Minocycline-Induced Acute Eosinophilic Pneumonia: Controversial Results of Lymphocyte Stimulation Test and Re-challenge Test

Emiko Ono¹, Eishi Miyazaki¹, Osamu Matsuno², Shin-ichi Nureki¹, Toshiyuki Okubo¹, Masaru Ando¹ and Toshihide Kumamoto²

Abstract

We report an instructive case of minocycline-induced eosinophilic pneumonia confirmed by re-challenge test, in which a preceding lymphocyte-stimulation test indicated acetaminophen as the etiologic agent. A 55-year-old woman developed high fever and lung infiltrates with pulmonary eosinophilia after exposure to minocycline, acetaminophen, theophylline and procaterol. All of the medicines were discontinued, resulting in prompt improvement. The lymphocyte stimulation tests provided a positive result for acetaminophen, but not for the other medicines; however, a negative result was given by a re-challenge test with acetaminophen. In contrast, symptoms and hypoxemia reappeared when minocycline was re-administered. We would like to emphasize that lymphocyte stimulation test results need to be carefully interpreted for individual drugs.

Key words: minocycline, acetaminophen, acute eosinophilic pneumonia, lymphocyte stimulating test, re-challenge test

(DOI: 10.2169/internalmedicine.46.6235)

Introduction

A significant number of drugs have been associated with eosinophilic pneumonia. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly reported drugs (1-4). The diagnosis of drug-induced eosinophilic pneumonia is supported by a temporal relationship to a drug, and the condition usually resolves with removal of the agent; however, it is not easy to determine the etiologic agent because antibiotics and NSAIDs are often co-administered. As re-challenge may induce serious lung injury, lymphocyte-stimulation test (LST) is widely used in Japan for the diagnosis of drug-induced lung diseases.

Here, we report a case of minocycline-induced acute eosinophilic pneumonia (AEP). This case demonstrated a positive result of LST against acetaminophen but not minocycline, whereas a challenge test was positive by minocycline but not acetaminophen.

Case Report

A 55-year-old woman visited a nearby clinic with a low-grade fever and non-productive cough. The patient had smoked 10 cigarettes daily for 35 years. Therapy was initiated with minocycline 200 mg daily, acetaminophen 600 mg daily, theophylline 200 mg daily and procaterol 100 μg daily. Her symptoms were reduced in a few days, but she developed high fever, non-productive cough and dyspnea seven days after the administration of these drugs. Her chest radiograph showed interstitial shadows in the bilateral lungs (Fig. 1), and she was therefore transferred to our hospital. At the time of admission, her blood pressure was 100/55 mmHg, pulse was 90 beats/min, temperature was 38.7°C, and respiratory rate was 16 breaths/min on room air. Fine inspiratory crackles were heard over the bilateral lung fields. Cardiac examination was normal.

The peripheral white blood cell count was 34,060/mm³, with 93.0% neutrophils, 3.1% lymphocytes, and 0.4%...
Figure 1. Chest X-ray at presentation shows reticulo-nodular shadow in both lung fields.

Figure 2. Chest computed tomography scan shows interlobular septal thickening and ground-glass opacity accompanied with low attenuation areas.

eosinophils. C-reactive protein was 15.2 mg/dl. Serological tests for common agents of atypical pneumonia were negative. Arterial blood gas determination revealed a pH of 7.508, PaO₂ of 61.6 Torr, and PaCO₂ of 37.5 Torr. Chest computed tomography (CT) scans showed interlobular septal thickening and ground-glass opacity in the bilateral lung fields in concordance with scattered low attenuation areas (Fig. 2). Bronchoalveolar lavage (BAL) yielded a cell count of 6.1×10⁷/ml, with 26.4% eosinophils, 5.1% lymphocytes, and 0% neutrophils. Cultures were negative. It was noticed that from day 11, her blood eosinophil count had progressively increased to a peak value of 4,442/mm³ at day 14.

All the medicines were stopped, which led to prompt improvement of symptoms, hypoxemia and pulmonary infiltrates. LST was performed against the four agents, including minocycline, resulting in significant proliferation of lymphocytes only for acetaminophen with the stimulation index of 4.4 (Table 1). In addition to acetaminophen, minocycline was still suspected as a cause of AEP because minocycline can induce eosinophilic pneumonia (1-3). Hence, we obtained the informed consent from the patient and her family to perform a re-challenge test. First, we administered acetaminophen; 20 mg on day 1st, 200 mg on day 2nd, and 600 mg daily for the following three days, when no reaction was seen. Next, she was prescribed minocycline. Ten hours after the re-challenge test with 100 mg of minocycline, fever exceeding 38°C and non-productive cough were induced. In addition, PaO₂ decreased from 83.5 Torr to 57.0 Torr. Moreover, twenty-four hours after the re-challenge, BAL disclosed refractory pulmonary eosinophilia (3,000/mm³, 40% of total cells). From the above results, we concluded that the AEP in this case was induced by minocycline.

**Table 1. Summary of Results with Lymphocyte Stimulation Test, Skin Patch Test and Re-challenge Test**

<table>
<thead>
<tr>
<th></th>
<th>LST (S.I)</th>
<th>Patch test</th>
<th>Re-challenge test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline</td>
<td>1.42</td>
<td>0x0/0x0</td>
<td>positive</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>4.41</td>
<td>0x0/0x0</td>
<td>negative</td>
</tr>
<tr>
<td>Theophylline</td>
<td>1.44</td>
<td>0x0/0x0</td>
<td>N.D.</td>
</tr>
<tr>
<td>Procatrol</td>
<td>1.04</td>
<td>0x0/0x0</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

Abbreviations; LST, lymphocyte stimulation test; S.I., stimulation index; N.D., not done

Eosinophilic pneumonia in this case, exhibiting acute onset, hypoxemia, interlobular septal thickening with ground-glass opacity, and prominent pulmonary eosinophilia, were indistinguishable from idiopathic AEP, first described by Allen et al (5). There was however a clear-cut temporal relationship between the expression of respiratory symptoms and exposure to the medicines. In addition, cessation of the medicines rapidly led to the definite improvement. In the present case, the etiologic agent was finally determined to be minocycline by a re-challenge test. Minocycline is known to induce several types of lung injury (1-3). According to the literature there have been 15 definite cases which were confirmatively diagnosed by a provocation test. Six cases among them were given a diagnosis of eosinophilic pneumonia. Interestingly, LST was performed in 14 patients, resulting in negative results in all patients examined, as well as in the present case. It is thus indicated that LST is not suitable for making a diagnosis of any type of minocycline-induced pneumonitis.

Acetaminophen has been shown to induce AEP (4). We
found 10 reported cases of acetaminophen-induced pneumonitis, most of which were reported from Japan. Only one case was confirmed by the re-challenge test, but the remaining 9 cases were diagnosed on the basis of LST results without re-challenge. In the present case, we encountered a false-positive LST result against acetaminophen. The problem of false positivity in the LST has been shown in medical herbs, which are occasionally determined to be etiologic agents of drug-induced pneumonitis on the authority of LST results (6).

In this case, we encountered a discrepancy between the results of LST and re-challenge test. The present case indicates that LST results should be carefully interpreted for each individual candidate drug. When the correct diagnosis of the etiologic agent among minocycline-containing regimens is necessary, a re-challenge test should be considered.

References


© 2007 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html