INTERNAL MEDICINE

□ CASE REPORT □

Extrinsic Allergic Alveolitis with Eosinophil Infiltration Induced by 1,1,1,2-Tetrafluoroethane (HFC-134a): A Case Report

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Abstract

A 22-year-old woman was admitted with symptoms of dyspnea and fever with pulmonary infiltrates noted on her chest X-ray study. She developed these symptoms in the workplace; her job included the removal of body hair using a diode-laser with 1,1,1,2-tetrafluoroethane (HFC134a, an alternative to chlorofluorocarbon) as a coolant. A chest X-ray examination revealed ground-glass opacities in the lower lung fields, and a chest computed tomographic study showed diffuse centrilobular opacities. An examination of the bronchoalveolar lavage fluid revealed increased lymphocytes with a slight increase in the number of eosinophils. An examination of the transbronchial biopsy specimens revealed eosinophil infiltration. A peripheral blood eosinophilia was also seen. The patient's symptoms, chest X-ray findings, and arterial blood gas analysis all returned to normal within a week. A challenge test of 1,1,1,2-tetrafluoroethane (HFC134a) inhalation was performed, which resulted in an elevation of body temperature, the development of a cough, and laboratory data indicating increased inflammation. We then determined the patient's diagnosis to be extrinsic allergic alveolits with eosinophil infiltration, caused by HFC134a.

Key words: extrinsic allergic alveolitis, HFC-134a, eosinophilia

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Introduction

Extrinsic allergic alveolitis (EAA) is a syndrome resulting from the repeated inhalation of finely dispersed antigenic material. These antigenic materials encompass a wide variety of organic particles, such as mammalian and avian proteins, fungi, thermophilic bacteria, and certain small-molecular-weight volatile and nonvolatile chemical compounds. We herein present a case of EAA with eosinophil infiltration, the etiologic agent of which was HFC-134a, which is used to replace chlorofluorocarbons in refrigerant and aerosol applications, including its medical use in metered-dose inhalers.

Case Report

A 22-year old woman was admitted to our hospital with a two-day history of dry cough, shortness of breath, and dyspnea in December 2006. She was employed in an aesthetic salon one week prior to admission, and her main job was the removal of body hair using a diode-laser with HFC-134a, an alternative to chlorofluorocarbon, as a coolant. She had no smoking history and no previous history of respiratory illness, including bronchial asthma. Her symptoms had initially developed two days before admission, and she was therefore absent from work for two days. Thereafter, however, her symptoms spontaneously disappeared. As a result, she thus returned to work, but the symptoms later developed again. She initially presented to a local hospital. Because wheezing was present, she was diagnosed with bronchial

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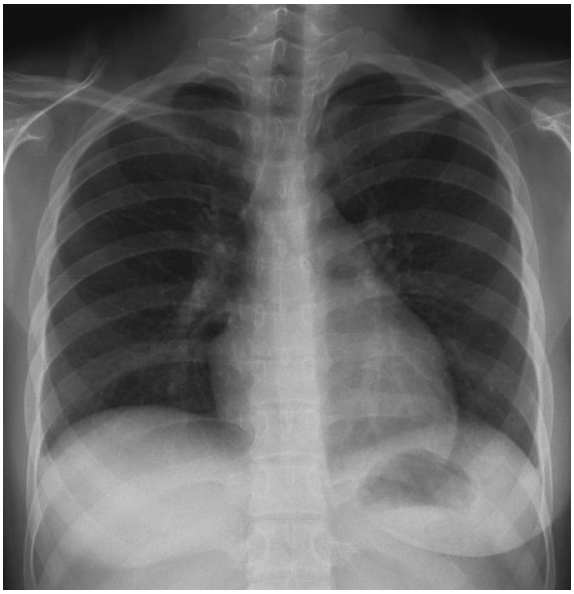

Figure 1. **A chest X-ray on admission. A chest X-ray revealed bilateral reticular shadows and ground glass opacities in both lower lung fields.**

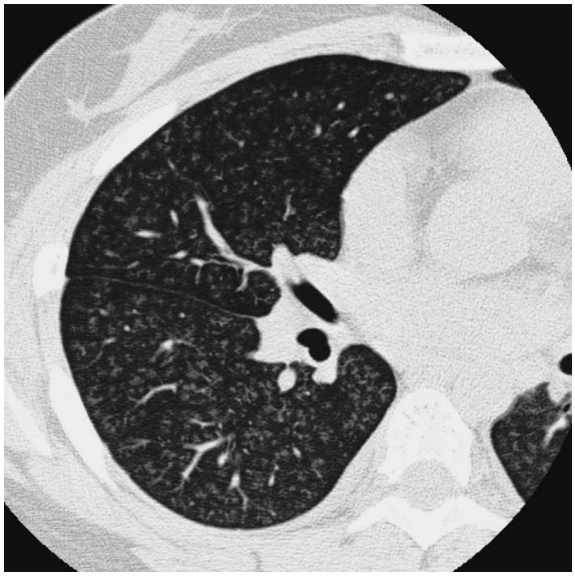

Figure 2. **A computed tomography on admission. Chest CT showed diffuse centrilobular nodules.**

asthma, and treated with an inhaled bronchodilator, which was not effective. Hydrocortisone sodium succinate 300 mg was administered intravenously and then she was admitted to our hospital. Upon admission, her temperature was 39.5 ℃, blood pressure was 120/77 mmHg, pulse rate was 90 beats per minute with a regular rhythm, and her respiratory rate was 30 breaths per minute. Bilateral fine crackles were not audible, and the wheezing had ceased. Arterial blood gas analysis revealed acute respiratory failure with a pH value of 7.484, PaO_2 of 58.5 torr, $PaCO_2$ of 44.0 torr in room air. The peripheral blood examination showed a WBC count of 12,800/μl (normal range, 4,000/μl to 8,000/μl) with a differential cell count of 82.6% neutrophils (normal range 41% to 64%), 9.6% lymphocytes (normal range, 30 to 46%), 2.4% eosinophils (normal range, 1% to 6%), 0.2% basophils (normal range, 0% to 2%), and 5.2% monocytes (normal range, 14% to 18%). On the following day, the white blood cell count was 12,700/μl, with 50% neutrophils, 26% lymphocytes, 16% eosinophils (2,030/μl), 1% basophils, and 6% monocytes. C-reactive protein (CRP) was 15.2 mg/dl (normal range, <0.5 mg/dl). Routine serum chemistries, including angiotensin-converting enzyme and the total serum complement activity were within normal limits. The results of pulmonary function testing showed a reduction of vital capacity (VC) of 2.34 l (72.4% of predicted), carbon monoxide diffusing capacity (DLco) of 15.65 ml/min/mmHg (62.2% of predicted). The patient's chest X-ray findings revealed bilateral fine nodular shadows and ground-glass opacity (Fig. 1), and chest computed tomography (CT) scan revealed diffuse centrilobular nodules in both lung fields (Fig. 2). A bronchoalveolar lavage (BAL) from the right middle lobe, performed 4 days after the onset of symptoms, demonstrated an increase in the number of total cells ($71.4^{\times}10^4$/ml) with predominant lymphocytosis (50.7% of the total cell count), and eosinophilia (15.3%). The CD4/CD8 ratio of lymphocyte surface markers of the BAL fluid was 1.10. The BAL fluid was also cultured for bacteria, fungi, mycobacterium, viruses, and Legionella organisms; all cultures were negative for the growth of these organisms. The specimens obtained by transbronchial lung biopsy (TBLB) showed moderate lymphocyte infiltration into the interstitium and a moderate eosinophil infiltration in the alveoli. Although granuloma formation was not detected in the specimen obtained by TBLB, radiologic and BAL fluid findings were compatible with EAA. We then observed the patient while unmedicated. Her fever and cough were resolved, and the inflammatory reaction spontaneously diminished within a week. With the patient breathing room air, the arterial blood gas analysis improved; the pH value was 7.433, the $PaCO_2$ was 37.3 torr, and the PaO_2 was 93.3 torr. Peripheral eosinophilia also decreased to 5.3% (270/μl). The patient's return to her home immediately after the resolution of her symptoms and the normalization of her laboratory tests, was used as a challenge test. She experienced no return of her symptoms and her laboratory data revealed no remarkable change, indicating a result of the challenge test to be negative. Because the present patient agreed to undergo the challenge test, we then performed the test of HFC-134a inhalation, according to a previously reported method, which listed clinical (elevation of body temperature, development of respiratory symptoms or other symptoms) and laboratory findings (neutropenia, elevation of inflammatory data including ESR, CRP, reduction of PaO_2, VC, or DLco) (6). Considering that a severe reaction may be harmful to the patient, a mild provocation was performed. As a result, a dry cough developed and her body temperature was elevated by more than 1℃, as compared with that prior to exposure. Her peripheral white blood cell count increased from 4,000/μl to 9,900/μl. Her ESR increased from 10 mm to 21 mm per hour, and her CRP of 0.1 mg/dl increased to

1.0 mg/dl. Pulmonary function test worsened slightly; VC of 3.21 l (99.4% of predicted) to 3.13 l (96.9% of predicted), DLco of 19.35 ml/min/mmHg (76.9% of predicted) to 18.16 ml/min/mmHg (72.1% of predicted). According to the diagnostic criteria for a challenge test of EAA (6), HFC-134a was regarded as the etiologic agent. The patient was discharged, and she resigned from her job. She has been in good health without any symptoms, and has been followed-up regularly on an outpatient basis.

Discussion

EAA is an immunoreactive disease, in which recurrent exposure to an inhaled antigen leads to immunologic sensitization, with a predominantly cell-mediated lung response. Subsequent exposures then cause an inflammatory response in the lung that can produce symptoms of dyspnea, cough, and fever. The patient in the present case showed fever, hypoxia, diffuse pulmonary centrilobular nodules, and immediate complete resolution in a week without any medication. Although granuloma formation was not detected in the specimen obtained by TBLB, the BAL fluid showed lymphocytosis, and the results of a challenge test of HFC-134a inhalation allowed us to make a diagnosis of EAA caused by HFC-134a. Because it is known that HFC-134a exposure does not affect the CRP level (1), the elevation of CRP in our case was particularly significant.

In this case, BAL eosinophilia was shown, and the specimen of TBLB showed infiltration of eosinophils into the lung parenchyma. It is known that the cell profile of BAL fluid may be related to the time elapsed between the last antigen exposure and the obtaining of the BAL fluid (6). When the BAL fluid is obtained shortly after provocation (within a week), an increase in the relative number of eosinophils is observed. Therefore, BAL fluid eosinophilia in the present case may be regarded as a clinical course indicator of hypersensitivity syndrome. An additional consideration in this case is the significant increase in the number of eosinophils in the BAL fluid, when compared with that previously reported (6). The percentage of eosinophils in the BAL fluid was too low for eosinophilic pneumonia, and the radiological findings of this case differed from those of eosinophilic pneumonia. However, it was evident that eosinophils were increased in the alveoli and bronchiole. Although wheezing is reported to occur in some HP patients, it is not a characteristic sign of HP, and eosinophilic infiltration may account for the wheezing auscultated before admission, in similar fashion to the transient wheeze reported in the previous study (4).

The present case is noteworthy in several respects. First, to our knowledge, EAA caused by HFC-134a inhalation has not been previously reported. Although it is known that the acute and chronic toxicities of HFC-134a reported in animal studies are low (2) and no effects on lung function was seen in humans (3), our case indicates the possibility of pulmonary involvement in some individuals exposed to HFC-134a inhalation, because of specific host susceptibility. In addition, this case reveals not only a lymphocyte predominant pneumonitis but also a moderate BAL fluid eosinophilia. Although an increase in the relative number of eosinophils can be partially explained by the clinical course of HP, this case may have included an aspect of eosinophilic alveolitis. The detailed mechanism and the significance of marked eosinophil infiltration remain unknown, and further studies are thus needed.

Although a rare entity, additional cases may therefore continue to be encountered until the pubic becomes aware of these effects. HFC-134a inhalation should thus be added to the list of agents associated with HP with eosinophilia infiltration.

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