CASE REPORT

Amoxicillin-Induced Eosinophilic Pneumonia with Granulomatous Reaction: Discrepancy between Drug-Induced Lymphocyte Stimulation Test Findings and the Provocation Drug Test

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A 59-year-old man was admitted to the hospital with pulmonary infiltration, fever, erythema, and eosinophilia. Two weeks before admission, he received amoxicillin, acetaminophen, and shoseiryu-to (a Japanese herbal medicine) for a common cold. Bronchoalveolar lavage was performed, and an increased number of eosinophils was recovered. Transbronchial biopsy specimens showed granuloma and interstitial thickening with eosinophils and lymphocytes. Drug-induced eosinophilic pneumonia was suspected, so all drugs were discontinued. The symptoms and infiltration shadow disappeared. A drug-induced lymphocyte stimulation test (DLST) was positive for acetaminophen but not for amoxicillin. In contrast to the DLST, a provocation test revealed that amoxicillin induced the drug allergy. A very striking observation was the coexistence of pulmonary eosinophilia and granulomatous lung infiltrations. In addition, there was a discrepancy between the DLST and provocation test findings. To our knowledge, there is no previous report of drug-induced eosinophilic pneumonia with a granulomatous reaction.

Key words: *amoxicillin, drug-induced lymphocyte stimulation test, drug-induced pneumonia, granuloma, provocation test*

Allergic reactions to β-lactam drugs, especially penicillin, are commonly reported. The most common β-lactam-induced drug reactions are maculopapular or morbilliform and urticarial eruption.[1] Drug-induced pneumonia, however, is relatively rare.[2–5] There are only a few reports of the clinical manifestations of penicillin-induced eosinophilic pneumonia.[6,7] A drug-induced lymphocyte stimulation test (DLST) measures the proliferation of T cells in response to a drug in vitro. DLST is rather useful for diagnosing patients with drug eruption.[8] In contrast to drug eruption, the usefulness of a DLST for identifying the offending drug in drug-induced pneumonia has not been established. Nevertheless, DLST is widely used in Japan for the diagnosis of drug-induced pneumonia,[5,9] but DLST was not useful for our patient. The drug allergy was diagnosed by a provocation test. We report the first case of a granulomatous reaction in the lung occurring in a patient with eosinophilic pneumonia.

Case Report

A 59-year-old man with fever and dermatologic eruption was admitted to a local hospital. Two weeks before admission, he received amoxicillin (750 mg/d, three times daily), acetaminophen (400 mg/d, as needed), and shoseiryu-to (a Japanese herbal medicine) (9 g/d, three times daily) for a common cold at a clinic for 5 days. He developed erythema on the abdomen 5 days later, and all drugs were discontinued at that time. Thereafter, the erythema appeared on his entire body, and high fever developed 9 days later. Chest computed tomography (CT) demonstrated diffuse ground-glass opacities, reticular shadows, and alveolar septal thickening (Figure 1A). Bronchoalveolar lavage (BAL) was performed and revealed pulmonary eosinophilia (total cell counts 6.8×10^5/mL, with eosinophils 83%, lymphocytes 9%, neutrophils 1%, and alveolar macrophages 7%.

One week after admission (2 weeks after discontinuing the drug), he was transferred to our hospital for further

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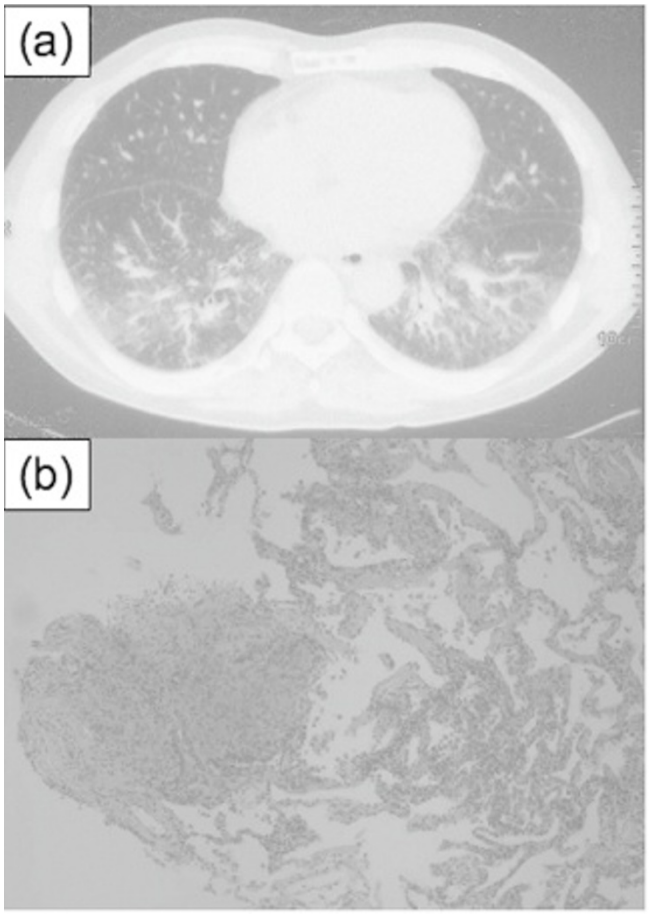

Figure 1. *A*, Chest computed tomography demonstrated diffuse ground-glass opacities, reticular shadows, and alveolar septa thickening. *B*, Transbronchial lung biopsy specimen revealed lymphocytic and eosinophilic interstitial infiltrate with granuloma formation (hematoxylin and eosin stain, ×100 original magnification).

evaluation of the disease. His past medical history revealed neither asthma nor any occupational exposure to toxic fumes, dust, or animals. Physical examination revealed a temperature of 38.4°C and blood pressure of 120/70 mm Hg. Lung auscultation revealed fine crackles in the lower lung field. There was no heart murmur. Arterial blood gases were as follows: pH 7.413; HCO_3 23.1 mmol/L; partial pressure of carbon dioxide 37.1 mm Hg; partial pressure of oxygen, 81.3 mm Hg; and base excess −1.0 mmol/L. The white blood cell count was 7.9×10^3, with 8.4% eosinophils. His hemoglobin concentration was 12.6 g/dL. C-reactive protein was 7.83 mg/L (normal range 0.0–0.3 mg/L). Blood chemistry revealed a mild increase in aspartate aminotransferase and alanine aminotransferase. The total serum immunoglobulin (Ig)G, IgM, and IgA levels were 1,470 g/dL, 191 mg/dL, and 320 mg/dL, respectively, and total serum IgE was 816 IU/mL (normal range < 170 IU/mL). A cytoplasmic pattern of antineutrophil cytoplasmic antibodies with reactivity against myeloperoxidase was not detected. Angiotensin-converting enzyme was not elevated. A chest radiograph on admission indicated that the shadows that were disseminated over both the mid– and lower lung zones had disappeared. Chest CT revealed alveolar septal thickening and the disappearance of ground-glass opacities.

BAL was performed. Sterile saline (150 mL) was instilled into the right B8 segment in 50 mL aliquots. No pathogen was identified. The BAL count was 6.04×10^5/mL, with eosinophils 33.3%, lymphocytes 27.4%, neutrophils 0%, and alveolar macrophages 39.3%. The CD4 to CD8 ratio in the BAL fluid was 0.88. The BAL culture grew no organism. A transbronchial lung biopsy was performed and revealed lymphocytic and eosinophilic interstitial infiltrate with granuloma formation (Figure 1B). There was no evidence of necrotizing vasculitis. A presumptive diagnosis of drug-induced pneumonia was made. The chest radiograph, chest CT scan, and clinical findings returned to normal 3 weeks after discontinuing the target drugs without specific treatment.

A DLST for amoxicillin, shoseiryu-to, and acetaminophen, expressed as a stimulatory index (over 180% is considered positive), yielded values of 123%, 101%, and 209%, respectively. These clinical symptoms were more consistent with penicillin allergy because drug eruption often occurs in penicillin allergy. Eleven days after admission to our hospital, a drug provocation test was performed by oral administration of 3.3% of the daily dose of the drugs (10% of the single medication dose) with careful observation. The provocation tests were performed with the suspected drugs individually. Following provocation with amoxicillin, but not acetaminophen or shoseiryu-to, the dermatologic manifestations (erythema) reappeared 11 hours later without pulmonary symptoms. The white blood cell count and eosinophils (%) before the provocation test were $5.80 \times 10^3/mm^3$ and 14%, respectively, and gradually rose to $8{,}500 \times 10^3/mm^3$ and 23.9%, respectively, 1 week after the provocation. We therefore concluded that the drug-induced pneumonia was induced by amoxicillin.

Discussion

The overall prevalence of penicillin-induced pneumonia is difficult to determine, but it is not a common adverse reaction compared with penicillin-induced dermatologic eruptions. There are several reports of penicillin-induced eosinophilic pneumonia,[2–5,7] but amoxicillin-induced eosinophilic pneumonia is very rare, with only one

reported case in the literature that was diagnosed based on a DLST.[7]

Granulomas of any sort that are identified in the lung parenchyma raise the spectre of sarcoidosis, mycobacteria, fungi infection, and drug reaction. Acebutolol, cocaine, cromolyn sodium, fluoxetine hydrochloride, methotrexate, nitrofurantoin, procarbazine, pentazocine, sirolimus, and tripelennamine are the drugs that are most often cited as producing a granulomatous pneumonia with or without interstitial infiltration.[10] To our knowledge, there is no report of penicillin-induced pneumonia associated with a granulomatous reaction. In addition, other than Churg-Strauss syndrome, the coexistence of pulmonary eosinophilia and granulomatous lung infiltration has not been reported. Our case was not Churg-Strauss syndrome because there was no evidence of asthma, neuropathy, systemic organ failure, or vasculitis. This case of drug-induced pneumonia involved at least two immunologic mechanisms: delayed hypersensitivity (granuloma formation) and eosinophilic inflammation. We have no explanation for their coexistence.

Diagnostic tests are dependent on the type of immune reaction (antibody or T cell mediated). DLST demonstrates the specificity of the T-cell reaction to the drug. In Japan, drug-induced pneumonia and liver injury are diagnosed on the basis of DLST results,[4,5,7,8] although a drug provocation test is the most reliable method for diagnosing a drug allergy.[11] Recent reports, however, indicate that the DLST is unreliable for the diagnosis of drug-induced liver injury.[11] In our case, a drug provocation test supported the diagnosis, but the results were completely opposite to those of the DLST. Provocation with 3.3% of the daily amoxicillin dose in the present case caused the dermatologic manifestations to reappear without the pulmonary symptoms. Wengrower and colleagues also reported that antibiotic challenges with penicillin caused a drug-induced skin eruption without reactivation of the pneumonia.[4] These findings suggest that the threshold dose for causing drug-induced skin eruptions is different from that causing drug-induced pneumonia.

In conclusion, we report here the first case of granuloma formation in the lung occurring in eosinophilic pneumonia. Caution must be used in interpreting the DLST for a diagnosis of drug allergy. The clinical course, exclusion of an alternative cause, and drug readministration are useful clues to the diagnosis of drug-induced pneumonia.

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