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CASE REPORT

A case with life-threatening interstitial pneumonia associated with bucillamine treatment

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Abstract We report a case of bucillamine-induced interstitial pneumonia accompanied by severe hypoxemia in an 83-year-old woman who had rheumatoid arthritis. Respiratory failure worsened even after withdrawal of bucillamine and administration of high-dose corticosteroids, and mechanical ventilation was required. A review of 15 cases with bucillamine-induced pulmonary injury suggests that advanced age may be associated with the development of severe interstitial pneumonia. Bucillamine can cause corticosteroid-resistant and life-threatening lung injury, especially in the elderly.

Keywords Bucillamine · Elderly · Interstitial pneumonia · Lung injury · Rheumatoid arthritis

Introduction

Bucillamine is a disease-modifying anti-rheumatoid drug that has been used in the treatment of rheumatoid arthritis (RA) since 1987 [1]. Bucillamine has caused more than a dozen reported cases of lung injury, although most cases have recovered without sequelae following withdrawal of the drug alone, or with corticosteroid therapy [2–13]. We present a patient with severe, corticosteroid-resistant interstitial pneumonia associated with bucillamine toxicity.

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Case presentation

An 83-year-old woman was admitted to the hospital because of severe dyspnea and cough. She had been in good health until eight months earlier, when generalized arthralgia and morning stiffness developed. Since the symptoms had worsened despite treatment by a local physician, she visited our hospital. Bilateral and symmetric soft tissue swelling of the proximal interphalangeal, metaphalangeal and wrist joints were found at her initial visit. Her morning stiffness around these joints was lasting for 4 h. Though rheumatoid factor and anticyclic citrullinated peptide antibodies were negative, a diagnosis of RA was made on the basis of clinical findings [14]. Her symptoms were relieved promptly by administration of prednisolone (7.5 mg once a day) and bucillamine (100 mg once a day). Two months after starting the medication, she noticed the onset of dyspnea accompanied by a nonproductive cough that worsened for several days, and visited the emergency room. Her body temperature was 36.9 °C, pulse was 136/min, respiration was 32/min, and blood pressure was 116/68 mmHg. She was alert, with an oxygen saturation of 60% in ambient air, which increased to 91% after receiving oxygen at 5 l/min by a reservoir bag. The patient was comfortable while resting in bed, but became short of breath when she tried to speak in complete sentences. Coarse crackles were heard in both lungs and the heart sounds were normal. There was no peripheral edema, joint swelling, or digital clubbing. Arterial blood gas analysis at ambient air gave a pH of 7.46, a $PaCO_2$ of 38 torr, and a

PaO_2 of 33 torr. Laboratory studies showed a white blood cell count of 14,670/μl, hemoglobin 14.0 g/dl, platelet count 35.1 × 10^4/μl, C-reactive protein 8.71 mg/dl, KL-6 660 U/ml, surfactant protein-D 223 ng/ml, brain natriuretic peptide 79.0 pg/ml, immunoglobulin (Ig) G 812 mg/dl, IgA 211 mg/dl, IgM 90 mg/dl, matrix metalloproteinase-3 123.6 ng/ml, β-D-glucan less than 5 pg/ml, and serum endotoxin less than 0.8 pg/ml. The serum levels of glucose, aspartate aminotransferase, lactate dehydrogenase, urea nitrogen, and creatinine were normal, and there were no autoantibodies to rheumatoid factor, anti-nuclear antibody, or anti-neutrophil cytoplasmic antibodies. One notable finding was a decrease in the serum IgG level by 50% without lymphocytopenia at admission, while the values before drug administration had been normal (IgG 1,611 mg/dl, IgA 327 mg/dl, IgM 123 mg/dl). The lymphocyte stimulation test using bucillamine after corticosteroid therapy was negative. No infectious agent, including cytomegalovirus, *Pneumocystis jiroveci* or other fungi, was identified in sputum or blood cultures.

A chest radiograph revealed bilateral, diffuse infiltrates mixed with diffuse ground-glass opacities (GGOs) and linear shadows, while chest radiographs obtained ten weeks earlier were normal (Fig. 1a, b). A computed tomographic (CT) scan of the thorax demonstrated bilateral, diffuse GGOs predominantly distributed in the upper and middle lung fields, but no honeycombing or traction bronchiolectasis (Fig. 1c). The diagnosis of acutely developed interstitial pneumonia, including the possibility of drug-induced lung injury, was made based on the clinical course and radiologic findings. Bucillamine was discontinued on the first hospital day, with high-dose methylprednisolone (1 g/day for 3 days) given on the first three hospital days, followed by 60 mg of prednisolone per day. Over the following two days, the dyspnea progressed to hypoxemia despite respiration through a reservoir mask filled with 12 l/min of oxygen. On the third hospital day, the trachea was intubated and ventilatory assistance provided. Arterial oxygenation improved after the initiation of ventilatory support. On the 12th hospital day, the patient was weaned from ventilatory assistance, and prednisolone was tapered gradually. The value of KL-6 was increased to 1,273 U/ml on the 26th hospital day, then decreased to 695 U/ml, while serum IgG had decreased to around 630 mg/dl throughout

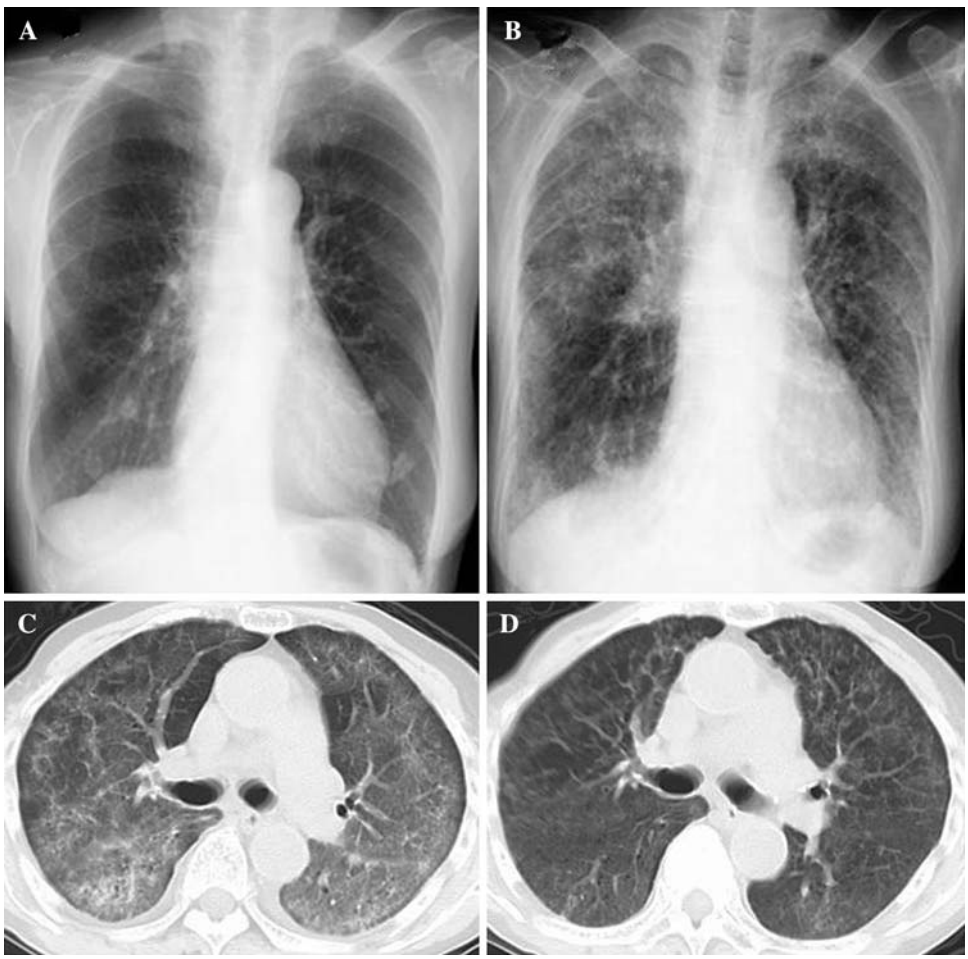

Fig. 1 **a** A chest radiograph obtained ten weeks prior to admission showed no abnormality. **b** A chest radiograph on admission demonstrated bilateral, diffuse infiltrates mixed with ground-glass opacities (GGOs) and linear shadows. **c** Computed tomographic (CT) scan of the thorax on admission revealed bilateral, diffuse GGOs. **d** CT scan on the 60th hospital day demonstrated a decrease in GGO and fine reticulonodular shadows

the hospital course. On the 60th hospital day, a CT scan showed a moderate amount of GGOs accompanied by reticular shadows throughout the lungs, even after two months of corticosteroid therapy (Fig. 1d). On the 74th hospital day, she was discharged on foot under oxygen supplementation (1 l/min at rest, and 2 l/min on exertion), since severe oxygen desaturation was found on exertion.

Discussion

Here, we report on a case of bucillamine-induced pulmonary toxicity that presented as interstitial pneumonia two months after the administration of bucillamine, with no other possible causes such as other drugs associated with lung toxicity, infection, inhalation of noxious particles, or activation of RA. No autoantibodies or infectious agents, such as cytomegalovirus, *Pneumocystis jiroveci* or other fungi, were detected. In addition, the patient did not have interstitial lung disease before the medication, as indicated by a normal chest radiograph at the initiation of bucillamine therapy. Since bucillamine- and gold-induced pulmonary injury decrease serum immunoglobulins, low levels of IgG, IgA and IgM also support this diagnosis [4]. Although we could not exclude the possibility of RA-interstitial lung disease (ILD) instead of drug-induced lung injury, acute interstitial lung disease is extremely rare in RA-ILD [15].

All published case reports referring to bucillamine and lung toxicity were identified from the PubMed database. The search term "bucillamine" was combined with the terms "pneumonitis" and "pulmonary disease." One study surveyed ten cases with lung injury associated with bucillamine and one letter did not give case details [16, 17]. Information on 15 patients including the present case (11 females and 4 males) is summarized in Table 1 [2–13]. All patients were diagnosed with RA without lung involvement at the initiation of bucillamine therapy. The mean age was 62.3 ± 10.6 years (range 44–83). The duration of exposure to bucillamine ranged from two to 48 months, and was less than six months in ten cases (68%). Nine patients (60%) were receiving concurrent corticosteroids, and nonsteroidal anti-inflammatory agents, gold, and sulfasalazine were concomitantly administered in three, one, and one cases, respectively. Radiological findings described in previous reports include patchy GGOs and mottled infiltrates in a peribronchial or peripheral distribution, diffuse linear or interstitial shadows, with no honeycomb

Table 1 Summary of reported patients with bucillamine-associated lung injury searched by PubMed

No.	Age	Sex	Duration of Buc (M)	Concomitant drugs	PaO_2 (torr)	Radiographic findings	DLST	Management[a]	*S/R*	Prognosis	Ref
1	53	M	3	mPSL 20 mg/w, NSAID	67	Acinar, reticulonodular	(−)	D/C, **PSL 60 mg**	(+)	CR	[2]
2	65	F	2	NSAID, gold	52	Reticulolinear	(+)	D/C, **PSL 40 mg**	(+)	CR	[3]
3	74	F	4	PSL 5 mg	60	Mottled shadows	(−)	D/C, Pulse × 3	(−)	CR	[4]
4	66	M	36–48	PSL 7.5 mg, SF	60	Mottled, reticular	(−)	D/C, **Pulse × 1**	(+)	CR	[4]
5	54	F	18	PSL 5 mg	66	Mottled shadows	(−)	D/C	(+)	CR	[4]
6	68	F	2	None	53.3	GGOs	(+)	D/C, **PSL 50 mg**	(+)	CR	[5]
7	51	M	21	None	N/A	Patchy consolidation	N/D	D/C, PSL 50 mg	N/A	CR	[6]
8	57	F	4	PSL 5 mg	62*	GGOs	(+)	D/C, **PSL 40 mg**	(+)	CR	[7]
9	70	F	17	PSL 5 mg, MTX	54.3	GGOs, reticular	(−)	D/C	(+)	CR	[8]
10	51	F	4	NSAIDS	69.8	GGOs, fine nodular	N/D	D/C	(+)	CR	[9]
11	61	M	6	None	80	GGOs, reticular	(+)	D/C, PSL 30 mg	(−)	CR	[10]
12	44	F	13	None	82.7	GGOs, fine nodular	(−)	D/C	(+)	CR	[11]
13	74	F	3–4	PSL 15 mg	41.3	Mottled shadows	(+)	D/C, PSL 30 mg	(−)	CR	[12]
14	64	F	5	PSL 7.5 mg	77.7	GGOs	(+)	D/C	(+)	CR	[13]
15	83	F	2	PSL 7.5 mg	33	GGOs, reticular	(−)	D/C, Pulse × 1, MV	(−)	PR, HOT	Present case

Buc bucillamine, *PaO_2* partial pressure of oxygen at ambient air except for case 8, *DLST* drug lymphocyte stimulation test by bucillamine, *S/R* spontaneous remission of clinical findings and/or radiographic findings by withdrawal of bucillamine, *Ref* reference, *NSAID* non-steroidal anti-inflammatory drugs, *D/C* discontinuation of bucillamine, *CR* complete remission, *Pulse* high-dose pulsed corticosteroid therapy, *SF* sulfasalazine, *GGOs* ground-glass opacities, *N/A* not available, *N/D* not done, *MTX* methotrexate, *MV* mechanical ventilation, *PR* partial remission, *HOT* home oxygen therapy

[a] Bold terms on in the "Management" column indicate the use of corticosteroid therapy to achieve complete remission of lung injury despite partial resolution of pulmonary infiltrates and symptoms upon discontinuation of bucillamine

appearance or chronological heterogeneity reported. Diffuse or patchy mottled shadows associated with bronchiolitis obliterans-organizing pneumonia were predominant in several cases (cases 3, 4, 5, 7, and 13). Since these radiographic findings mixed and overlapped, it is difficult to establish characteristic radiographic patterns of bucillamine-induced lung toxicity. The drug lymphocyte stimulation test was positive in six cases (40%). Hypoxemia on arterial blood gas analysis was mentioned in ten cases, and respiratory failure (PaO_2 at ambient air <60 torr) was found in six cases (40%). Ten (68%) were clinically and/or radiographically improved after withdrawal of bucillamine alone, while five of those were treated with corticosteroids to achieve further resolution 10–60 days after the withdrawal of drug. Case 11 received prednisolone (30 mg/day) at admission despite the lack of hypoxemia. Detailed information about the reasons for corticosteroid therapy was not given in case 7. The other three patients, including the present case, had severe respiratory failure that required immediate, high-dose corticosteroid administration. No other patients received mechanical ventilation. Most patients experienced complete clinical and radiological improvement, but our case required home oxygen therapy at discharge. No patients died from these complications.

The present case differed from previous reports in several ways. First, she had severe hypoxemia that required mechanical ventilation. Second, she was poorly responsive to corticosteroid therapy and oxygen supplementation was necessary after two months of corticosteroid therapy, whereas other reported cases showed near-complete resolution after treatment. If we define "severe disease" as prominent hypoxia ($PaO_2 < 50$ torr) and/or resistance to corticosteroids, then cases 3, 13 and our patient had severe disease. These three patients were older than the others (mean ages were 77 vs. 58.6 years, respectively), and concurrently received corticosteroids. The severe lung toxicity in these patients may result from advanced age, though the relationship was obscured by the small number of patients. Decreased perception of dyspnea in the elderly may be a possible explanation for the lack of awareness of the disease until it progresses, though this remains purely hypothetical [18].

In conclusion, bucillamine can induce life-threatening interstitial pneumonia, especially in the elderly.

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References

1. Sekiguchi N, Kameda H, Amano K, Takeuchi T. Efficacy and safety of bucillamine, a D-penicillamine analogue, in patients with rheumatoid arthritis. Mod Rheumatol. 2006;16:85–91.
2. Hara A, Sakamoto O, Matsumoto M, et al. A case of bucillamine-induced interstitial pneumonia. Nihon Kyobu Shikkan Gakkai Zasshi. 1992;30:1743–8 (in Japanese).
3. Tanaka H, Nakahara K, Goto K. A case of bucillamine-induced pneumonitis. Nihon Kyobu Shikkan Gakkai Zasshi. 1992;30:695–701 (in Japanese).
4. Inokuma S, Sakata M, Yoshida A, Shiratori K, Kiyosawa H. Bucillamine induced pulmonary injury occurs with immunoglobulin decrease. J Rheumatol. 1996;23:1282–5.
5. Fukino K, Shiota T, Nakaya Y, et al. A case of drug-induced interstitial pneumonitis in rheumatoid arthritis treated with bucillamone. Bronchology. 1997;19:232–6 (in Japanese).
6. Lee YH, Kim YR, Ji JD, et al. A case of BOOP developed during bucillamine treatment for rheumatoid. Korean J Intern Med. 2001;16:36–9.
7. Matsushima H, Takayanagi N, Sakamoto T, et al. A case of drug-induced interstitial pneumonitis in rheumatoid arthritis treated with bucillamine. Nihon Kokyuki Gakkai Zasshi. 2001;39(1):55–9 (in Japanese).
8. Miwa Y, Kaga S, Hanaoka R, et al. A case of rheumatoid arthritis complicated with a pneumonitis during concomitant treatment with methotrexate and bucillamine. Ryumachi. 2002;42:70–5 (in Japanese).
9. Kishimoto N, Fujii K. A case of pulmonary infiltration with eosinophilia (PIE) syndrome induced by bucillamine treatment of rheumatoid arthritis. Nihon Kokyuki Gakkai Zasshi. 2002;40:321–5 (in Japanese).
10. Tanimura K, Shimizu M, Matsuhashi M, Shinohara M, Sagawa A. A case of interstitial pneumonia caused by bucillamine: a study using serological markers. Mod Rheumatol. 2006;16:39–43.
11. Nanke Y, Yamada T, Kamatani N. Asymptomatic interstitial pneumonitis induced by bucillamine in a patient with rheumatoid arthritis. Mod Rheumatol. 2005;15:381–2.
12. Kajiya T, Kuroda A, Hokonohara D, Tei C. Radiographic appearance of bronchiolitis obliterans organizing pneumonia (BOOP) developing during Bucillamine treatment for rheumatoid arthritis. Am J Med Sci. 2006;332:39–42.
13. Saito Y, Nei T, Abe S, et al. A case of bucillamine-induced interstitial pneumonia with positive lymphocyte stimulation test for bucillamine using bronchoalveolar lavage lymphocytes. Intern Med. 2007;46:1739–43.
14. Arnett FC, Edworthy SM, Bloch DA, et al. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.
15. Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc. 2007;4:443–8.
16. Negishi M, Kaga S, Kasama T, et al. Lung injury associated with bucillamine therapy. Ryumachi. 1992;32:135–9 (in Japanese).
17. Kurashima K, Nakao S, Fujimura M, Matsuda T. Bucillamine-induced hypersensitivity pneumonitis. Chest. 1992;101:1479–80.
18. Battaglia S, Sandrini MC, Catalano F, et al. Effects of aging on sensation of dyspnea and health-related quality of life in elderly asthmatics. Aging Clin Exp Res. 2005;17:287–92.