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【 CASE REPORT 】

Bucillamine-induced Pneumonitis in a Patient with Rheumatoid Arthritis-associated Interstitial Pneumonia: A Case Report and Review of the Literature

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Abstract:
An 81-year-old woman with rheumatoid arthritis (RA) who had been treated with bucillamine presented with dyspnea. Computed tomography of the chest showed ground-glass opacities and consolidations in both lungs and honeycombing in both basal lung areas. An elevation of the serum Krebs von den Lungen-6 level and hypoxemia were seen. Lymphocytosis with a decreased CD4/CD8 ratio was seen in the bronchoalveolar lavage fluid. A transbronchial lung biopsy specimen showed organizing pneumonia. Based on a diagnosis of bucillamine-induced pneumonitis (BIP) with RA-associated pre-existing interstitial pneumonia, she was successfully treated with the cessation of bucillamine and systemic corticosteroid therapy. The risk factors and prognosis of BIP are discussed.

Key words: bucillamine-induced pneumonitis, interstitial pneumonia, rheumatoid arthritis, methotrexate

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Introduction

Bucillamine is a commonly used disease-modifying anti-rheumatoid drug in Japan, although its anti-rheumatoid effect is not as strong as methotrexate (MTX), which is a key drug in the treatment of rheumatoid arthritis (RA). Bucillamine, as well as MTX, is known to cause interstitial pneumonia (1-18). Pre-existing interstitial lung disease (ILD) is a risk factor for MTX-induced pneumonitis, and MTX-induced pneumonitis often shows a diffuse alveolar damage (DAD) pattern, resulting in fatal outcomes in some patients (19-22). However, information on the risk factors and the prognosis of bucillamine-induced pneumonitis (BIP) is still limited.

A case of BIP in a patient with ILD of a usual interstitial pneumonia (UIP) pattern associated with RA, in which BIP resolved with the prompt cessation of bucillamine and systemic corticosteroid therapy, is herein presented. Risk factors and the prognosis of BIP are discussed along with a review of the pertinent literature.

Case Report

An 81-year-old woman with a 1-month history of dyspnea was referred to our hospital for a detailed examination. She had smoked 30 pack-years. She had a 3-month history of arthralgia and morning stiffness for which she was treated with bucillamine (200 mg/day) and prednisolone (4 mg/day) based on a diagnosis of RA by a local physician, and her RA symptoms improved. Fine crackles were audible in the bilateral lower lung lobes at the first visit to the local physician, and reticular shadows in the bilateral lower lung fields were seen on a chest radiograph taken before the initiation of bucillamine (Fig. 1A). Her other medical history included angina pectoris and mitral regurgitation, and she had undergone mitral valve replacement at 80 years of age. Her mother also had RA. On physical examination, she was afebrile and had tachypnea with a respiratory rate of 24 breaths per minute, and fine crackles were audible in both lungs. No physical findings suggestive of congestive heart failure (pitting edema of the lower extremities and jugular

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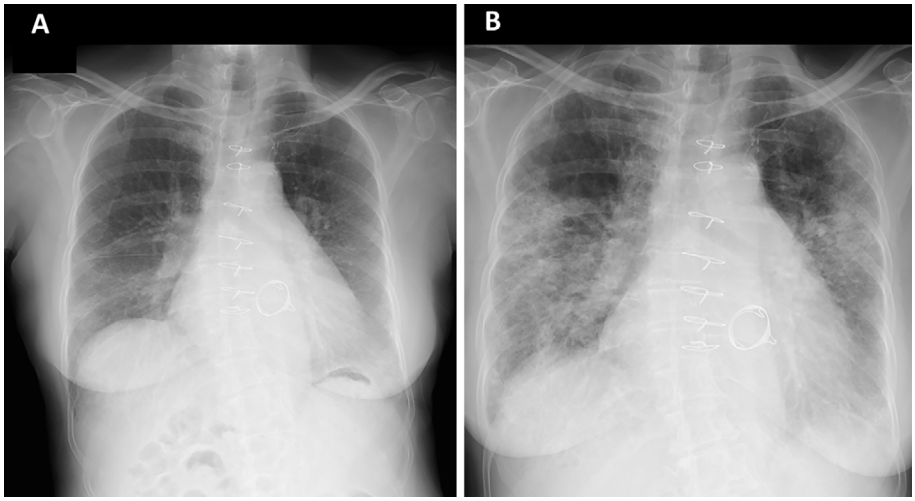

Figure 1. **A chest radiograph taken before the start of bucillamine at the first visit to the local physician showing reticular shadows in the bilateral lower lung fields (A). A chest radiograph taken at initial presentation showing infiltrative opacities in addition to reticular shadows in the bilateral middle and lower lung fields (B).**

venous distention) were observed. The laboratory data showed leukocytosis (10,900/μL) with neutrophilia (81.5%), elevated serum levels of lactate dehydrogenase (408 U/L), C-reactive protein (5.51 mg/dL), Krebs von den Lungen-6 (2,140 U/mL), surfactant protein-D (299.0 ng/mL), rheumatoid factor (352 IU/mL), and anti-cyclic citrullinated peptide antibody (≥1,200 U/mL), and hypoxemia (partial pressure of arterial oxygen of 87.2 mmHg on nasal oxygen at 3 liters per minute). A lymphocyte stimulation test (LST) with peripheral blood lymphocytes for bucillamine was negative (stimulation index, 168%). The plasma brain natriuretic peptide, serum immunoglobulin, and β-D-glucan levels were normal, while all other serum autoantibodies were negative. The results of respiratory function testing were: vital capacity 1.11 L (53.9% predicted), forced vital capacity 1.08 L (52.4% predicted), forced expiratory volume in 1 second 1.03 L (77.4% predicted), and diffusion capacity of the lung for carbon monoxide 2.23 mL/min/mmHg (17.7% predicted). A chest radiograph showed infiltrative opacities with reticular shadows in bilateral middle and lower lung fields (Fig. 1B). Computed tomography (CT) of the chest showed ground-glass opacities and consolidations in both lungs (Fig. 2A and B), in addition to reticular opacities, honeycombing, and traction bronchiectasis in both lower lobes, suggesting pre-existing ILD (UIP pattern) associated with RA (Fig. 2C and D). Ground-glass opacities and consolidations are absent in both basal lung areas. A bronchoalveolar lavage fluid (BALF) analysis showed a cell count of 2.45×10^5/mL, with a cell differential of 44.0% macrophages, 25.5% lymphocytes, 26.0% neutrophils, and 4.5% eosinophils, and a CD4/CD8 ratio of 0.2. No microorganisms were detected in a BALF culture. A transbronchial lung biopsy specimen obtained from the right upper lobe showed alveolar organizing pneumonia (OP), septal thickening, and inflammatory cell infiltration (Fig. 3). Based on a diagnosis of BIP superimposed on RA-associated ILD (UIP pattern), systemic corticosteroid therapy with intravenous methylprednisolone (1,000 mg per day for 3 days) followed by oral prednisolone (30 mg per day) was started. She then became asymptomatic, and the chest radiological findings of BIP, hypoxemia, and elevated serum levels of lactate dehydrogenase, C-reactive protein, Krebs von den Lungen-6, and surfactant protein-D improved. Four months later, prednisolone was tapered to 10 mg daily without any recurrence of BIP.

Discussion

In this case, infiltrative opacities in addition to pre-existing ILD appeared about 3 months after the initiation of bucillamine, and the clinical and radiological features, such as BALF lymphocytosis with a decreased CD4/CD8 ratio and bilateral consolidations on chest CT suggesting an OP pattern, are consistent with previously reported cases of BIP (1, 2, 4-6, 8-10, 12-14, 16, 17). Although possible involvement of infection, congestive heart failure, and acute exacerbation (AE) of pre-existing ILD associated with RA could not be fully excluded, the diagnosis of BIP is the most plausible based on the characteristic clinical and radiological features and the temporal association between the initiation of bucillamine and the onset of pneumonitis. ILD (including RA-associated ILD) other than idiopathic pulmonary fibrosis (IPF) is known to cause AE, as well as IPF. Most studies of AE of ILD other than IPF used the definition of AE of IPF (23). A new definition of AE of IPF was proposed in 2016, and AE triggered by drug toxicity was added as a triggered AE of IPF, because AE of IPF was divided into idiopathic and triggered AE for continued study of these important events (24). The most common histologic pattern of AE of chronic ILD is DAD; less commonly, patients have OP or extensive fibroblastic foci (25). MTX usage was re-

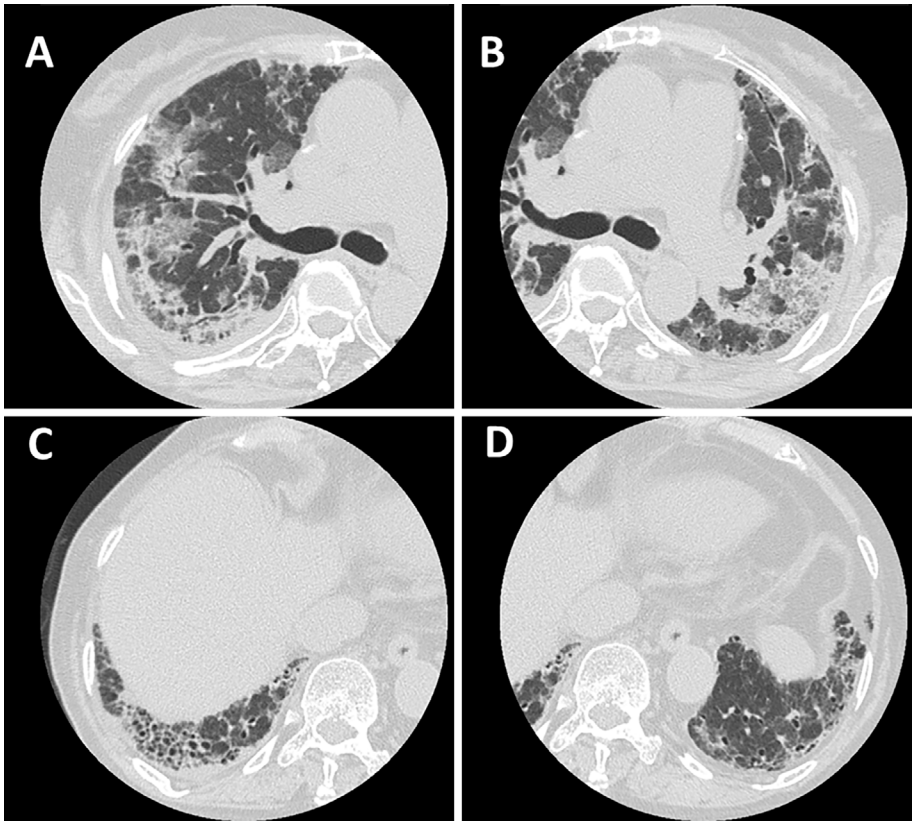

Figure 2. **Computed tomography of the chest showing ground-glass opacities and consolidations in both lungs (A, B), in addition to reticular opacities, honeycombing, and traction bronchiectasis in both lower lobes (C, D), which suggest pre-existing interstitial pneumonia (usual interstitial pneumonia pattern) associated with rheumatoid arthritis. Note that both ground-glass opacities and consolidations are absent in both basal lung areas.**

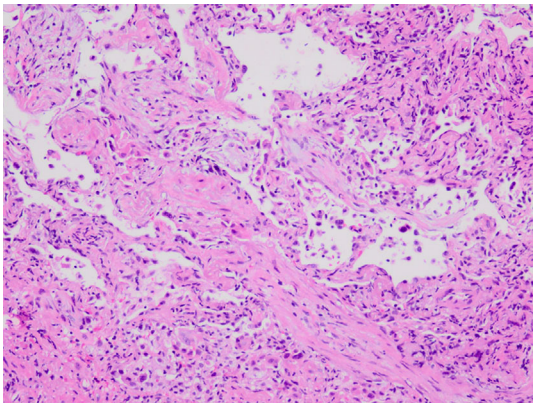

Figure 3. **A transbronchial lung biopsy specimen obtained from the right upper lobe showing alveolar septal thickening, inflammatory cell infiltration, and organizing pneumonia (Hematoxylin and Eosin staining, ×100).**

ported to be associated with the development of AE of RA-associated ILD. However, AE of RA-associated ILD in MTX-treated patients occurred 3 or more years after MTX treatment, the duration of which is longer than the usual first-year occurrence of MTX-pneumonitis (26). Based on these observations and due to similarities with previously reported cases of BIP, the present patient likely had BIP rather than AE of RA-associated ILD triggered by bucillamine toxicity.

Previous reports suggest that pre-existing ILD is a risk factor for both the development and a poor outcome in MTX-induced pneumonitis (19-22). In addition, it has been reported that a UIP pattern on chest CT and MTX usage are associated with the development of acute exacerbations of RA-associated ILD (26). However, the risk factors for BIP have not yet been clarified. Therefore, 39 previously reported cases of BIP were reviewed (1-18), and their clinical features are summarized in Table. Cases in which other anti-RA drugs that can cause pneumonitis, such as MTX and gold, were used concomitantly were excluded. The mean age at the onset of BIP was 63.3 years (range, 44-83 years), and 29 of 39 (74.4%) patients were female. BIP developed about 7.7 months (mean 229.9 days, range, 60-1,440 days) after the initiation of bucillamine. Bucillamine improved RA symptoms in 33 of 36 patients. The LST with peripheral blood lymphocytes for bucillamine was positive in 9 of 21 patients in whom the LST was performed. The findings of chest CT were an OP pattern, hypersensitivity pneumonitis (HP) pattern, and eosinophilic pneumonia (EP) pattern (determined by both chest CT and BALF findings) in 22, 5, and 1 of 28 patients, respectively, in whom chest CT findings were available to classify the lung injury patterns of

Table. **Reported Cases of Bucillamine-induced Pneumonitis.**

Age (y)	63.3 (44-83)*
Sex (male/female)	10/29**
Duration of bucillamine treatment (days)	229.9 (60-1440)*
Cumulative dose of bucillamine (g)	37.2 (6-144)*
Effect of bucillamine on RA symptoms (effective/not effective/NA)	33/2/4**
Lymphocyte stimulation test for bucillamine (positive/negative/NA)	9/12/18**
Chest CT findings (OP pattern/HP pattern/ EP pattern/NA)	22/5/1/11**
Pre-existing interstitial pneumonia on chest CT (yes/no/NA)	2/26/11**
Lymphocytosis in bronchoalveolar lavage fluid (yes/no/NA)	18/1/20**
Decreased CD4/CD8 ratio in bronchoalveolar lavage fluid (yes/no/NA)	7/4/28**
Treatment (cessation of bucillamine only/systemic corticosteroid therapy)	13/26**
Outcome (alive/dead)	38/1**

RA: rheumatoid arthritis, NA: not available, CT: computed tomography, OP: organizing pneumonia, HP: hypersensitivity pneumonitis, EP: eosinophilic pneumonia, *: data expressed as means (range)
**: data expressed as numbers of cases

BIP. Only 2 of 28 patients whose chest CT regarding the presence or absence of pre-existing ILD were described had pre-existing ILD (5, 6), although the detailed patterns of pre-existing ILD were unknown. A BALF analysis showed lymphocytosis in 18 of 19 patients, and a decreased CD4/CD8 ratio was seen in 7 of 11 patients. Pneumonitis resolved in all 39 patients with a cessation of bucillamine and/or systemic corticosteroid therapy. However, one patient died of respiratory failure due to intractable pneumothorax (1). From these observations, BIP usually appears to have a favorable outcome because its lung injury pattern usually manifests as an OP pattern, HP pattern, and EP pattern, which all respond well to systemic corticosteroid therapy. Whether or not bucillamine can be used safely in patients with RA-associated pre-existing ILD is still remains unclear, because there are only a few such cases in previous reports of BIP, BIP with pre-existing RA-associated ILD might be manageable with appropriate treatment. It has been reported that clinically significant ILD occurs in 10-20% of cases and it is considered to be an important contributor to morbidity and mortality within the RA population (27). Therefore, the actual number of cases of RA with ILD who were treated with bucillamine might be greater than expected. No risk factors for bucillamine-induced pneumonitis could be identified from a review of the literature in this study.

The chemical structure of bucillamine is almost the same as that of D-penicillamine (14). The drug has been associated with three different pulmonary reactions, namely bronchiolitis obliterans (BO), Goodpasture's syndrome (GPS), and pneumonitis (28, 29). The lung injury patterns of D-penicillamine-induced pneumonitis are presumed to include the HP pattern, EP pattern, and OP pattern, and they usually have good outcomes after the cessation of D-penicillamine and systemic corticosteroid therapy, while BO and GPS are usually intractable. The clinical features of D-penicillamine-induced pneumonitis may be similar to those of BIP, although there are only a few available case reports, and detailed chest CT findings were not available in most cases (28-34).

In conclusion, a case of BIP in a patient with RA-associated ILD (a UIP pattern), in which BIP was successfully treated after the cessation of bucillamine and systemic corticosteroid therapy, was described. To the best of our knowledge, this is the first case report of BIP with RA-associated ILD (UIP pattern). To determine the safety of administering bucillamine ito patients with RA-associated pre-existing ILD, further investigations involving a large number of patients will be needed.

The authors state that they have no Conflict of Interest (COI).

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