas during the autumn season sometimes improved her chest tightness. Several periods of exacerbations occurred in the autumn and winter seasons. Steroids were increased during exacerbations, including the exacerbation just before the biopsy. Steroids, and possibly concomitant admission to hospital, were effective only for the treatment of exacerbations, and not for attenuation of the gradual worsening of the disease over the years. She died as a result of an exacerbation after a short discharge from hospital and stay at her home in August 2008.

Discussion

With an improvement of technologies and awareness concerning workplace safety in special working environments, it is rare to see patients with occupation-related HP such as farmer’s lung, even in our hospital which is situated in a rural area of Japan. An increasing number of home-related HP cases have been reported (1), and most of the HP patients we see in our hospital developed HP in office areas or in home environments. About half of these patients are negative to commercially available antibody tests, such as those for Aspergillus fumigatus or Trichosporon spp. In most cases of home-related HP, we cannot identify the causative antigen (1, 4). This is because we do not have sufficient information concerning the causative antigen of home-related HP, and therefore do not have the means to detect the IgG titer or an immunological marker for use in a routine test for antigens frequently present in our home environments. Latent developed home-related chronic HPs are sometimes indistinguishable from idiopathic pulmonary fibrosis, as demonstrated in case 2, because they do not have an obvious background of antigen exposure. It is important to establish a home-related antigen-antibody testing system in order to differentiate home-related chronic HP from IPF.

Although Cladosporium spp. have been known as allergens in bronchial asthma (5), they have not been recognized as common antigens in HP. We found only a few reports of Cladosporium-related HP (6). Cladosporium spp. is a black fungus that can be seen everywhere in our living environments, such as on decaying plants, in soil, fiberglass duct liner, paints, textiles, and occurring in high concentrations in water-damaged building materials. Spores of Cladosporium can be detected indoors and outdoors. It is reported that 53% of fungal spores detected in air are those of Cladosporium spp. (3). These fungi proliferate at a temperature higher than 20°C and in a humidity higher than 80% (7). Thus, these fungi grow well everywhere in the rainy season and increase their spores indoors and outdoors, and can grow inside homes even in the winter if the house is heated and humidified. In case 2, exacerbation and an increase in KL-6 were observed from the autumn to winter seasons. Even though the patient was not using a humidifier in her house, she might have been exposed to something similar inside her house in those seasons.

Anti-Cladosporium antibody was detected in all 90 sera that we tested, including 22 sera from normal volunteers (data not shown). In both of the patients, a high antibody titer (10,240 times), compared to normal control (40 to 640), was observed. Because of the ubiquitous presence of Cladosporium spp. in our environment, and the ubiquitous presence of antibody in our sera, the antibody titer to Cladosporium spp., but not the presence of the antibody, should be taken as a marker of Cladosporium-related HP, although a high anti-Cladosporium antibody titer is not sufficient to diagnose Cladosporium-related HP, as we have seen a high antibody titer in a co-worker of case 1.

In both cases described here, the effect of steroid therapy was limited in attenuating the progress of the disease, when the patients remained in the causative environments. Although it is difficult to isolate patients from the causative antigen, especially in cases involving a sensitized response to an antigen that is ubiquitously present in the living environment, it is important to do so, as at this time there is no effective tool to treat HP. Jacobs et al (8) reported cases with home-related chronic HP, who were diagnosed as UIP, BOOP, or NSIP to whom isolation and cleaning living environments were performed and stable diseases were achieved. In case 2, the patient’s house was refurbished several times after developing her symptoms. Her home was clean in terms of the number of airborne fungal spores, compared to other patients’ homes, but this was not enough to stabilize her disease. However, we should have undertaken repeated cleaning-environmental challenge from the early phase of the disease, and should do so for most patients with pulmonary fibrosis, until the diagnostic measures and treatment strategy for home-related chronic HP are established. For that purpose, it is crucial to compile a list of causative antigens.
References