Eosinophilic Pneumonia (EP) Associated with Rheumatoid Arthritis in which Drug-Induced Eosinophilic Pneumonia could be Ruled Out

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Abstract

A 72 year-old man. He was diagnosed with rheumatoid arthritis in 2002. In January 2005 he noted productive cough and fever; he was diagnosed as eosinophilic pneumonia (EP). We discontinued administration of bucillamine and methotrexate and started to treat with oral prednisolone 30 mg daily. To rule out drug-induced EP, prednisolone was tapered by 10 mg per week. Consolidation occurred in the right lower lobe when prednisolone was decreased to 5 mg daily. After increasing the dose of prednisolone to 30 mg daily again, consolidation was promptly resolved. It was considered to be important to rule out drug-induced EP.

Key words: chronic eosinophilic pneumonia, rheumatoid arthritis, drug-induced eosinophilic pneumonia

Introduction

Rheumatoid arthritis (RA) is characterized by arthritis starting from synovitis, spreading whole articular inflammation, and breaking articular cartilage and bone. RA is known to be complicated with subcutaneous nodules, ocular lesion, peripheral neuropathy, and lung and pleural diseases. Lung diseases associated with RA are classified into usual interstitial pneumonia pattern, bronchiolitis obliterans organizing pneumonia pattern, nonspecific interstitial pneumonia pattern, and eosinophilic pneumonia (EP). However, EP associated with RA is rare. We encountered a case of EP and eosinophilic pleural effusion associated with RA and report it here.

Case Report

The Case, a 72 year-old man with smoking history of about 40 pack-year was diagnosed as RA at an orthopedics clinic of a local hospital in December 2002. Thereafter, he had been treated with bucillamine, methotrexate, and prednisolone (PSL) due to onset of rheumatoid arthritis. In January 2005, he noted dyspnea on exertion, productive cough, and fever. Chest radiography showed consolidation in his left lower lung and bilateral pleural effusion and he was diagnosed having pneumonia. In spite of being treated with antibiotics, his symptoms and signs did not completely improve and relapsed two weeks after the antibiotic treatment. He was referred to our hospital for the diagnosis and treatment of the illness in April 2005.

On physical examinations, he was emaciated. His body temperature was 37.5°C. Early inspiratory rhonchi were heard over both lung fields. Pitting edema was found on both lower legs. Swan neck transformations were found on both 1st fingers, and both 2nd-5th fingers showed ulnar deviation. There was subluxation in his foot. Yellow nails, which were thought to due to bucillamine, were found on both hands and toes.

In the radiological examinations, chest X-ray showed emphysematous change, bilateral pleural effusion, and consolidation in the left mid to lower lung field (Fig. 1). Chest computed tomographic (CT) scan showed non-segmental consolidation in the left S3 and increasing density in diffuse...
Figure 1. Chest radiography showed emphysematous change, bilateral pleural effusion, and consolidation in the left mid to lower lung field.

The laboratory data showed the following (Table 1): white blood count was 3,600/μl, with neutrophils 73% and eosinophils 2%. CRP was 6.6 mg/dl and ESR was 66 mm in one hour. On arterial blood gas analysis, PaO₂ was 54.1 Torr under inhaling 3 l/min oxygen by nasal tube and there was no increase of PaCO₂. The serum markers of interstitial pneumonia, KL-6, SP-D, and SP-A, were normal values. All of the serum markers of rheumatoid arthritis showed a very high score; RF 543 IU/ml, MMP3 >800 ng/ml, and CA-RF 297.6 AU/ml. Antibody titers of Mycoplasma, Chlamydia, and viruses were negative on admission or two weeks later. β-D glucan level in the serum was within normal limits. These results suggested that infection of the examined pathogens was considered to be neglected. IgE was not increased at 5 IU/ml, and all examined IgE-RAST was negative.

In the results of the respiratory Function tests (Table 1), there was mild obstructive impairment, FEV₁/FVC ratio 72.4% and FEV₁ 1.82 liters (% of predicted value 84.7%), and restrictive change, % of predicted value for FVC 73.4% and % of predicted value for RV 56.7%. Lung diffusibility was also reduced, DLCO 3.65 ml/min/mmHg (%predicted level was 16.4%) and DLCO/VA 1.19 ml/min/mmHg/l. Airway reversibility test showed that the FEV₁ was increased by 22.7% and 440 ml after inhalation of 0.3 mg salbutamol sulfate. Provocative concentration of methacholine causing a 20% fall in FEV₁ (PC20-FEV₁) was 4.99 mg/ml, indicating mild accentuation of bronchial responsiveness. The diagnosis of bronchial asthma was reached on the basis of these results of pulmonary function tests.

Bronchoalveolar lavage (BAL) was conducted from the left B3. On the findings of BAL fluid, white blood cells demarcation showed that eosinophils made up 34.5% (Table 1). Transbronchial lung biopsy was not conducted due to exacerbation of the respiratory failure.

Based on pleural effusion puncture examinations, the complication of eosinophilic pleural effusion was defined; eosinophil in pleural effusion 19%. Although RF in pleural effusion was 539 IU/ml, LDH was not increased and sugar was not decreased. Those findings were not typical of pleural effusion associated with RA.

In the clinical course a diagnosis of chronic EP was made on the above-mentioned examinations. Because some cases of bucillamine-induced EP have been reported, we discontinued administration of bucillamine and methotrexate and started to treat with oral PSL 30 mg daily. Four weeks later, consolidation on the left S3 and pleural effusion had disappeared. To rule out drug induced EP PSL was tapered by 10 mg per week, and then pleural effusion relapsed when PSL was decreased to 10 mg daily and consolidation occurred in the right lower lobe when PSL was decreased to 5 mg daily. Although we conducted BAL from left B3 at the time of recurrence, we could not judge whether pneumonia was EP or another kind of pneumonia due to the small volume of BAL fluid collected. Arthralgia on both hands also appeared. After increasing the dose of PSL 30 mg daily again, consolidation and pleural effusion were promptly resolved (Fig. 3). Although there was no proof, we thought it was the recurrence of EP from the clinical course.

The above-mentioned examinations and clinical course suggested that EP was associated with RA but not induced by any drugs. Eosinophilic pleural effusion was also considered to be a complication of EP because there was no other possible cause of eosinophilic pleural effusion.

Discussion

It is well known that RA complicates lung diseases and some papers reported that 40 to 60% of patients with RA have complication of lung diseases including bronchial and bronchiolar diseases based on examinations of high resolution CT (1-7). Lung diseases associated with RA are classified into usual interstitial pneumonia pattern, bronchiolitis obliterans organizing pneumonia pattern, and nonspecific interstitial pneumonia pattern.

EP associated with RA is very rare; only seven case reports have been published since the first report was published in 1980 (8-14). However, the case reported by Payne and Connellan in 1980 was diagnosed based on only radiological findings without histological or BAL findings, therefore the diagnosis of EP seems uncertain (14). Yousem et al reported that there was one case of EP in forty autopsy cases with RA complicated with lung diseases (15). The length from diagnosis of RA, sex, rheumatoid factor, and eosinophil counts in peripheral blood did not correlate with complication of EP. As six of eight cases with EP including
Figure 2. Chest computed tomographic scan showed non-segmental consolidation in the left S3 and increasing density in diffuse lung fields.

Table 1. Laboratory Data

<table>
<thead>
<tr>
<th>Blood examination</th>
<th>Blood gas analysis</th>
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<tbody>
<tr>
<td>WBC 3600 /μl</td>
<td>Neutrophils 73%</td>
</tr>
<tr>
<td>BUN 20 mg/dl</td>
<td>Creatinine 0.71 mg/dl</td>
</tr>
<tr>
<td>AST 18 IU/l</td>
<td>ALT 12 IU/l</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>ALD 265 IU/l</td>
</tr>
<tr>
<td>O2 31/min</td>
<td>pH 7.416</td>
</tr>
<tr>
<td>CO2 35 Torr</td>
<td>PaO2 54.1 Torr</td>
</tr>
<tr>
<td>HCO3− 22 mmol/l</td>
<td>PaCO2 35 Torr</td>
</tr>
</tbody>
</table>

Respiratory Function tests

| VC 2.48 L | FRC 2.18 L | DLCO 3.65 ml/min/mmHg |
| %VC 73.4% | %FRC 67.3% | %DLCO 16.4% |
| FVC 2.48 L | RV 1.01 L | DLCO/VA 1.19 ml/min/mmHg/L |
| %FVC 73.4% | %RV 56.7% | %DLCO/VA 27.9% |
| FEV1.0 1.82 L | TLC 3.56 L | |
| %FEV1.0 84.7% | %TLC 71.1% | |
| FEV1.0% 73.4% | RV/TLC 28.4% | |

Bronchoalveolar lavage (Lt. B3)

Mac 30.5%, Lym 19.5%, Neu 15.5%, Eos 34.5%

the present case had accompanying exacerbation of joint pain, it is likely that poor control of rheumatoid arthritis is associated with the complication of EP.

As there is the problem that the possibility of drug-induced EP could not have been excluded in the cases previously reported cases, the present case is the first case which ruled out drug-induced EP. In addition, there have been no reports that showed the complication of eosinophilic pleural effusion.

Among those previously reported cases, the case reported by Kikawada et al (11) was treated with PSL 40 mg daily after the diagnosis of EP. PSL was tapered and stopped within one month, and then EP recurred about three years later. Exacerbation and improvement of EP was repeated after that time. That case indicates that EP associated with RA often relapses in the case of rapid tapering of PSL or inadequate dosing of PSL as well as idiopathic EP. Decreasing PSL to 10 mg daily rapidly in order to rule out drug-induced EP resulted in relapse of EP in their case.

There are many reports about antirheumatic drug-induced eosinophilic pneumonia with drugs such as gold (16-18), methotrexate disease modifying anti-rheumatic drugs (DMARDs) (19, 20), and nonsteroidal anti-inflammatory drugs (NSAIDs) (21). We had no proof of recurrent EP. Be-
cause we used only an intermediate dose of PSL and did not use antibiotics, the clinical course suggested that there was the recurrence of EP. However drug-induced pneumonia was not completely ruled out due to the small volume of BAL fluid collected during the recurrence. If EP complicates with patients with RA, it is necessary to diagnose carefully keeping in mind drug-induced EP as well as other types of interstitial pneumonia.

Conclusions

We reported the experience treating a rare case of EP associated with RA. It is precious case because this is the first report in which drug-induced EP was ruled out and eosinophilic pleural effusion was detected.

References