Humidifier Lung: Possible Contribution of Endotoxin-induced Lung Injury

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Abstract

A 56-year-old man was admitted with cough, fever, myalgia, and arthralgia. Chest computed tomography demonstrated bilateral diffuse ground-glass opacities predominantly in the upper lungs. Subpleural non-segmental consolidation was observed in the late phase. Hypersensitivity pneumonitis was suspected, and an environmental provocation test with the incidental use of a home ultrasonic humidifier was positive. Unlike typical hypersensitivity pneumonitis, serum KL-6 levels were normal. Although several microorganisms were isolated from the humidifier water, there was no evidence for immune sensitization. We detected high amounts of endotoxin in the humidifier water, which may have contributed to the lung injury of this patient. (Internal Medicine 41: 1179-1182, 2002)

Key words: ultrasonic humidifier, hypersensitivity pneumonitis

Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a syndrome that results from repeated inhalation of various causative antigens (1–3). The term humidifier lung, also known as humidifier fever or Monday morning sickness, is applied to cases of HP caused by inhalational exposure to contaminated ventilation units (1–7). In general, prolonged exposure to contaminating fungal antigen results in immune sensitization and causes immune-mediated lung injury in susceptible individuals. We report herein an unusual case of humidifier lung, which may involve a different mechanism than the generally reported HP.

Case Report

A 56-year-old man first noted fever, cough, myalgia, and arthralgia in the end of January 2002. The symptoms worsened even while taking medications for the common cold. He was admitted to a local hospital on February 5, 2002. The patient, a current smoker (10 cigarettes per day for 38 years), had a history of duodenal ulcer and chronic gastritis. Bilateral fine crackles were heard on auscultation of the chest. Chest roentgenogram and computed tomography (CT) showed bilateral diffuse ground-glass opacities predominantly in the upper lungs (Fig. 1A). Laboratory examination revealed peripheral blood leukocytosis (21,500 cells/μl), and elevation of the C-reactive protein (CRP) level (19.1 mg/dl). Sputum cultures showed normal flora. Influenza viruses and mycoplasma antigen tests were negative. The symptoms and radiographic findings did not improve with administration of cefotiam and minocycline for 6 days, but did gradually improve after administration of imipenem/cilastatin for the subsequent 4 days (Fig. 2).

He was referred to our hospital for further evaluation on February 15, 2002. Bilateral fine crackles were still heard and a chest CT and high-resolution CT showed subpleural non-segmental consolidation with diminished diffuse ground-glass opacities (Fig. 1B, Fig. 3). Pulmonary function tests were within normal ranges [% vital capacity: 102%, forced expiratory volume in one second/ forced vital capacity: 91.4%, % single breath carbon monoxide diffusing capacity (DLco): 82.8%]. White blood cell count and serum CRP were within normal ranges (4,700 cells/μl and 0.15 mg/dl, respectively). Serum KL-6 levels were in the normal range throughout the clinical course. Lymphocyte stimulation tests for several drugs, which had been taken at home and at the local hospital, were all negative. Serum β-D-glucan was not detected. Bronchoalveolar lavage (BAL) from the left B5b revealed markedly increased numbers of total cells (6.68×10^5/ml), lymphocytes (30.3%), and neutrophils (13.0%). The CD4/CD8 ratio of BAL lymphocytes was 1.28. A transbronchial lung biopsy specimen showed non-specific inflammatory changes with bronchiolitis and alveolitis without granulomas.

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Figure 1. (A) Chest computed tomography (CT) on admission to a local hospital showed bilateral diffuse ground-glass opacities predominantly in the upper lungs. (B) Chest CT on admission to our hospital revealed subpleural non-segmental consolidation with diminished diffuse ground-glass opacities.

Figure 2. Clinical course of the patient. Symptoms including cough, sore throat, arthralgia, and myalgia. Challenge 1 and 2 indicate the first and the second environmental provocation tests. CTM: cefotiam, MINO: minocycline, IPM/CS: imipenem/cilastatin, BT: body temperature, WBC: white blood cell count, CRP: C-reactive protein, BFS: bronchofiberscopy.
Although HP was suspected, the first environmental provocation test was negative. However, during the second environmental provocation the patient experienced the same symptoms. Chest CT demonstrated new lesions in the lower lungs. Laboratory examinations revealed peripheral blood leukocytosis (18,000 cells/μl), and elevation of CRP (13.2 mg/dl). Decrease of PaO₂ (64.1 mmHg) and DLCO (54.9% of predicted) were also noted. A detailed history revealed that the symptoms occurred immediately after the use of an old humidifier at the end of January 2002. The humidifier was the type with a permanent basin to which water was added as needed. Moreover, the humidifier had been kept for a long time in the closet. He used the humidifier during the second but not first environmental provocation test.

Several microorganisms including Escherichia coli, Acinetobacter species, Bacillus species, Klebsiella oxytoca, Klebsiella pneumoniae, Rhodotorula species, Candida parapsilosis, and Actinomyces species were isolated from the humidifier water. The extract of the humidifier water was prepared for detection of precipitins as follows: the humidifier water was treated with ultrasound for 15 minutes and then freeze-dried. This extract was dissolved in sterile phosphate-buffered saline at a maximum dilution of 50x. Serum was also diluted at a maximum of 5x as mentioned above. Serum precipitins were not detected by the Ouchterlony’s double gel immunodiffusion method with serial dilutions of the extract and serum. A skin patch test and a lymphocyte stimulation test against the humidifier water (1-3). However, the present case lacked such evidence: the serum precipitin test, a skin patch test, and a lymphocyte stimulation test against the humidifier water were all negative.

Inhalation of endotoxin may be involved in the pathogenesis in the present case, since the humidifier water contained high enough amounts of endotoxin to cause the pulmonary and systemic symptoms. The fact that the onset of symptoms in the present case occurred immediately following the use of the humidifier for the first time favors this notion. It has been suggested that bacterial endotoxin may play a role in humidifier lung (12-15). The reports of bath water fever and humidifier lung demonstrated high concentrations of endotoxin (0.1-5.0 μg/ml) in the causative water (13, 14). Endotoxin is an extremely potent agent of lung injury and the inhalation of endotoxin can cause symptoms such as chills and fever, a decrease in DLCO, an increase in airway hyperresponsiveness, and increases in neutrophils as well as lymphocytes in BAL and blood, in a dose-dependent fashion (16, 17). Bacterial endotoxins and fungal toxins have also been proposed as causative agents of organic dust toxic syndrome (ODTS) (3). ODTS in farmers is defined as a febrile illness following exposure to organic dust (1-3). Typically, fever and flu-like symptoms occur 4 to 8 hours after dust exposure. ODTS patients generally have no precipitins, and usually present with normal findings on respiratory and radiological examination (1-3).

The lung injury in the present case is unusual in some other respects. The chest CT in the present case showed ground-glass opacities predominantly in the upper lungs without micronodules. In contrast, acute or subacute HP generally shows diffuse ground-glass opacities and patchy or widespread airspace opacity with poorly defined micronodules predominantly in the middle to lower lungs (1, 2). The chest CT in the late phase of the present case showed subpleural non-segmental consolidation, which is an unusual finding for acute or subacute HP. Furthermore, serum KL-6 levels were not elevated throughout the clinical course. The increase of serum KL-6 is thought to be a hallmark of the normal HP such as Japanese summer-type HP and farmer’s lung (18, 19).

We concluded that the present case might be at least partly due to a toxic lung inflammation caused by endotoxin presented in the highly polluted humidifier water. In contrast to the usual HP, humidifier lung, possibly in general, may be induced by not only hypersensitivity reactions but also by toxic reactions to endotoxin, or both. Recent studies demonstrated a considerable inter-individual variability in endotoxin responsiveness depending on polymorphisms in the genes encoding the pro-
inflammatory cytokines, the LPS receptor, CD14, in humans, and the Toll-like receptor (16). The variability in endotoxin sensitivity may contribute to the differences in the clinical and pathological features among the patients with humidifier lung.

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References