IL-5 Predominant in Bronchoalveolar Lavage Fluid and Peripheral Blood in a Patient with Acute Eosinophilic Pneumonia

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We describe an acute eosinophilic pneumonia (AEP) patient with bronchoalveolar lavage fluid (BALF). Eosinophil cell number (47%), content of interleukin (IL)-5 (8.22×10^2 pg/ml) and eosinophil cationic protein (9.25 μg/ml) were high in BALF. No eosinophilia was seen in peripheral blood on admission; however, content of IL-5 was 9.47×10^2 pg/ml. After methylprednisolone pulse therapy, he improved rapidly with a reduction in eosinophil cell number (7%) and the content of IL-5 (<100 pg/ml) in BALF. However, a high content of IL-5 (6.9×10^2 pg/ml) and transient eosinophilia (17.5%) were seen in peripheral blood. It is important to distinguish between AEP and infectious pneumonia, because of the differing treatments. If the diagnosis of AEP is doubtful, BALF should be performed early.

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Key words: eosinophils, cytokine, bronchoalveolar lavage, respiratory distress

Introduction

Eosinophilic pneumonia has been reported as pulmonary infiltration of the lung by eosinophils that may or may not be accompanied by infiltration in the peripheral blood (1). The etiology of eosinophilic pneumonia has been described by helminthic infections (2), drugs (3), environmental exposure (4), and collagen diseases (1). The clinical course of these diseases is chronic, and is characterized by persistent or recurrent pulmonary infiltration.

On the other hand, it has been reported that acute eosinophilic pneumonia (AEP) is characterized by severe hypoxemia, diffuse infiltrates and an increased cell number of eosinophils in bronchoalveolar lavage (BAL) and/or lung biopsy specimens (5, 6). We describe acute eosinophilic pneumonia with clinical features, BAL fluid (BALF) and follow-up study. Also, we measured eosinophil active cytokines [IL-3, granulocyte/macrophage colony-stimulating factor (GM-CSF) and IL-5], and eosinophil cationic protein in BALF. This is the first report of measurement of cytokine contents of BALF and serum in acute eosinophilic pneumonia.

Case Report

A 21-year-old Japanese man was admitted to our hospital because of acute respiratory failure. He had no history of atopic disease or bronchial asthma. Further, his history revealed that he was indeed healthy prior to this illness. He was an athlete in college, and began to smoke two weeks before admission. During this time he noticed dry cough, shortness of breath, and fever (37.4°C). He visited a physician and was diagnosed as having pneumonia, and was administered minocycline (200 mg/day). On the next day, he complained of severe dyspnea and was referred to our hospital. Physical examination revealed severe respiratory failure. His temperature was 37.6°C, pulse rate of 84/min, blood pressure of 130/70 mmHg, respiration rate of 40/min in room air, and his lips and nails showed cyanosis. Cardiac examination was entirely within normal limits, and auscultation of his lungs revealed no rales. His abdomen was benign, and without organomegaly, and his extremities revealed neither clubbing nor edema. The neurological examination was intact. The peripheral white blood cell count was 16,300/μl, hematocrit was 45.2%, and platelet count was 21.1×10^9/μl. The differential white cell count was 16% bands, 72% neutrophils, 5% lymphocytes, 3% monocytes, 1% basophils, and 3% eosinophils. Routine serum chemistries and
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Fig. 1. Chest radiograph (a) and chest CT, scans (b, c) on admission. Diffuse bilateral infiltrates are found in middle lung fields and bilateral pleural effusions.

urinalysis were within normal limits. A room-air arterial blood gas analysis revealed a pH of 7.42, PaCO₂ of 39.7 mmHg, PaO₂ of 39.6 mmHg, and a saturation of 72.5%. The calculated alveolar-arterial oxygen difference was 49.2 mmHg. Gram and acid-fast stains of the sputum were negative. Cold agglutinins were negative, and serum IgE was 207 IU/ml. The admission chest radiograph (Fig. 1a) and CT scans (Fig. 1b and c) showed diffuse bilateral pulmonary infiltrates and bilateral pleural effusions. Bronchofiberscopy (BFS) on the second day revealed a reddish and edematous condition on the tracheal wall. Bronchoalveolar lavage (BAL) (50 ml × 3 times, recovery rate: 67%) yielded a brownish cloudy fluid with a cell number of 2.5×10⁶/ml. The differential count was 32% macrophages, 17% lymphocytes, 3.5% neutrophils, and 47.5% eosinophils. Eosinophil cationic protein (ECP) in BALF, measured in duplicate by the use of radio-immunoassay kits (¹²⁵I-ECP RIA kit, Pharmacia Diagnostics, Uppsala, Sweden), was 9,250 ng/l (normal controls; 12.3±6.1 ng/l). As shown in Fig. 2a and b, we

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<td>GM-CSF</td>
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Eosinophil survival (%)

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<tr>
<th>Antibody</th>
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<tr>
<td>GM-CSF</td>
<td>rhIL-5 (100 µg/ml): 93%</td>
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<td>rhIL-5 (0 µg/ml): 19%</td>
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Eosinophil survival (%)

Fig. 2. Neutralization experiments of serum and BALF by monoclonal antibodies against cytokines in eosinophil survival assay. Serum (10% v/v) and BALF (10% v/v) are treated with antibodies (1 µg/ml) for 1 hour at room temperature and cultured with freshly isolated human healthy controls’ eosinophils (2.5×10⁶) and Habri-Care medium (American type culture collection, USA) supplemented with 10% inactivated defined calf serum (HyClone Laboratories Inc., USA). Eosinophil viability with and without rhIL-5 was 78% and 10% in Fig. 2a and 93% and 19% in Fig. 2b, respectively. Eosinophil viability was measured on day 4. Data are presented as the mean±SEM.

Monoclonal antibodies (anti-IL-3, anti-IL-5 and anti-GM-CSF) were donated by G.J. Gleich (Mayo Clinic, Rochester, MN, USA). *p<0.05 Significantly different with anti-IL-5 monoclonal antibody and without antibody. IL-3: interleukin 3, rhIL-5: recombinant human interleukin 5, GM-CSF: granulocyte/macrophage colony-stimulating factor.
examined eosinophil survival assay in BALF and serum which could measure eosinophil active cytokines (IL-3, IL-5 and GM-CSF) as reported before (7). Anti-IL-5 monoclonal antibody (mAb) significantly neutralized eosinophil survival in BALF and serum. Furthermore, the contents of IL-5 in BALF and serum by ELISA (8) were 8.22x10^2 pg/ml and 9.47x10^2 pg/ml, respectively. The content of IL-5 in normal healthy control serum was <100 pg/ml. On the 4th day after admission, a pulmonary function test revealed a mixed respiratory disorder (%VC: 50.1%, FEV1: 72.7%) and decreased %DLco (46.4%).

On the 6th day after admission, methylprednisolone pulse therapy (500 mg intravenously every 12 hours) was initiated for 3 days. The patient improved rapidly, with normalization of his resting room-air arterial blood gas determinations within 5 days after treatment. On the 6th day after treatment, the white cell count was 6,910/μl, with 6% bands, 35% neutrophils, 29.5% lymphocytes, 10% monocytes, and 7% eosinophils. On the 16th day after treatment, the white cell count was 6,490/μl, with 4% bands, 57% neutrophils, 31.5% lymphocytes, 12.5% monocytes, and 3% eosinophils (Fig. 3). Pulmonary function test on the 10th day after treatment was also revealed to be within normal limits. Bronchofiberscopy on the 15th day after treatment revealed normal endobronchial anatomy and the BALF cell number was 8.2x10^4/μl, with 76.6% macrophages, 16.4% lymphocytes, and 7% eosinophils. The contents of IL-5 in BALF and serum were <1.0x10^2 pg/ml and 6.9x10^2 pg/ml, respectively. The chest radiograph and CT scans at discharge showed no infiltrate shadow. On the third week after discharge, he was asymptomatic and also had a normal chest examination and radiograph. The third month after discharge BFS revealed normal endobronchial anatomy. The cell number and differential count of BALF showed no significant difference compared with normal subjects. The level of IL-5 in serum reduced to within the normal range.

Discussion

We describe a patient with acute respiratory distress characterized by a slight fever, severe hypoxemia, dry cough, diffuse pulmonary infiltrates and bilateral pleural effusions, increased number of eosinophils in bronchoalveolar lavage, no evidence of infection, no history of atopic disease, and complete resolution of all abnormalities after the administration of corticosteroid pulse therapy, and no recurrence. Allen and colleagues previously reported (6) that acute eosinophilic pneumonia (AEP) is distinct from chronic eosinophilic pneumonia (CEP). Chronic eosinophilic pneumonia is an idiopathic syndrome characterized by pulmonary and peripheral blood eosinophilia infiltrates on radiography, and symptoms last longer than two weeks. Typically it affects middle-aged, atopic women. The patients with CEP present symptoms that have lasted an average of 7.7 months. The present case differed from CEP in several ways. First, he did not fit the demographic picture. Secondly, he had symptoms for only one day before respiratory failure developed. Furthermore, our patient was febrile, and had a low partial pressure of oxygen. Thirdly, he neither required prolonged corticosteroid therapy nor had evidence of recurrent disease during the follow-up period after therapy.

The distinguishing feature of AEP is that it is short, less than a week, and the condition progresses rapidly to acute respiratory failure. All AEP patients are reported to have respiratory distress, tachypnea, and pronounced hypoxemia (PaO2: 60 mmHg) and someone required mechanical ventilation (6). The pneumonia resolves within 1–8 days with steroid therapy and no recurrences have been reported (5, 9, 10).

The pathophysiological mechanism of AEP remains obscure; however, it may be due to a hypersensitivity in the lung. The production of IL-5 presumably derived from CD4+ cells in the lung seems to be much higher than that in serum, because BALF was diluted with saline (50 ml x 3 times washing). Elevated IL-5 in the lung may initiate recruitment of eosinophils (11), increase eosinophil survival (12), and release chemical mediators from eosinophils (13) which increases the permeability of the vessels. Elevated IL-5 in BALF was immediately reduced by the treatment. However, it is interesting that the levels of IL-5 in the serum remain high before and after treatment. These data suggest that IL-5 producing cells are still present after the treatment. In the future it will be interesting to study the mechanism for eosinophil migration from the peripheral blood stream to lung.

Finally, it is important to distinguish between acute eosinophilic and infectious pneumonias, because of the differing treatments. When the diagnosis of AEP is not confirmed, BALF should be performed early.

References


Fig. 3. Cell number of peripheral blood in clinical course.


