Eosinophilic bronchitis presenting with only severe dry cough due to bucillamine

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Introduction

Although an increasing number of drugs have been implicated in the aetiology of eosinophilic pneumonia characterized by the development of pulmonary infiltrates and peripheral blood eosinophilia, eosinophilic bronchitis without alveolitis due to some pharmacologic agents has not been reported. Bucillamine \([N-(2\text{-mercapto}-2\text{-methylpropionyl})\text{-L-\text{ cystenine}}]\) is a commonly used drug for treatment of rheumatoid arthritis in Japan, which has recently been added to the growing list of pharmacologic agents associated with infiltrative pulmonary lesions. A case of eosinophilic bronchitis induced by this drug presenting with only severe dry cough is described. The results of transbronchoscopic bronchial biopsy, a lymphocyte stimulation test, and a challenge test supported this diagnosis.

Case Report

A 60-year-old woman was admitted to our hospital on 19 June 1993 because of severe non-productive cough. The chest X-ray films on admission revealed no pulmonary infiltrates. Her peripheral blood showed marked eosinophilia. Additional history elucidated that the patient had been taking bucillamine, 200 mg daily, during the previous 10 weeks for treatment of rheumatoid arthritis.

On physical examination, body temperature was 35.8°C, blood pressure 130/68 mmHg, and pulse rate 70 beats min \(^{-1}\). On auscultation the respiratory sound was clear and forced expiratory rhonchi was not audible. No heart murmur was noted. There was no lymphadenopathy or oedema. Swan neck deformity of the fingers was seen.

On laboratory findings the arterial blood gas levels while breathing room air were: \(P_O_2\) 79.4 torr, \(P_CO_2\) 46.2 torr and pH 7.37. The white blood cell count was 7700 \(\mu\text{L}^{-1}\) with a differential of 54% segmented neutrophils, 0% stab, 17.9% lymphocytes, 6.7% monocytes, and 20.2% eosinophils. The haemoglobin level was 12.8 g dl \(^{-1}\) with a haematocrit value of 37.2%. The erythrocyte sedimentation rate was 10 mm hr \(^{-1}\). The C-reactive protein was 0.09 mg dl \(^{-1}\), IgE level 43 U ml \(^{-1}\), RA 0.0 IU ml \(^{-1}\), \(C_s\) 80.0 mg dl \(^{-1}\), \(C_4\) 30.0 mg dl \(^{-1}\) and CHs 40.6 U ml \(^{-1}\).

The following laboratory values were normal or negative: urinalysis, stool examination for ova and parasites, serum electrolytes, total protein, albumin, and mycobacterial and fungal cultures of the sputum.

The ECG revealed a normal sinus rhythm. The chest X-ray film and chest CT scan on admission revealed no pulmonary infiltrates. Pulmonary function test was almost normal; FVC (l) 2.75, \%FVC (%) 117-5, FEV\(_1\) (l) 2.3, \%FEV\(_1\) (%) 126-4, FEV\(_2\) (%) 83-6, TLC (l) 3.87, \%TLC (%) 103-8, \%RV (%) 77-3, \%RV TLC \(^{-1}\) (%) 74-6, \%DLCO (%) 96-0, \%DLco \(VA^{-1}\) (%) 101-1. Cell differential of the sputum showed eosinophilia.

Bronchoalveolar lavage (BAL) was performed using a total volume of 100 ml of sterile saline solution (28% recovery). Differential cell analysis revealed 82.0% alveolar macrophages, 12.0% lymphocytes, 1.0% neutrophils, 5.0% eosinophils, and an absolute total cell count of 1.4 x 10\(^5\) cells ml \(^{-1}\).

A transbronchoscopic bronchial biopsy (Plate 1) from the bifurcation of the right upper lobe bronchus and truncus intermedius showed eosinophil infiltration in the propria mucosae. The lymphocyte stimulation test (LST) with bucillamine was negative.
Regarding the clinical course suggestive of drug-induced bronchitis (eosinophilic bronchitis), the bucillamine therapy was discontinued. Within 6 days the severe cough was resolved and the peripheral eosinophils decreased to 4%. As the lymphocyte stimulation test with bucillamine was negative, the patient was challenged with bucillamine, 100 mg tablet administered every day, under informed consent. After 11 days, the patient developed a non-productive cough. The white blood cell count increased to 7200 μl⁻¹ with 7.4% eosinophils from 6900 μl⁻¹ with 4.6% eosinophils. Consequently, bucillamine was permanently discontinued, then the symptoms subsided and laboratory findings returned to normal.

**Discussion**

Eosinophilic pneumonia represents a clinical manifestation of an immunologic response or allergic reaction. A number of drugs have been reported to be the cause of pulmonary infiltrates (1-3), and non-steroidal, anti-inflammatory agents have been implicated as aetiologic factors for acute interstitial pneumonia (4-5). Cooper (6) described the clinical aspects and pathogenic mechanisms of cytotoxic and non-cytotoxic drug-induced pulmonary diseases.

In eosinophilic pneumonia, eosinophils may infiltrate not only the lung parenchyma but also the bronchial and the bronchus, when the parenchymal inflammation is severe (7). However eosinophilic bronchitis exists not only as a part of eosinophilic pneumonia. Although chronic desquamative eosinophilic bronchitis is considered to be characteristic of bronchial asthma, eosinophilic bronchitis without asthma (8) has been reported. Therefore a type of eosinophilic bronchitis without alveolitis, so-called 'drug-induced bronchitis', can exist as a manifestation of allergic reaction.

In our case, no pulmonary infiltrates on chest X-ray films and chest CT and normal pulmonary function including diffusing capacity support the lack of alveolitis.

To evaluate the bronchial reversibility, spirometry was performed before and after inhalation of 300 μg of salbutamol sulphate following intravenous injection of 250 mg of aminophylline. As the bronchodilator treatment did not significantly improve FEV₁ (from 2.32-2.39 l) or FVC (from 2.69-2.69 l), it was thought that the bronchomotor tone was not increased in the patient.

The airway responsiveness to methacholine was assessed according to the method by Cockcroft et al. (9). The provocative concentration required to cause a 20% fall from the baseline FEV₁ (PC₂₀) was 10 mg ml⁻¹.

Because the total cell count and percentage of lymphocytes of BALF were within the normal limit, mild eosinophilia of BALF is thought to have resulted from eosinophilic bronchitis rather than from eosinophilic pneumonia. The specimens of transbronchoscopic bronchial biopsy demonstrated eosinophilic infiltration in the bronchial mucosa.

Thus, eosinophilic bronchitis in our case should be distinct from the chronic desquamative eosinophilic bronchitis in bronchial asthma, for lack of 'bronchial hyperresponsiveness' and 'bronchial reversibility', which are the fundamental factors of bronchial asthma (7). Therefore, eosinophils infiltrated in the bronchial mucosa may be necessary but not sufficient to cause asthma.

We believe that, in the present case, a bronchial hypersensitivity reaction to bucillamine resulted in the eosinophilic bronchitis without alveolitis presenting with severe non-productive cough and blood eosinophilia. Upon cessation of bucillamine therapy there was clinical improvement of the illness. Rechallenge with bucillamine produced similar symptoms and eosinophilia.

Although extrapulmonary complications of bucillamine are well known, few cases of bucillamine-induced pneumonitis have been reported (10-12) and there is no reported case of eosinophilic bronchitis without alveolitis due to this agent.

We described the first case of eosinophilic bronchitis without bronchial smooth muscle contraction nor alveolitis presented with severe non-productive cough caused by bucillamine.
References