Clinical Evaluation of 12 Cases of Antimicrobial Drug-induced Pneumonitis

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The diagnosis of drug-induced pneumonitis is generally difficult, and it is made clinically by Tamura’s criteria. We experienced 12 cases (7 definite and 5 possible cases) of antimicrobial drug-induced pneumonitis (one of case was the first case caused by carbapenem). Symptoms such as fever (11/12), cough (10/12) and dyspnea (10/12) and laboratory data such as eosinophilia (7/12), elevation of IgE (4/6) and hypoxia (11/12) were commonly seen in these patients, although they were not specific. Lymphocyte stimulation test (5/11) and provocation test (4/8) were quite suggestive of drug allergy. Bronchoscopy has been used for confirmation of pneumonitis. Transbronchial lung biopsy revealed alveolitis (4/9) or alveolar fibrosis (3/9), and bronchoalveolar lavage showed lymphocytosis (6/6) and depression of OKT4/T8 ratio (3/5). The combination of bronchoscopic and immunological examinations were more confirmative for diagnosis.

Key words: Antibiotics, Pneumonitis, Bronchoalveolar lavage

Numerous antimicrobial agents have been developed due to the increasing need for treatment of infectious diseases. Adverse reaction such as liver or renal damage is easily recognized, but lung damage is often underestimated or disregarded because of the difficulty of diagnosis. The disregard might be dangerous for the patients of bacterial pneumonia treated with antimicrobial agents due to the incidental complication of drug-induced pneumonitis. The primary clue for its diagnosis is the close relationship of the timing between drug administration and the appearance of symptoms and signs. Twelve patients with antimicrobial drug-induced pneumonitis were studied by transbronchial lung biopsy, bronchoalveolar lavage, or lymphocyte stimulation test.

MATERIALS AND METHODS

1. Patients

Twelve patients (7 men and 5 women, 27–79 years old) who were treated with antimicrobial drugs due to upper respiratory tract infection (4 patients), chronic obstructive pulmonary diseases (2 patients), pneumonia (1 patient), pulmonary tuberculosis (1 patient), renal abscess (1 patient), skin abscess (1 patient) and prophylactic administration (1 patient) were admitted to Nagasaki University Hospital from 1984 to 1987 for further examination of abnormal shadows. They were diagnosed as drug-induced pneumonitis according to Tamura’s criteria (1). The cases which were definite showed a) occurrence of pneumonitis within 1–6 weeks after drug administration, and b) positive drug sensitivity tests such as drug-induced lymphocyte stimulation test or skin reaction test, or a) and c) positive provocation test. The cases labeled as possible cases showed a) and d) symptoms such as fever, cough, dyspnea and skin eruption, or a) and e) eosinophilia or leukocytosis in peripheral blood.
2. Clinical examination

Peripheral blood (leukocytes, eosinophils), liver function tests (GOT, GPT, LDH), immunological tests (IgG, IgE, PPD skin test), arterial blood gas, pulmonary function tests (% vital capacity, % forced expiratory volume one, pulmonary diffusion capacity for carbon monoxide) and chest roentgenogram were examined on admission.

3. Fiberoptic examination

By employing fiberoptic bronchoscopy, broncho-alveolar lavage (BAL) or transbronchial lung biopsy (TBLB) were performed in the lobe of the lesion. The patients in whom BAL was performed were all non-smokers. While the bronchoscopy tube was wedged into the bronchus, 50 ml of saline was injected followed by aspiration; this procedure was repeated three times. After BAL fluid was centrifuged, the number of cells was counted and flow-cytometry was used to analyze OKT4 and OKT8 positive cells. The TBLB specimen was fixed in 10% formaldehyde and stained using hematoxylin eosin.

4. In vitro and in vivo tests for drug allergy

Peripheral blood was drawn and centrifuged on Ficoll Conray to separate lymphocytes. 1 x 10^6 lymphocytes were incubated with various concentrations (1–500 μg/ml) of drugs serially diluted in RPMI 1640 at 37°C for 72 hours. ³H-thymidine (0.25 uCi) was added and incubated for 16 hours. Lymphocyte stimulation test was measured using a liquid scintillation counter. Stimulation index was calculated as follows; the ratio of the maximum count of drug containing lymphocytes divided by the count of lymphocytes only. A ratio more than 1.8 was judged to be positive.

Skin prick test was done by injection of a 1:10 to 1:1000 concentration of the normal dose of antimicrobial drugs diluted with normal saline. The wheal was compared with the that of the control (saline) or to that of normal people; a wheal diameter of tested eruption twice bigger than the control was judged to be positive.

Provocation test was performed by administering the typical dose of antimicrobial agents with careful observation. Symptoms (cough, dyspnea, fever, general malaise, shaking chill), signs (crepitation, tachycardia, cyanosis), laboratory data (erythrocyte sedimentation rate, CRP, leukocyte, eosinophil), chest roentgenogram, and respiratory function test (PaO₂, vital capacity, forced expiratory volume one and pulmonary diffusion capacity for carbon monoxide) were examined. Any change in these data compared to before challenge was judged to be positive.

RESULTS

1. Clinical features

Various antimicrobial agents were administered to these patients (Table 1). Fever was observed in 11 patients out of 12 (91.7%), eruption in 4 patients (33.3%), cough in 10 patients (83.3%), and dyspnea in 10 patients (83.3%). Fine crackle was noticed in 11 patients. It took 1 to 26 days from the beginning of drug administration until the onset of drug-induced pneumonitis. Five patients were treated with steroids, but 2 of them died due to the aggravation of underlying disease or pneumonia. The rest of the patients were cured even by the discontinuation of drug administration.

2. Clinical data

Leukocytosis was noticed in 4 patients out of 12 (33.3%) and eosinophilia (more than 500/mm³ or 10%) in 7 (58.3%) (Fig. 1). GOT (<39 μu/ml) and GPT (<33 μu/ml) were elevated in 2 patients (16.7%) and LDH (<435 u/ml) was elevated in 4 patients out of 11 (36.4%). IgG (<2010 mg/dl) was not elevated in all patients but IgE (<300 iu/ml) was elevated in 4 out 6 (66.7%). PPD skin test was negative in 4 out of 7 (57.1%). Hypoxia (<80 Torr) was observed in 11 out 12 patients (91.7%). Ventilation impairment was presented and the incidence of restrictive type (%VC: < 80%), obstructive type (FEV 1.0%: < 70%) and combined type were 33.3%, 11.1% and 22.2%, respectively. Diffusion capacity (DLCO/VA: >3.0) was decreased in 4 out of 9 patients (44.4%).

Chest roentgenogram of drug-induced pneumonitis was evaluated. The distribution of the shadow was bilateral except in one patient and the shadow was either acinar (9 patients) or alveolar (8 patients) (Fig. 2). Three patients showed pleural effusion. The shadow disappeared within 2 to 60 days.
Table 1. Antimicrobial drugs which induced pneumonitis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Drugs</th>
<th>Dose (g)</th>
<th>Days until onset</th>
<th>Case</th>
<th>Drugs</th>
<th>Dose (g)</th>
<th>Days until onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>minocycline (oral)</td>
<td>0.1</td>
<td>7.0</td>
<td>9</td>
<td>ofloxacin</td>
<td>0.3</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bacampicillin (oral)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>clindamycin (DIV)</td>
<td>1.2</td>
<td>3.0</td>
<td>10</td>
<td>cepiramide (DIV)</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>rifampicin (oral)</td>
<td>0.45</td>
<td>20.0</td>
<td></td>
<td>minocycline (oral)</td>
<td>0.8</td>
<td>7.0</td>
</tr>
<tr>
<td>4</td>
<td>imipenem /cilastatin (inhalation)</td>
<td>0.3</td>
<td>1.0</td>
<td></td>
<td>cefaclor (oral)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>ampicillin (oral)</td>
<td>1.5</td>
<td>7.0</td>
<td></td>
<td>cefmenoxime (DIV)</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>cefotiam (DIV)</td>
<td>2.0</td>
<td>15.0</td>
<td>11</td>
<td>cefaclor (oral)</td>
<td>1.5</td>
<td>26.0</td>
</tr>
<tr>
<td>7</td>
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<td>2.0</td>
<td>5.0</td>
<td></td>
<td>piperacillin (DIV)</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>cefoperazon (DIV)</td>
<td>2.0</td>
<td>3.0</td>
<td>12</td>
<td>minocycline (oral)</td>
<td>1.2</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>ofloxacin (oral)</td>
<td>0.6</td>
<td></td>
<td></td>
<td>ceftazidime (DIV)</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Clinical data of the cases of antimicrobial drug-induced pneumonitis.

3. Transbronchial lung biopsy and bronchoalveolar lavage

Transbronchial lung biopsy revealed alveolitis (4/9, 44.4%), organization including Masson body formation (3/9, 33.3%), alveolar thickening (3/9, 33.3%) or eosinophilic infiltration (1/9, 11.1%). BAL in 6 patients of drug-induced pneumonitis showed an increase in total cell counts (>2.0×10^7,
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5/6, 83.3%), lymphocytosis (>10%, 6/6, 100%) (Table 2). Neutrophilia (>2.0%) and eosinophilia (>1%) were observed in 1 each out of 6 (16.7%) (Table 2). The ratio of OKT4/T8 in the BAL was decreased in 3 out of 5 (60%).

4. Lymphocyte stimulation and provocation tests

In vitro and in vivo tests for drug-induced pneumonitis were performed. According to the former criteria for drug-induced pneumonitis, 7 cases (from 1 to 7) were definite cases. The causative antimicrobial agents were minocycline, clindamycin, rifampicin, imipenem/cilastatin, ampicillin, cefotiam, and cefotaxime in each cases. The lymphocyte stimulation test was positive in 5 out of 11 cases (45.5%), and the provocation test was positive in 4 out of 8 cases (50%) (Table 3). There were no positive findings in the 4 patients who had the skin prick test.

**DISCUSSION**

The diagnosis of drug-induced pneumonitis is quite difficult, because there are so many causes such as radiation pneumonitis, hypersensitivity pneumonitis, oxygen toxicity or pneumonia, which show similar symptoms, signs and chest roentgenogram. Nontoxic drug-induced pneumonitis shows various clinical features such as chronic

<table>
<thead>
<tr>
<th>Case</th>
<th>No. of cells</th>
<th>Macrophage</th>
<th>Lymphocyte</th>
<th>Neutrophil</th>
<th>Eosinophil</th>
<th>OKT4/T8</th>
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</thead>
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<tr>
<td>2</td>
<td>$2.719 \times 10^7$</td>
<td>61.1%</td>
<td>24.8%</td>
<td>3.0%</td>
<td>11.1%</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>$6.845 \times 10^7$</td>
<td>41.3%</td>
<td>57.2%</td>
<td>1.6%</td>
<td>0%</td>
<td>0.47</td>
</tr>
<tr>
<td>8</td>
<td>$2.238 \times 10^7$</td>
<td>71.8%</td>
<td>27.5%</td>
<td>0.2%</td>
<td>0.5%</td>
<td>2.62</td>
</tr>
<tr>
<td>9</td>
<td>$4.64 \times 10^7$</td>
<td>70.6%</td>
<td>26.8%</td>
<td>1.6%</td>
<td>0%</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>$6.316 \times 10^7$</td>
<td>58.0%</td>
<td>41.0%</td>
<td>0.1%</td>
<td>0%</td>
<td>0.279</td>
</tr>
<tr>
<td>11</td>
<td>$1.586 \times 10^7$</td>
<td>70.0%</td>
<td>27.0%</td>
<td>0.5%</td>
<td>0%</td>
<td>2.08</td>
</tr>
</tbody>
</table>

ND: not done

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Table 3. Lymphocyte stimulation test and provocation test in antimicrobial drug-induced pneumonitis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Lymphocyte stimulation test</th>
<th>Provocation test</th>
<th>Case</th>
<th>Lymphocyte stimulation test</th>
<th>Provocation test</th>
</tr>
</thead>
</table>
| 1    | ND                          | minocycline (+)  | 8    | cefoperazone               | cefoperazone (--)
|      | clindamycin 2.1             | clindamycin (+) |      | norfloxacin 1.0            | norfloxacin 1.0  |
|      | cefotaxime 1.1              | cefotaxime (-)   |      | ofloxacin 1.1              | ofloxacin (--)
| 3    | rifampicin 2.83             | rifampicin (+)   | 9    | bacampicillin 1.51         | ofloxacin (--)
|      | isoniazide 0.7              |                  |      | cefotaxime (-)             |                  |
|      | ethambutol 0.87             |                  |      | ofloxacin (--)             |                  |
| 5    | ampicillin 1.94             | ND               | 11   | cefaclor 1.02              | cefaclor (--)
|      |                  | cefaclor (-)     |      | clindamycin 1.12           | clindamycin (--)
| 6    | cefotiam 3.96               | ND               |      | piperacillin 1.2           | piperacillin (--)
| 7    | cefotiam 2.15               | ND               | 12   | clindamycin 1.6            | ND               |
|      | norfloxacin 1.54            |                  |      | azthreonam 1.1             |                  |

*a*: new 3rd generation cephem, ND: not done

Antimicrobial drug-induced pneumonitis is well reported in the cases treated by nitrofurantoin, sulfasalazine, amphotericin B (with leukocyte transfusions), sulfonamide, para-aminosalicylic acid, and penicillin. It is difficult to differentiate the aggravation of pneumonia from the occurrence of antimicrobial drug-induced pneumonitis. A primary clue in drug-induced pneumonitis is the relationship between the timing of drug administration and the aggravation of the disease.

According to the criteria, 12 cases (6 definite cases and 6 suspected cases) were diagnosed and the causative drugs were ampicillin, cefotiam, cefotaxime, imipenem/cilastatin, clindamycin, rifampicin, minocycline and other undetermined drugs. The clinical features of these cases were studied. They frequently showed fever, cough, and dyspnea. Their clinical data showed a high incidence of eosinophilia, elevation of IgE and negative PPD skin test. These data could suggest the immunological mechanism of hypersensitivity and an alteration in the normal immune balance. Most patients showed hypoxia, impaired pulmonary function of restrictive and/or obstructive type and reduction of diffusion capacity, however these results could be affected by a preexisting pulmonary disease.

Chest roentgenogram of these patients showed bilateral alveolar or acinar infiltrative shadows. Characteristic roentgenogram was as varied as clinical features; chronic pneumonitis manifests as basilar reticular pattern with volume reduction, and hypersensitivity lung disease shows peripheral acinar infiltrates or diffuse reticular infiltrates with pleural effusion (2).

The pathology of drug-induced pneumonitis could be consistent with that of hypersensitivity pneumonitis which shows giant cell granuloma without caseous necrosis or alveolar and interstitial infiltrates with mononuclear cells or eosinophils (3). These typical findings were not common but alveolitis (interstitial mononuclear infiltration and proliferation of type 2 pneumocyte) or alveolar thickening (interstitial fibrosis) were commonly observed. These data suggested that the pathology is not diagnostic but an important clue for diagnosis.

BAL in 5 non-smokers showed an average total
cell count of \(1.40 \times 10^7/\text{ml}\) and an average percentage of macrophage, lymphocyte and neutrophil of 91.2\%, 4.1\% and 1.6\%, respectively with an average ratio of OKT4/T8 cells of 1.9 (4). BAL in drug-induced pneumonitis showed characteristic increase of total recovered cell counts and lymphocytosis. Most of them showed depressed OKT4/T8 ratio and a few showed eosinophilia. Akoun et al reported that BAL findings in five cases of drug-induced pneumonitis showed lymphocytosis (31–72\%) and inverted OKT4/T8 ratio (0.16–0.5) (5). BAL of the case of sulfasalazine-induced pneumonitis showed marked influx of eosinophils and a moderate increase in lymphocytes and basophils (6). These results suggested that some cases of drug-induced pneumonitis is involved in at least two immunological mechanism, hypersensitivity and cell-mediated immunity.

The skin test is often performed before administering beta-lactam antibiotics but none of our cases of drug-induced pneumonitis were positive in the skin test. In vitro tests for drug allergy are the lymphocyte stimulation test and the macrophage migration inhibition test; the former test is quite useful for diagnosis. The provocation test, also quite useful, should be performed in the hospital with special precaution due to its high risk level. However, since drug-induced pneumonitis might have several mechanisms other than an immunological mechanism, these tests may not necessarily be useful in all cases. This is one of the reasons why the diagnosis is difficult.

The antibodies (IgG or IgE) against antimicrobial drugs and complements are also valuable to assess immunological mechanisms, and other organs other than lungs might be involved in drug allergy, but these have not been examined. The clinical course of these cases was not bad after discontinuation of drugs and/or administration of steroid and they recovered within 2 to 60 days.

Beta-lactam antibiotics are the most commonly used but should be administered with caution due to possible hypersensitivity. Penicillin, such as aminobenzil penicillin or piperacillin, showed the interstitial or alveolar pattern in the chest roentgenogram with fever or eruption within 3–22 days after drug administration. The laboratory data in these cases primarily revealed an allergic reaction such as eosinophilia or elevation of IgE. The lymphocyte stimulation test or provocation test was positive, too. They improved by discontinuation of the drug or administration of steroid. Wengrower et al reported one case characterized by the combination of generalized exfoliative dermatitis and pneumonitis (7). Suzuki et al reported two cases of piperacillin-induced pneumonitis with a ground-glass appearance on chest roentgenogram (8).

Cephem is also known to induce a hypersensitivity similar to penicillin. A case of ceftizoxime-induced pneumonitis with a ground-glass appearance in chest roentgenogram was confirmed by lymphocyte stimulation test (9). Dreis et al reported a case who developed dyspnea and diffuse interstitial infiltrates after exposure to cephradine. The diagnosis was confirmed by transbronchial biopsy and rechallenge (10). The diagnosis was confirmed by transbronchial biopsy and rechallenge (10). Imipenem/cilastatin is a newly developed carbapenem and our case is the first case of drug-induced pneumonitis from this drug as far as we know. Minocycline-induced pneumonitis is reported to show fever, dyspnea, eruption, and eosinophilia with reticulo-acinar shadow which could be induced by hypersensitivity to minocycline (11–13). Macrolide is not known to induce pneumonitis. However, fosfomycin, which is supposed to be safe even in allergic patients, has been reported to induce pneumonitis (14).

The differential diagnosis of antimicrobial drug-induced pneumonitis from aggravation of pneumonia is quite difficult. Our study suggested that any antimicrobial drug could induce pneumonitis and that both bronchoscopic and immunological examinations are important for diagnosis. Tamura’s criteria does not include bronchoscopic findings which provide more information on the lungs. The lymphocyte stimulation test also could be applied using cells from BALF, although no precise data have been reported to date. Immunological examinations such as lymphocyte stimulation test or provocation test and bronchoscopic examination such as bronchoalveolar lavage or transbronchial lung biopsy could be added to the criteria for diagnosis. A “definite” case should show positive drug sensitivity tests such as lymphocyte stimulation test or provocation test and findings of pneumonitis.
shown by BALF or TBLB. It is important that clinicians keep in mind the possibility of antimicrobial induced-pneumonitis, because of the increased usage of antimicrobial agents.

REFERENCES