

Significant Improvement from Chronic Beryllium Disease Following Corticosteroid Pulse Therapy

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Abstract: Chronic beryllium disease (CBD) is a rare disease characterized by diffuse interstitial pulmonary granulomatosis. We report a case of CBD which exhibited marked improvement both subjectively and objectively following pulse therapy. The patient was a 36-year-old man whose chief complaint was dyspnea and a dry cough. Since July 1990, the patient had been working in the development of an automatic or mechanical technique for producing beryllium-copper alloy. It appeared likely that the patient may have been exposed to metal beryllium fumes generated from an opening located just above the furnace. The Be concentration exceeded 25 $\mu\text{g}/\text{m}^3$ transiently in the breathing zone in this workplace. A chest X-ray film taken in October 1994 showed fine granular shadows throughout the entire lung fields.

Around August 1998, the patient's dyspnea became aggravated. An X-ray taken at that time showed linear and reticular shadows, in addition to the diffuse fine granular shadow. In October 1998, after 3 days of methylprednisolone pulse therapy, oral prednisolone 30 mg was initiated. With this treatment, the patient's pulmonary function tests and blood gases improved. Once the patient's condition had improved sufficiently, the dosage of prednisolone was decreased by 2.5 mg every two weeks. The patient continues to be monitored.

Key words: Beryllium, Chronic beryllium disease, Corticosteroid pulse therapy, Diffuse interstitial pulmonary fibrosis, Lymphocyte transformation test

Chronic beryllium disease (CBD) is a rare disease characterized by diffuse pulmonary interstitial granulomatosis. Twenty-four cases of CBD have been reported in Japan¹.

CBD occurs as a result of inhalation exposure to beryllium compounds (particularly beryllium oxide [BeO]), and is caused by a type IV allergic response².

We report a case of CBD which showed marked improvement both subjectively and objectively following pulse therapy.

Case: The patient was a 36-year-old man with a chief complaint of dyspnea and a dry cough.

Past history: There was no remarkable medical or fam-

ily history.

Occupational history: The patient was employed as an industrial engineer in 1988.

Since July 1990, the patient had been working in a beryllium-related field developing an automatic mechanical technique for producing beryllium-copper alloy. More specifically, he had been engaged in designing automatic mechanical procedures for raking out sludge that was the result of dissolving BeO and copper at the reduction furnace during the production of beryllium-copper alloy (containing approximately 4% beryllium) and during the production of beryllium-copper alloy (containing approximately 2% beryllium) from beryllium alloy.

Present illness: In October 1994, a routine chest X-ray (Fig. 1) showed fine granular shadows throughout the

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Fig. 1. Chest radiograph on October 13, 1994.



Fig. 2. Chest radiograph on October 2, 1998.

lung fields. There were no other symptoms or signs. Pulmonary-function tests indicated that the percent vital capacity (%VC) was 87%, and that the percent forced expiratory volume in one second (FEV1.0%) was 81%. At that time, the patient was prohibited from continuing this work. A follow-up chest X-ray obtained in November showed findings similar to the findings of the previous month. A beryllium-specific lymphocyte transformation test (Be-LT) was negative (100–190%) until March 1994, but by November had clearly turned positive (927%). A chest X-ray in March 1995 showed almost the same shadows as were seen on the previous examination in October. There were no symptoms or signs. Pulmonary-function tests showed a %VC of 85% and FEV1.0% of 80%. However, since the Be-LT gave a stronger positive reaction (2,108%), the patient was suspected of having CBD. At that time, relocation of personnel from the Be workplace was carried out. After the patient experienced mild dyspnea in July 1995, betamethasone (1.5 mg) was started in August. The symptoms improved, and the dosage of betamethasone was gradually decreased.

Around August 1998, the patient's dry cough, anorexia, weight loss, and dyspnea became aggravated. On October 5, the patient visited the company-affiliated clinic. On examination, the patient had dyspnea (Hugh-Jones IV) and cyanosis of the lips and nails. A chest X-ray showed linear and reticular shadows, in addition to the diffuse fine granular shadows (Fig. 2). The patient's pulmonary function had decreased (%VC, 47%; FEV1.0%, 62%). On blood gas analysis, the PaO₂ was 50.4 torr and the PaCO₂ was 42.6 torr, indicating marked hypoxemia. The patient was admitted to the division of respiratory disease at our university hospital on October 6 for defin-

itive diagnosis and treatment.

On admission, the patient's height was 170 cm, weight 58 kg, temperature 36.7 °C, and blood pressure 120/80 mmHg. His pulse was 84 per minute and regular, and his respiratory rate was 18 per minute and regular. Mild cyanosis of the fingers was noted. Heart sounds were normal; no murmurs were heard. Respiratory sounds were normal.

Laboratory findings on admission included normal white-blood-cell and red-blood-cell counts. Serological testing revealed an increase in ACE (27.4 IU/l).

Immunological testing showed increased IgG, IgM, and IgD levels, decreased T-cells (CD3) (38.8%), and a CD4/CD8 ratio of 0.51 (Table 1).

Chest CT on October 9 showed diffuse granular shadows in both lung fields and linear shadows in the upper and middle lung lobes. Slightly enlarged lymph nodes were noted in the pretracheal and subaortic arch regions (Fig. 3).

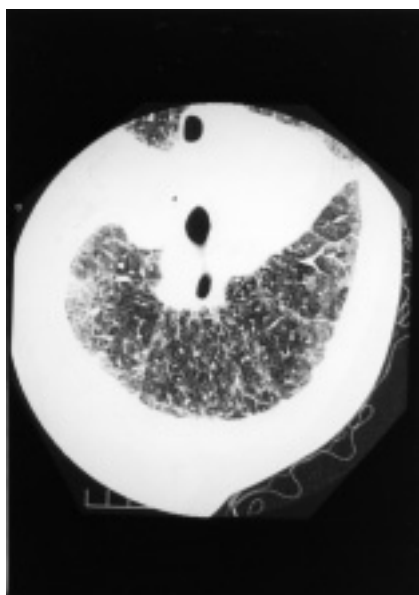
Bronchoscopic examination on October 13 revealed no bronchial constriction or vascular dilatation. The secretions were normal. There were no contributory findings noted in the endobronchial cavity.

Bronchoalveolar lavage fluid (BALF) was collected from the right B5a lung segment. The findings are shown in Table 2. Bronchoalveolar lavage cells showed a noticeable increase in CD3, and a decrease in CD19. The CD4/CD8 ratio was 35%. A decrease in macrophages and an increase in lymphocytes, neutrophils, and eosinophils were observed.

Transbronchial lung biopsy specimens were bronchoscopically collected from the right B3a and B8a lung segments. As shown in Fig. 4, multiple nodules, composed of histiocytes containing Langhans-type giant cells, had

Table 1. Laboratory findings on admission

Hematology		Serum	
WBC	4,400/ μ l	ESR	30 mm/h
seg	47%	CRP	0.5 mg/dl
stab	0%	CH50	41.5 U/ml
eos	6%		
baso	1%	Immunology	
lym	38%	IgG	3,040 mg/dl
mono	8%	IgM	308 mg/dl
RBC	$566 \times 10_4/\mu$ l	IgD	18 mg/dl
Hb	16.7 g/dl	IgE	243 IU/ml
Ht	48.3%	CD3	38.8%
Plt	$22.4 \times 10_4/\mu$ l	CD19	18.2%
		CD4	11.6%
		CD8	22.6%
		CD4/CD8	0.51
Biochemistry		PPD (0.05r)	$7 \times 8/25 \times 20$
Na	141 mEq/l	Sputum culture	
K	4.1 mEq/l	normal flora	(+)
Cl	104 mEq/l	Mycobacterium	(-)
BUN	13 mg/dl	Arterial blood gas(O ₂ 3L/min)	
Cr	0.6 mg/dl	pH	7.39
UA	7.0 mg/dl	pCO ₂	47.7 torr
TP	8.7 g/dl	pO ₂	76.6 torr
Alb	4.0 g/dl	Arterial blood gas(room air)	
AST	26 mU/ml	pH	7.47
ALT	22 mU/ml	pCO ₂	42.6 torr
LDH	185 mU/ml	pO ₂	50.4 torr
ALP	32 mU/ml		
CHE	4,500 mU/ml		
ACE	27.4 IU/l		

**Fig. 3.** Chest CT scan on October 9, 1998.**Table 2. BAL analysis on October 13, 1998**

Recovery	50%
Total cell counts	$2.0 \times 10^5/\text{ml}$
Macrophage	74.9%
Lymphocyte	14.8%
Neutrophil	3.6%
Eosinophil	6.7%
CD3(T cell)	94.3%
CD19(B cell)	0.1%
CD4	24.3%
CD8	69.3%
CD4/8	0.35%

formed in the cell interstitium. In addition, a non-necrotic epithelioid granulomatosis and invasion of small lymphocytes were observed surrounding the nodules.

The patient was finally diagnosed as having an acute exacerbation of CBD based on the following findings: (1) occupational history of beryllium exposure (Be fumes as BeO); (2) histopathological evidence of epithelioid cellular granulomatosis of the lung; (3) beryllium sensitization (positive Be-LT); (4) diffuse fine granular shadows on X-ray films and CT scan of the chest; (5) restrictive and diffusing disorders documented on pulmonary-function tests, and hypoxemia on blood gas analysis; and (6) symptoms and signs.

During the patient's hospital stay, bronchoscopy was done on October 13. After 3 days of methylprednisolone pulse therapy, oral prednisolone 30 mg was initiated. The results of pulmonary function testing and blood gas analy-

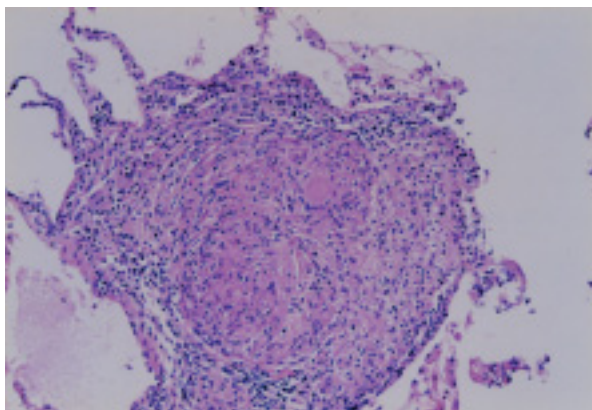


Fig. 4. Pathologic findings of a transbronchial lung biopsy.

sis before and after corticosteroid pulse therapy are shown in Table 3. The %VC, pulmonary diffusing capacity, and hypoxemia tended to improve. After the patient's condition improved sufficiently, the prednisolone dosage was decreased by 2.5 mg every two weeks. The patient was discharged from hospital on December 11.

Discovered in the first half of the 19th century, beryllium became an indispensable metal for the development of the nuclear and aerospace industries in the 1940s. Recently, the demand for beryllium-copper alloy has risen as a result of its use as a point of contact and a spring material for electronic machine parts. The health hazards of beryllium exposure have been reported from about 1943, with some 900 reported cases, a significant portion from the United States³⁾.

In Japan, low temperature calcination and the high purity of active BeO have received much attention as being major contributing factors of CBD, and have actually been found to be involved in the occurrence of CBD in 22 of 24 previously reported Japanese cases¹⁾.

The first Japanese case of CBD was reported in 1964 and involved a man engaged in the chemical analysis of beryllium⁴⁾. In the 1970s, 22 additional cases of CBD apparently involving BeO exposure were reported. Most of these CBD patients had been occupationally exposed to beryllium in the 1960s, when the safety of the workplace environment was not as well managed as today. Since then, the work environment in Be-related factories has improved remarkably. As a result, coupled with the enforcement of rules on the prevention of hazards by specific chemical substances in 1972, there has been no occurrence of new patients at the Be-related factories. Nevertheless, two cases of CBD were reported in the

Table 3. Pulmonary function tests and blood gas analysis

	1998/			1999/		
	10/7	10/16	10/26	11/26	12/17	2/22
VC (ml)	2400	3050	3240	3640	2890	3360
%VC (%)	59.3	76.5	80.0	89.9	71.3	83.0
FEV _{1.0} (ml)	1280	1710	1960	2170	1950	2370
FEV _{1.0} % (%)	59.3	60.6	65.8	64.8	67.0	77.4
%DLco (%)	45.2	52.1	59.4	58.2		67.7

	1998/			1999/		
	10/6	10/15	10/20	11/2	1/11	2/22
pH	7.39	7.43	7.41	7.40	7.47	7.42
Paco ₂ (torr)	47.7	45.2	42.7	38.6	40.1	40.1
Pao ₂ (torr)	76.6	110.4	78.4	88.3	70.5	75.7

	O ₂ 3 L/min	room air

1980s^{5, 6)}. One case involved a woman engaged in shaving beryllium-copper alloy⁵⁾, and the other involved a man responsible for lengthening beryllium-copper alloy wire⁶⁾.

The present case involved an engineer involved in the development of production technology who was conducting examinations of equipment. This equipment was being re-introduced for the purpose of automating the disposal of sludges that occur in the process of reducing imported BeO powder in an arc furnace and in the process of making an ingot of about 2% Be-copper alloy from 4% Be-copper alloy in an arc furnace and a reducing furnace in an area where workers are generally not allowed. At these workplaces, two workers were assisting the patient as needed, but no health-related abnormalities occurred in these workers. It appears likely that the patient may have been exposed to metal beryllium fumes, which are assumed to change immediately to BeO when exposed to air, that were generated from an opening just above the furnace, rather than by the BeO powder itself. The results of the environmental measurement taken in October 1994 confirmed that the Be concentration exceeded $25 \mu\text{g}/\text{m}^3$ transiently in the breathing zone in this workplace. Local ventilation equipment of the ring-hood type was installed in the workplace, but the local ventilation equipment sometimes failed to work during the construction work of the automation process. Furthermore, it was confirmed that wearing of a dust-proof mask became incomplete when one worker gave an instruction to the other worker during work.

Our patient's Be-LT findings were negative until March 1994, and then turned positive in November 1994. Given these findings, it can be assumed that the time during which beryllium exposure was directly involved with the occurrence of CBD was from March to November 1994, when the mechanization of the sludge processing at the reduction furnace was actually being tested.

Both a decrease in the ratio of T-lymphocytes in the peripheral blood and an increase in the ratio of T-lymphocytes to bronchoalveolar lavage cells were observed. The CD4/CD8 ratio decreased in the peripheral blood and the BALF. It is frequently reported that CBD is associated with the accumulation of T-lymphocytes in the peripheral blood, an increase in the ratio of T-lymphocytes to bronchoalveolar lavage cells, and an increase in the CD4/CD8 ratio. In our patient, although T-lymphocytes in the BALF were markedly increased, the CD4/CD8 ratio decreased. CD8 cells are suppressor/cytotoxic cells. These findings may reflect the fact that the immune response is fully maintained and is not significantly inhibited in cases, such as ours, of early CBD⁷⁾. Confirmation of this phenomenon must await further follow-up to examine changes in the lymphocyte subsets in BALF. With respect to humoral immunity, since hyper-

gammaglobulinemia and elevated serum levels of IgG, IgM, and others were observed in our patient, as has also been reported elsewhere, much attention has been given to the involvement of humoral immunity, as well as cell-mediated immunity, due to beryllium exposure, in the occurrence of CBD.

On the other hand, biochemical testing showed an increase in ACE, as has been seen with sarcoidosis. ACE has been shown to decrease or increase depending on the pathologic state of CBD⁸⁾. Given this, our patient requires further follow-up.

As soon as a definite diagnosis of CBD is made, whether acute or chronic, beryllium exposure should be terminated and rest, symptomatic therapy, and occasional oxygen inhalation therapy needs to be initiated. Although no definitive therapy for CBD has been established, adrenocortical hormone agents are very effective therapy for respiratory symptoms, such as coughing and dyspnea. Such drugs are known to occasionally have a marked effect on symptoms, particularly with acute aggravations of CBD. The corticosteroid pulse therapy that was used with our patient was similar to the large doses of steroid hormone used with renal transplantation by Kounts *et al.* in 1969⁹⁾. In Japan, pulse therapy was used for idiopathic interstitial pneumonia by Yoneda *et al.* in 1978¹⁰⁾. Since then, it has been considered that this therapy is applicable mainly to cases of idiopathic interstitial pneumonia¹¹⁾. We believed that corticosteroid pulse therapy was indicated in our patient, since his CBD was aggravated relatively rapidly. However, if the medication is interrupted, even after the patient's condition stabilizes, CBD has been found to frequently relapse or become aggravated. In some reports, CBD gradually progressed or was spontaneously cured¹²⁻¹⁴⁾. Clearly, our patient requires further monitoring.

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