Hypersensitivity Pneumonitis Caused by a Home Ultrasonic Humidifier Contaminated with *Candida guilliermondii*

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Abstract:

We herein report the first documented case of acute hypersensitivity pneumonitis in which *Candida guilliermondii* was the possible causative organism. A young Japanese woman presented to our hospital with relapsing respiratory symptoms accompanied by high fever. A detailed interview revealed that the onset of the symptoms occurred shortly after using a humidifier in her home. Her symptoms showed spontaneous improvement soon after admission, and an examination of her bronchoalveolar lavage fluid revealed the specific infiltration of inflammatory cells, which predominantly consisted of lymphocytes. Precipitin testing showed a positive reaction to *C. guilliermondii*, which was isolated from the home humidifier. Repeated history taking is essential for diagnosing occult respiratory disorders.

**Key words:** *Candida guilliermondii*, hypersensitivity pneumonitis, pleuritis, recurrent pneumonia

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**Case Report**

A 32-year-old woman was referred to our hospital with recurrent fever accompanying a productive cough and dyspnea, which had occurred intermittently over a period of 7 weeks. The patient had previously been treated with antibiotics including macrolides (azithromycin and clarithromycin), beta-lactams (sulbactam/ampicillin and ceftriaxone), and fluoroquinolone (garenoxacin), which resulted in no improvement of her symptoms. Her medical history included infantile asthma and atopic dermatitis. She was a non-smoker and was not taking any particular medicines.

On admission, her vital signs were as follows: blood pressure, 93/70 mmHg; heart rate, 111 per min; respiratory rate, 25 per min; oxygen saturation, 93% in ambient air. A physical examination revealed bilateral crackles at her back as...
well as lower back pain, which was aggravated by deep breathing. Laboratory tests showed that her peripheral white blood cell count was elevated (26,280/mL), with 95.0% neutrophils; the eosinophil count was not elevated. The patient’s serum levels of C-reactive protein (15.7 mg/dL), procalcitonin (6.79 ng/mL), and immunoglobulin E (1,355 IU/mL) were also elevated. A chest X-ray showed areas of bilateral ground-glass opacity, and computed tomography revealed peripheral-dominant reticular shadows and non-segmental pulmonary infiltrates (Fig. 1). Bacterial cultures of the blood and sputum were negative.

After admission, her high fever and respiratory symptoms spontaneously remitted within a few days without any treatment. The inflammatory reactions also subsided to a normal range within 5 days. The patient underwent bronchoscopy, and the results of a bronchoalveolar lavage examination showed the infiltration of inflammatory cells: lymphocytes, 79% (CD4, 52.5%; CD8, 32.7%; CD4/8 ratio, 1.6); eosinophils, 13%; macrophages, 6%; neutrophils, 2%; and basophils, 0%. The results of the microbiological and pathological tests were unremarkable. The patient’s clinical course and findings satisfied the clinical criteria for acute HP.

Following the spontaneous resolution of the patient’s symptoms, she remained afebrile, and chest computed tomography on admission day 10 showed a complete improvement. Repeated history taking revealed that her symptoms developed after the using an ultrasonic humidifier in her home. The humidifier had been used as an exhibit, and she had used the device without cleaning it. Thus, water had remained inside the humidifier for more than one year. When she was discharged from our hospital, she was instructed not to use the humidifier any more, and she has not suffered from recurrence for more than 1 year.

To confirm the diagnosis of acute HP, we performed an investigation to identify possible offending antigens. We cultured a water stain on the inner wall of the humidifier tank, and three fungi were isolated: *C. guilliermondii*, *Candida parapsilosis*, and *Candida lipolytica*. The organisms were cultured with Czapek Dox broth at 25°C for 60 days, and dry antigen powders were prepared. The three antigens were dissolved in distilled water (1 mg/mL), and precipitin reaction testing was performed using the agar gel double-diffusion method (Ouchterlony method). The results showed a positive reaction against *C. guilliermondii*, which was isolated from the home humidifier, indicating that her hypersensitivity pneumonitis was possibly caused by a home ultrasonic humidifier, which was contaminated with *C. guilliermondii* (Fig. 2).
Specific antigen causes the characteristic radiographic findings; therefore, a definite conclusion has not yet been reached (7). Her respiratory symptoms and atypical CT findings perplexed us, but we successfully diagnosed the case based on clues related to her recurrent course, which were uncovered by repeated interviews. The precipitin reaction test revealed that *C. guilliermondii* isolated from the humidifier was a possible offending antigen in the present case. Although an antigen inhalation provocation test—an essential test for the diagnosis of HP—was not performed, this case would be the first documented case of *C. guilliermondii*-associated HP.

Various clinical diagnostic criteria for HP have been proposed, but a definitive consensus has not yet been reached (3). The results of an international multicenter cohort study including 116 patients with HP revealed six predictive factors for HP: i) exposure to an offending antigen, ii) presence of precipitating antibodies, iii) repetitive episodes, iv) inspiratory moist rales, v) acute onset of symptoms after exposure, and vi) body weight loss (8). Our patient satisfied these criteria, and we consider the diagnosis of HP in the present case to be highly definite. The diagnosis of HP due to the ultrasonic humidifier was confirmed by the patient’s clinical improvement after she stopped using the humidifier. Patients with acute HP usually recover after the removal of the causative agent; however, some severe cases may require corticosteroid therapy (9). In this case, the systemic and respiratory symptoms resolved shortly after admission without any specific treatment.

The clinical history, including the living situation, occupation, and animal contact are keys to the diagnosis of HP. In contrast, lung function tests are of no use in differentiating the disease from other respiratory conditions (8). Furthermore, the findings of chest radiography are unspecific or may trigger HP: bacteria, fungi, animal/plant proteins, low molecular weight chemicals, and metals (3). Among these, fungi are increasingly recognized as a prominent source of allergens (19). Immune-allergy testing revealed that *C. guilliermondii* might have been a causative organism in this case. *C. guilliermondii* is an environmental fungus that occasionally evokes invasive infections in humans (20). The isolation of *C. guilliermondii* from a portable ultrasonic humidifier used by a patient with HP was previously reported, but its relevance to the onset of the disease was uncertain (21). Although an inhalation challenge test was not performed due to the patient’s refusal, we considered that the patient’s HP was likely to have been caused by *C. guilliermondii* based on the results of the precipitin reaction test. Although the rate of concordance between the precipitin reaction test (Ouchterlony method) and the inhalation challenge test is unknown, a specific antibody analysis can provide supportive evidence for HP; this significant predictor of HP has an odds ratio of 5.3 (95% confidential interval: 2.7-10.4) (8). According to a recent review on HP in which the clinical probability of HP was proposed (22), a diagnosis of HP was considered to be 97-98% probable in our patient, based on the following facts: exposure to an offending antigen, recurrent episodes of symptoms, the onset of symptoms within 4-8 hours after exposure, the presence of respiratory crackles, and the positive serum precipitin test.

In conclusion, we presented a case of *C. guilliermondii*-associated humidifier lung. Patients with HP show a wide variety of clinical and radiological manifestations that may mimic other lung diseases. In patients in whom respiratory symptoms persist or relapse, allergic etiologies should also be considered, rather than infectious diseases.

The authors state that they have no Conflict of Interest (COI).

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