

Case report

Hypersensitivity pneumonitis due to an ultrasonic humidifier

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We describe a woman with hypersensitivity pneumonitis that was related to using a home ultrasonic humidifier. A micronodular infiltrate was seen in her chest radiograph. The inhalation challenge test was performed with the humidifier, and she exhibited a positive response. The cultures of the humidifier water grew *Candida albicans*, *Rhodotorula* spp., and *Aspergillus* spp. The test for precipitating antibodies against the humidifier water gave a positive response, and specific IgG, IgM, and IgA antibodies against extracts of *A. fumigatus*, *C. albicans*, and *Rhodotorula* spp. were demonstrated in the patient's serum by ELISA. A strong, dose-dependent inhibition of *Rhodotorula* IgG-ELISA by humidifier water was observed, suggesting that *Rhodotorula* might be the cause of hypersensitivity pneumonitis in this patient.

Key words: humidifier lung; hypersensitivity pneumonitis; *Rhodotorula*; ultrasonic humidifier.

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Hypersensitivity pneumonitis is an immunologically mediated lung disease caused by repeated inhalations of an organic antigen. The basic histologic lesion consists of a diffuse mononuclear cell infiltration of the pulmonary interstitium, alveoli, and terminal bronchioles. Since there is no radiologic, physiologic, or immunologic test specific for hypersensitivity pneumonitis, the diagnosis is often based on a compatible temporal relationship of the symptoms to the history of environmental or occupational exposure.

Recently, the use of home ultrasonic humidifiers has become widespread. However, there have been few reports of humidifier lung disease due to ultrasonic humidifiers (1–5).

We describe a 34-year-old woman with hypersensitivity pneumonitis that was related to using a home ultrasonic humidifier.

Case report

A 34-year-old woman was admitted to hospital with an acute attack of fever (39°C), dry cough, dyspnea, and chest pain. The patient was a nonsmoker without history of atopy or other respiratory conditions, and she had not been exposed to any obvious source of organic dusts. The only remarkable facts

from anamnesis were that the day before hospital admission, the patient's children had developed cough and coryza requiring symptomatic treatment, and that an ultrasonic humidifier was installed in their bedroom.

The patient had suffered recurrent episodes with similar clinical manifestations, and, after detailed questioning, she recalled exposure to the home humidifier before each of the previous episodes. In the last episode, she had been sleeping in her children's room for 2 h while the home humidifier was being operated. Every episode had resolved spontaneously within 24–48 h.

She had never been examined before exhaustively. In the second episode, however, blood analysis had demonstrated leukocytosis (24 700 leukocytes/mm³) that decreased to 8800 leukocytes/mm³ 24 h later. In other episodes, leukocytosis was demonstrated in the acute phase.

At the time of hospital admission, the blood differential count showed 31 790 leukocytes/mm³ (95% neutrophils, 0.4% eosinophils). The hemoglobin, serum chemistries, electrolyte, and urinalysis values were normal. Arterial blood analysis showed pH of 7.43, PaCO₂ of 30.4 mmHg, and PaO₂ of 66 mmHg. The chest roentgenogram revealed bi-lateral bibasal micronodular infiltrates.

Hypoventilation was heard on chest auscultation, without crackles.

Forty-eight hours after admission, a new blood analysis demonstrated 6940 leukocytes/mm³ (73.6% neutrophils, 0.8% eosinophils). An arterial blood sample showed pH of 7.42, PaCO₂ of 33.8 mmHg, and PaO₂ of 86 mmHg. Pulmonary function tests (spirometry, lung volumes, and carbon dioxide diffusion test) were normal, except for reduced residual volume. A perfusion lung scan did not suggest pulmonary embolic disease. High-resolution computed tomography was normal. Results of serology tests (Q fever, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*) were negative. Determinations of serum immunoglobulins (IgG, IgA, and IgM) were within the normal range, as was total serum IgE (9 kU/l). Rheumatoid factor, antinuclear, antimitochondrial, and anti-smooth-muscle antibodies were all negative.

Skin prick tests to common aeroallergens were negative, and no reaction was observed to the intradermal test with *Aspergillus fumigatus* at 15-min and 6-h readings. Specific IgE antibodies (Pharmacia CAP System, Uppsala, Sweden) to *Alternaria tenuis*, *Cladosporium herbarum*, *A. fumigatus*, *Penicillium notatum*, and *Candida albicans* were not found in the patient's serum.

An inhalation challenge test using the ultrasonic humidifier was performed after obtaining written informed consent. The humidifier, which was provided by the patient, was placed at her bedside and operated for 1 h. During this challenge test, the patient was exposed to about 400 ml of humidifier water. Over the next 48 h, the patient's symptoms and signs were observed, and measurements were made of her body temperature, cardiac and respiratory frequency, leukocyte count, serum C-reactive protein level, and pulmonary function tests. This challenge test was interpreted according to the criteria of Yoshida et al. (6). A positive response was observed, as shown in Table 1, with return to normality 48 h later.

The cultures of the humidifier water grew *C. albicans*, *Rhodotorula* spp., and *Aspergillus* spp. A serum sample obtained from the patient was examined by the Ouchterlony gel double immunodiffusion method for the detection of precipitating antibodies to various antigens: *A. fumigatus*, *C. albicans*, *C. herbarum*, *P. notatum*, *A. tenuis*, *Termonomices vulgaris*, *Micropolispora faeni*, *Tricophyton mentagrophytes*, *Botritis cinerea*, *Merilium lacrimans*, *Phoma betae*, *Sporobolomyces* spp., *Fusarium* spp., *Chaetomium globulosum*, pigeon serum, and humidifier water. Strongly positive precipitins to humidifier water and *A. fumigatus* were present. Specific IgG, IgM, and IgA antibodies against extracts of *A. fumigatus*, *C. albicans*,

Table 1. Pulmonary function and laboratory tests after inhalation challenge with ultrasonic humidifier

	Baseline	8 h	24 h	48 h
FVC (l)	3.99	3.48	2.63	4.13
FEV ₁ (l)	3.56	3.28	2.44	3.48
TLC (l)	4.53	—	3.93	—
RV (l)	0.94	—	0.83	—
TLCO (mmol/min/kPa)	10.5	—	6.14	—
PaO ₂ mmHg	86	73	77	84
Leukocytes/mm ³	5700	22330	11500	6200
CRP mg/l	5.3	62.1	—	5
Body temperature (°C)	36.3	38.7	36.4	36.5
Heart rate/min	94	130	104	90
Respiratory rate/min	16	24	22	16
Pulmonary auscultation	Normal	Crackles	Crackles	Normal

CRP: C-reactive protein.

Rhodotorula spp., and humidifier water were determined in the patient's serum by the ELISA method. Serum samples obtained from 10 nonexposed subjects were used as controls. A result higher than 0.25 optical density (OD) was regarded as positive. The results of ELISA measurements are shown in Table 2. ELISA-inhibition studies were carried out as previously described (7) with humidifier water as inhibitor. Dose-dependent inhibition of *Rhodotorula* IgG-ELISA by humidifier water was observed, as shown in Fig. 1. In contrast, humidifier water did not inhibit IgG-ELISA against *A. fumigatus* or *C. albicans*. The specificity of this assay was confirmed by strong inhibition (up to 95%) of humidifier water ELISA with the humidifier water itself.

It is noteworthy that specific IgG, IgM, and IgA antibodies were detected by ELISA in the patient's serum against the fungi that were isolated from the humidifier water.

Discussion

We report a patient with hypersensitivity pneumonitis that was related to using a home ultrasonic humidifier. The water in ultrasonic humidifiers is likely to be contaminated with microorganisms such as

Table 2. Measurements of IgG, IgM, and IgA antibodies to humidifier water and fungi by ELISA

	IgG	IgM	IgA
Humidifier water	2.500	2.500	2.400
<i>Rhodotorula</i> spp.	1.800	0.800	0.800
<i>A. fumigatus</i>	0.900	2.500	1.260
<i>C. albicans</i>	0.600	1.160	0.400

Results expressed in OD (optical density).

Control sera values <0.150 OD in every case.

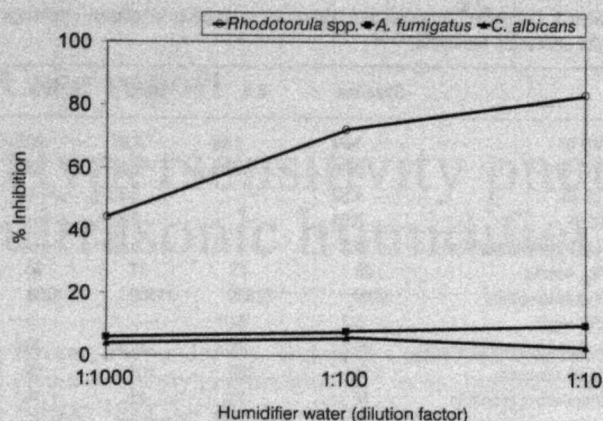


Fig. 1. IgG inhibition ELISA. Percent inhibition of *Rhodotorula* spp., *A. fumigatus*, and *C. albicans* extracts activity induced by increasing amounts of humidifier water.

fungi or bacteria if the humidifiers are not cleaned completely. These humidifiers readily disperse the causative antigens in droplets ranging in size from 0.5 to 3 μ m that can easily reach the distal airway spaces. The inhalation of these antigens by sensitized subjects may result in hypersensitivity pneumonitis (5).

The diagnosis of hypersensitivity pneumonitis due to ultrasonic humidifier in our patient was confirmed by positive challenge test as well as by clinical improvement by the avoidance of exposure to humidifiers. *Candida*, *Aspergillus*, and *Rhodotorula* contaminated our patient's ultrasonic humidifier, and IgG antibodies against these fungi were demonstrated in the patient's serum. However, levels of IgG against *Rhodotorula* were the highest, and the strong inhibition of IgG-ELISA to this fungus by humidifier water provides some evidence that *Rhodotorula* spp. may be the offending agent. This red yeast, which is often present in water-damaged constructions and material, has been previously reported to cause hypersensitivity pneumonitis (8). Several other microorganisms have been previously implicated as possible causal agents of ultrasonic humidifier lung, such as *Aureobasidium pullulans* (2), *Klebsiella oxytoca* (4), *Cephalosporium* (9), and various fungi (3). Although *in vitro* data suggested that *Rhodotorula* may have a causal role in this patient's symptoms, this may represent only an indication of exposure and a resulting immune response to the antigens without a definite association with the disease. It is possible that any of the identified organisms or perhaps another contaminant in the water was the offending agent. Antigen-specific bronchial challenge with these fungi would be needed to identify exactly the etiologic agent and establish its clinical relevance, but this test might be dangerous, and exposure to the humidifier is a more "natural" challenge.

Thermophilic actinomycetes isolated from furnace humidifiers or air heating systems are the most frequently implicated organisms in the origin of humidifier lung (10–12). Our patient, however, had no precipitating antibodies to thermophilic actinomycetes, such as *M. faeni* and *T. vulgaris*, and these organisms could not be isolated from the humidifier water. Thermophilic actinomycetes have been reported to be rarely isolated from ultrasonic humidifier water, probably because of the absence of a heated environment suitable for their growth (2). Thus, it seems unlikely that thermophilic actinomycetes cause ultrasonic humidifier lung.

Home ultrasonic humidifiers should be thought of as a possible cause of hypersensitivity pneumonitis in cases where no other obvious cause has been found. Ultrasonic humidifiers contain relatively inaccessible parts which are difficult to clean, such as the aerosol dispersion nozzle and the transducer chamber. To prevent contamination of humidifiers, it is necessary to keep the humidifiers clean by changing the water frequently and cleaning all the parts thoroughly (5).

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