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Long-term complications and prognosis of chronic beryllium disease

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Abstract. *Background:* Chronic beryllium disease (CBD) is a rare disease, and there are no previous reports that have followed CBD patients over several decades. Thus, the long-term complications and prognosis of this illness still remain unclear. *Objective:* The aim of this study was to investigate long-term complications and prognosis of CBD patients. *Study design and Methods:* This was a retrospective study based on the medical records of all CBD patients diagnosed at Kyoto University Hospital between the period 1973 to the present day. Ultimately, ten patients whose diagnoses had been made during the period 1973 to 1977 were included. Long-term physiological and radiological change, complications and prognosis of these patients were investigated. *Results:* Three patients completely remitted, and one died of cor-pulmonale. Among the remaining six patients, four have been followed up for more than thirty years in our institute. The majority developed mixed patterns of lung function impairment, cavity lesions of the lung, pneumothorax, and respiratory infections. *Conclusions:* Long-term prognosis of CBD was poor with several complications due to chronic parenchymal and airway lesions. *(Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 24-31)*

Key words: aspergillosis, chronic beryllium disease, noninvasive positive pressure ventilation, pneumothorax, prognosis

Introduction

Beryllium (Be) is an alkaline earth metal, which is widely used in industries as diverse as ceramics, metal machining, automotive, computer, aerospace, and electronics, due to its excellent qualities of hardness, elasticity, and heat and electric conductivity. Chronic beryllium disease (CBD) is a disease caused by inhalation of Be metal, Be oxide (BeO), and other alloys, and predominantly affects the lungs; it is characterized by granuloma formation in the lung (1, 2).

CBD was first described in United States (3), and cases of CBD have also been reported in North America, South America, Europe and Asia (4). In Japan, CBD is extremely rare, and less than 30 cases have been documented previously (5-7). It has been reported that the disease progresses gradually in many CBD patients and that some eventually die of cor-pulmonale and right heart failure (3, 8). However, there are no previous reports that have followed CBD patients over several decades, thus the long-term complications and prognosis of this illness still

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remain unclear. We identified ten patients from the same ceramic company who had been diagnosed with CBD between 1973 and 1977, in seven of whom the initial clinical course had been reported in 1976 (5). Among the ten patients, four have been followed in our institute for more than thirty years. In this report, we have reviewed the clinical course of the ten CBD patients, and investigated their long-term prognosis and complications.

Materials and methods

This retrospective study was performed on all CBD patients diagnosed in Kyoto University Hospital from 1973 to the present date. Eventually, the study was based on ten patients whose diagnoses of CBD had been made during the period 1973 to 1977. In seven of the ten cases, the diagnoses were made based on their history of exposure to Be, histological confirmation of granulomas and positive immunological test for Be sensitization (Tab. 1). In the remaining three cases, the diagnoses of CBD were based on the combination of Be exposure, positive immunological test for Be sensitization, and a compatible chest X-ray abnormality. Immunological test for Be sensitization comprised lymphocyte proliferation test (BeLPT) of peripheral blood or bronchoalveolar lavage fluid (BAL) and Be skin patch test. In this study, chest X-rays were considered to be compatible with CBD when they showed small or large nodules in bilateral lung fields with or with out other findings such as bilateral hilar lymphadenopathy (BHL), ground-glass opacity, and reticular opacity.

BeLPT was performed as follows: both BAL and the peripheral blood mononuclear cell fraction were suspended in RPMI medium (supplemented with 10% bovine serum albumin) and cultured with $BeSO_4$ (0.07 or 0.7 μg/ml) for 5 days. Tritiated thymidine was then added to the well and the cells incubated for a further 24 hours, after which they were harvested using filter paper. The radioactivity on the filter paper was measured using a beta counter. The result was considered to be positive when the ratio of the radioactivity of stimulated cells to unstimulated cells (stimulation index: SI) exceeded 2.0.

The following clinical data were recorded: onset age, gender, symptoms at onset, duration of exposure to Be, pulmonary function indices at diagnosis and at the last visit, follow up period, steroid treatment history, and the prognosis. Pulmonary function indices included percent predicted vital capacity (%VC), forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC), and percent predicted diffusing capacity for carbon monoxide (%DLCO). Published equations for adults were used to determine predicted values of each parameter (9, 10). Respiratory complications were also investigated. The study protocol was reviewed and approved by the Ethics Committee of Kyoto University and Central Clinic of Kyoto. This study had no external funding source.

Clinical course of the ten patients

The demographic and baseline characteristics, diagnostic procedures, treatment and outcome of the ten patients are summarized in table 1 and table 2.

Table 1. Clinical profiles of ten patients with CBD

Case no.	Age at onset / Gender	Symptoms at onset	Exposure duration	At diagnosis			Diagnostic method
				% VC	FEV_1/FVC	%DLCO	
1	24 / f	asymptomatic	6y 1m	80%	95%	76%	BeLPT
2	35 / f	asymptomatic	8y	91%	98%	NA	BeLPT
3	35 / m	cough	4y 9m	99%	86%	85%	OLB*, PT
4	47 / f	DOE, weight loss	3y 6m	41%	78%	NA	OLB, PT
5	28 / f	cough, malaise	1y	66%	91%	46%	OLB, PT
6	38 / f	cough, DOE	5y 11m	41%	78%	NA	OLB*, PT
7	25 / m	cough, sputum	7y 1m	100%	61%	68%	OLB*, BeLPT PT
8	31 / m	cough, DOE	3y 6m	NA	NA	42%	OLB*, PT, BeLPT
9	27 / m	general malaise	5y 2m	101%	88%	70%	PT, BeLPT
10	40 / f	asymptomatic	10y 5m	67%	76%	NA	TBLB, BeLPT

BeLPT, beryllium lymphocyte proliferation test; DLCO, carbon monoxide diffusing capacity; DOE, dyspnea on effort; f, female; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; m, male; m, month; NA, not available; OLB, open lung biopsy (*beryllium metal was detected from lung tissue); PT, skin patch test for beryllium; TBLB, transbronchial lung biopsy; VC, vital capacity; y, year

Table 2. Clinical profiles of ten patients with CBD

Case no.	Follow-up period	Steroid treatment	At last visit:		Prognosis
			% VC	FEV_1/FVC	
1	3y	-	NA	NA	spontaneously remitted in a year
2	12m	-	NA	NA	spontaneously remitted in a year
3	4y 9m	+	97%	80%	remitted in a year
4	13y 2m	+	53%	80%	improved
5	11y 2m	+	43%	97%	persistent disease
6	9y 5m	+	28%	82%	died of cor-pulmonale
7	32y	+	65.2%	46.6%	persistent disease
8	36y	+	60.8%	42.8%	persistent disease
9	33y	+	85.0%	77.0%	persistent disease
10	33y	-	76.1%	66.7%	persistent disease

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; m, month; NA, not available; VC, vital capacity; y, year

Case 1 and Case 2 were found to have a chest X-ray abnormality in a medical check-up, with no clinical symptoms. Chest X-ray showed miliary nodules in the entire lung field. Blood BeLPTs were positive in these patients, thus both patients were clinically diagnosed with CBD. Both patients were followed-up without treatment, and the pulmonary infiltrate had spontaneously disappeared in a year.

Case 3 was treated with oral corticosteroids (parametazone acetate) for 5 months, and the lung lesion had disappeared after one year. There was no recurrence of the lung lesion within the follow-up period of more than 4 years.

Cases 4 and 5 had restrictive lung function impairment at diagnosis (Table 1), and were treated with steroids. In Case 4, ground-glass opacity improved with the treatment (oral parametazone acetate for 6 years). In Case 5, despite the treatment with oral parametazone acetate for 2.5 years, large nodules persisted during the follow-up period of 11 years. These two patients changed to other hospitals, thus they are not currently being followed in our hospital.

Case 6 had large parenchymal nodules predominantly in both upper lung fields with reduced lung volume at diagnosis. Despite treatment with oral parametazone acetate for 2 years and 9 months, with occasional intramuscular (i.m.) injection of triamcinolone acetonide, restrictive lung function impairment worsened, and the patient died of cor-pulmonale after a follow-up period of 9 years.

Cases 7 to 10 are currently being followed at the outpatient clinic of our hospital.

Case 7

This 25-year-old man suffered from cough and sputum production, and had a chest X-ray abnormality in 1975 (Fig. 1). The chest X-ray revealed upper lung dominant nodules (Fig. 2A). Obstructive lung function impairment was found at the initial visit, and treatment with oral parametazone acetate and i.m. triamcinolone acetonide were started. There was no symptomatic, physiological, or radiographic improvement during the treatment period, thus the steroid treatment was tapered off within a year. During the follow-up period, cavity formation of bilateral upper lung fields developed, and he suffered from right pneumothorax twice. In 2003, thickening of the cavity was found (Figs. 2B, C), and aspergillus species were detected in the sputum. He was diagnosed with invasive aspergillosis, and treated with antifungal agents. However, the aspergillosis gradually worsened (Fig. 2D) with deterioration of a mixed pattern of lung function impairment. The patient now suffers from severe dyspnea, and requires continuous oxygen supplementation.

Case 8

This 31-year-old man presented at our hospital in 1971 due to cough and dyspnea on effort (DOE). He had had 3 years' exposure to Be in the ceramic factory, treating the metal with his naked hands. Chest X-ray revealed BHL and small nodules in bilateral lung fields (Fig. 3A). OLB was performed in 1973 to confirm the diagnosis of CBD. Oral parametazone acetate (12 mg/day) was administered

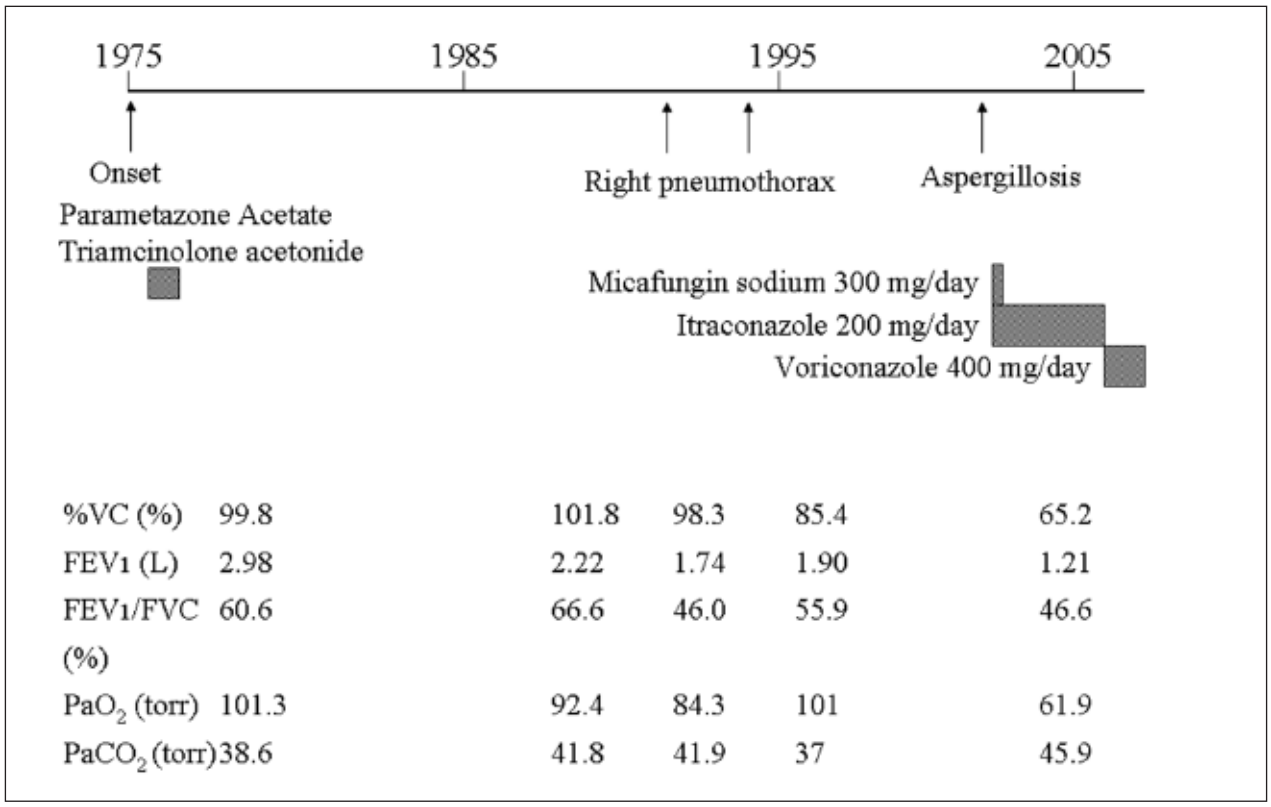


Fig. 1. Clinical course of Case 7

from March 1973 to March 1976, however there was no symptomatic or radiological improvement, thus the drug was tapered off. Since 1992, he suffered from recurrent bacterial airway infections, and was admitted to the hospital five times. Concurrently, a mixed pattern of lung function impairment with hypercapnea developed. After the initiation of oxygen supplementation in 2002, $PaCO_2$ increased to as high as 98 torr in 2003. Nighttime noninvasive positive pressure ventilation (NPPV) was started, and $PaCO_2$ decreased to approximately 60 torr. Chest radiographic changes were unremarkable (Fig. 3B).

Case 9

This 27-year-old male, who had been working in the laboratory, was diagnosed with CBD in 1974. Chest X-ray at onset showed BHL and mild nodular opacities bilateral lung in fields (Fig. 4A). He was treated with oral parametazone acetate from July 1975 to January 1976, however there was no clinical improvement during the treatment. During the following clinical course, nodular opacities became evident, and emphysematous change with cavity formation developed (Fig. 4B), although he had never smoked. In 2003, Mycobacterium avium complex (MAC) was detected in the sputum, and chest computed tomography (CT) scan showed dense shadows around the cavity (Fig. 4C). However, as MAC infection was not detected again, this diagnosis was not definite. Nevertheless, radiographic change suggested the possibility of MAC infection, thus clarithromycin has been administered since. In 2007, right pneumothorax was found on the chest CT scan (Fig. 4D), which was followed-up without treatment. Pulmonary function was preserved in this case, at least before the onset of pneumothorax (Tab. 2).

Case 10

This 40-year-old asymptomatic woman, who had treated Be metal with her naked hands, was

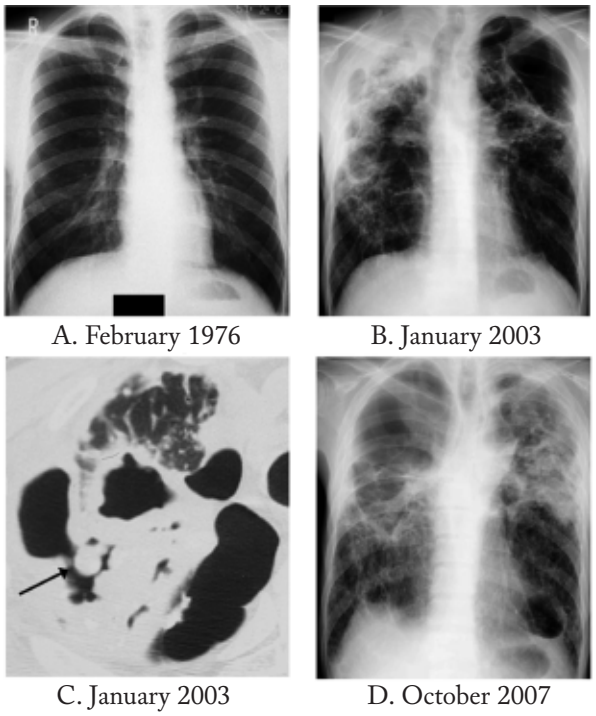


Fig. 2. Chest radiographic images of Case 7. A: Chest X-ray in February 1976. Mild small nodules were found in bilateral lung fields. B: Chest X-ray in January 2003. Cavity lesions developed in bilateral upper lung fields, and thickening of the wall developed at right apical cavity. C: Chest CT scan in January 2003. Thickening of the cavity wall and fungus ball (arrow) was detected. D. Chest X-ray in October 2007. The size of right apical cavity was increased, and dense opacities extended in both lung fields

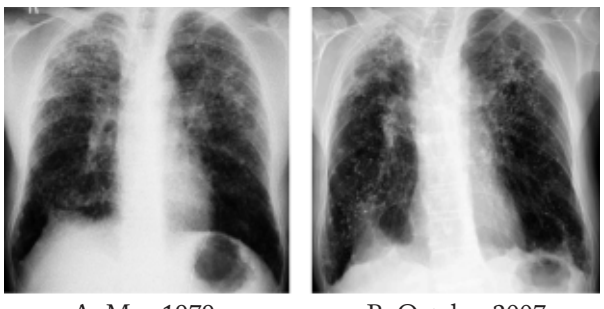


Fig. 3. Chest radiographic images of Case 8. A: Chest X-ray in May 1979. Nodular shadows were found predominantly in bilateral upper lung fields. B: Chest X-ray in October 2007. Decrease of upper lung volume with tracheal deviation and traction of diaphragm had gradually developed

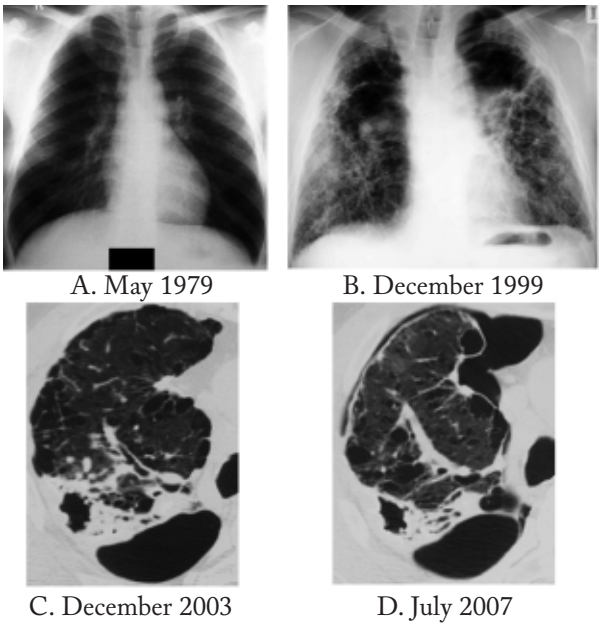
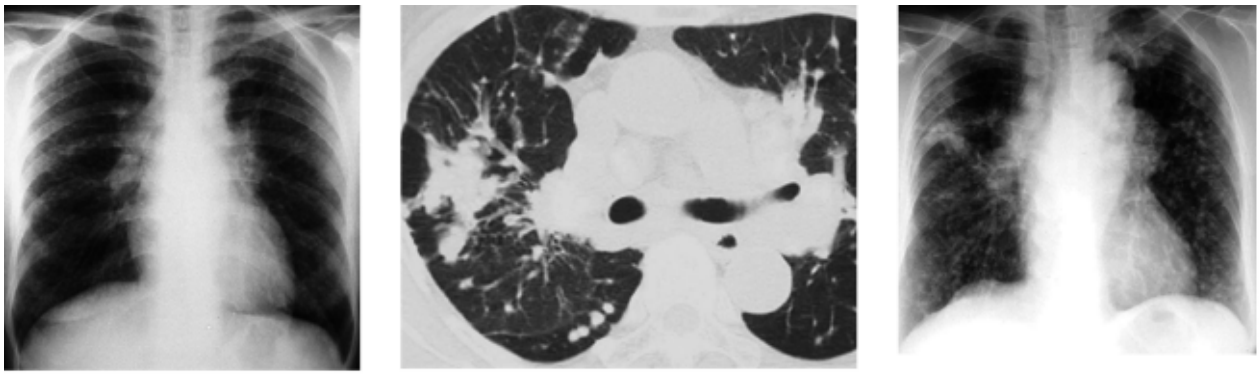


Fig. 4. Chest radiographic images of Case 9. A: Chest X-ray in May 1979. Mild nodular shadows were found in bilateral upper lung fields. B: Chest X-ray in December 1999. BHL and nodular opacities had worsened. Decreased attenuation was found in bilateral upper lung fields. C: Chest CT scan in December 2003. Dense shadows around cavity developed in the right upper lobe. D. Chest CT scan in July 2007. Pneumothorax was found in right lung

found to have BHL and nodular shadows on the chest X-ray (Fig. 5A) at a medical check-up, and was diagnosed with CBD in 1974. She was followed without treatment, and the lung opacity gradually deteriorated (Fig. 5B). In 2007, a pacemaker was implanted due to complete atrio-ventricular block (Fig. 5C). Recently, mixed type lung function impairment (Tab. 2) with mild hypoxemia (PaO_2 64.7 torr at the last visit) has developed.

Results

Among the ten cases with CBD, three patients remitted, six had persistent disease, and the remaining patient died of cor-pulmonale. The complications found in three patients (Cases 7-9), who have been followed long-term up to the present day, are summarized in table 3. Persistent CBD frequently led to the formation of cavity lung lesions, mixed pattern lung function impairment, pneumothorax, and respiratory infections.



A. July 1979 B. October 2006 C. May 2007

Fig. 5. Chest radiographic images of Case 10. A: Chest X-ray in July 1979. BHL with diffuse nodular shadows were detected. B: Chest CT scan in October 2006. Nodular lesions were focally fused to make a dense large nodule. C. Chest X-ray in May 2007. Nodular opacities became evident, and decreased attenuation was found in bilateral upper lung fields. A pacemaker was implanted due to the development of complete atrio-ventricular block

Discussion

In this report, we have reviewed the long-term clinical course of ten patients with CBD, who had all worked for the same ceramic company in Japan during the period 1973 to 1977. After making the diagnosis of CBD in four symptomatic cases, the authors then checked all chest radiographic findings of the employees in the ceramic company, from which they detected an additional six cases based on the presence of the chest radiographic abnormality. All ten patients stopped working in the ceramic plant after the diagnosis of CBD had been made. After the detection of these cases, the company improved air-conditioning of the workplace, and made workers wear masks and gloves. Since the introduction of these new working practices, annual chest X-ray surveillance of all workers has not detected any new CBD patients in this company. Although X-ray surveillance may not have been sensitive enough to detect mild CBD cases (11), the new working practice might have prevented the development of new CBD cases. Another possibility is a change in the ceramic manufacturing process which resulted in the almost complete absence of Be at the ceramic company which is the subject of the present report. Indeed, we have experienced no CBD patients after the detection of these ten cases. When we arrive at a diagnosis of a granulomatous disorder, we always screen patients with respect to their exposure to beryllium. However, Be sensitization is never investigated in the patients unless Be exposure has been suspected, thus we cannot completely exclude the possibility that CBD patients have been misdiagnosed with other disorders such as sarcoidosis.

Regarding lung function, it has been reported that airflow limitation is found earlier and more frequently than pure restriction in CBD patients (8, 12). In the patients in this study, restrictive change was more frequent than obstructive change at diagnosis (Tab. 1). However, mixed pattern lung function impairment developed during the long-term clinical course (Table 2, Table 3). The physiological change of the patients in this study suggested that mixed pattern lung impairment occurred frequently in the advanced stages of CBD, although concurrent infection might have affected the lung function. Radiologically, parenchymal nodules, septal lines, ground glass opacities and BHL have been reported to be found in CBD, and have been detected more sensitively by thin-section CT scan than by plain chest X-ray (11). However, cavity formation and pneumothorax have not been emphasized as radiographic findings of CBD. To the best of our knowledge, cavity formation and pneumothorax in CBD have been reported in only a few papers (6, 13). The present cases showed that cavity formation and pneumothorax are relatively frequent findings in the advanced stages of CBD, although the radiographic findings might also have been influenced by the infections.

Although no controlled clinical trial has been undertaken to evaluate corticosteroid therapy in

Table 3. Complications of the three patients with CBD

Case No.	Current Age (years)	Gender	Cavity Formation	Mixed Lung Function Impairment	Pneumothorax	Other Complications
7	57	m	+	+	+	aspergillosis
8	67	m	+	+	-	recurrent airway infection
9	59	m	+	-	+	MAC infection

f, female; MAC, *Mycobacterium avium* complex; m, male

CBD, dramatic response to such therapy has been documented (7, 14). However, long-term steroid therapy may increase the risk of respiratory infections such as aspergillosis (6), as was found in Case 7 of the present report. Patients treated with corticosteroid in this study did not show marked clinical improvement except for Case 3 who remitted with the therapy. However, because of the relatively short term treatment period, the effect of long-term steroid treatment can not be concluded from this study. Taking the frequent complication with chronic or recurrent respiratory infections into account, we think that steroids should not be continued without frequent clinical review in patients with CBD.

The number of patients in this report was too small to investigate prognostic factors of CBD. However, patients who were asymptomatic at disease onset and only found by medical check-up (Cases 1, 2, 10) tended to have a favorable prognosis. The exposure duration did not seem to affect the prognosis.

We recognize that our study has limitations. Firstly, the study was retrospective in design. Secondly, the cut-off values of BeLPT (SI 2.0) were based on small control samples (n=4 for blood, SIs ranged from 0.65 to 1.84; n=2 for BAL, SIs were 0.51 and 1.00). In addition, the test was not repeated to exclude false positive results. However, the SIs of BeLPT in the present patients (4.2-6.6 in blood, and 11.0-38.3 in BAL) were higher than the cut-off values used in previous studies (1.4-3.5 in blood and 3.8-5.1 in BAL) (15-18), which suggested a high possibility of Be sensitization in these patients. Thirdly, chest HRCT was not used in the initial radiographic assessment of CBD. Due to the lack of histological confirmation and HRCT data, we consider that Cases 1 and 2 were "possible CBD", but not "definite CBD", although there were no clinical signs in either case to suggest other lung diseases which can show miliary lung nodules. If these patients were excluded, the overall prognoses of the CBD patients might have been even worse.

In summary, the clinical courses of ten patients with CBD were reviewed. Although three patients remitted, six had persistent disease, and one died of cor-pulmonale. Long-term survivors frequently suffered from mixed pattern lung function impairment, chronic or recurrent respiratory infections, and pneumothorax. We conclude that long-term prognosis of CBD was poor with several respiratory complications.

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