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Hard Metal Lung Disease with Favorable Response to Corticosteroid Treatment: A Case Report and Literature Review

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Hard metal lung disease (HMLD) is a pneumoconiosis caused by occupational exposure to hard metals such as tungsten carbide and cobalt, but the treatment strategies for HMLD have not been well established. A 68-year-old Japanese man with occupational history as a grinder of hard metals for 18 years referred to our hospital because of dry cough and dyspnea. A chest computed tomography (CT) on admission revealed centrilobular micronodules, ground-glass opacities, and reticular opacities in the peripheral zone of both lungs. Mineralogic analyses of lung tissues detected components of hard metals, such as tungsten, titanium and iron, and the same metals were also detected in the sample of the dust of his workplace. Thus, the patient was diagnosed as having HMLD based on occupational exposure history and radiologic and mineralogic analyses of the lung. Corticosteroid therapy was initiated, which resulted in partial improvements in his symptoms, radiological and pulmonary functional findings. In a review of the 18 case reports of HMLD treated with corticosteroids, including our case, the majority of patients (77.8%) showed favorable responses to corticosteroid treatment. Furthermore, the presence of fibrotic changes, such as reticular opacity, in radiological examinations was associated with the resistance to corticosteroids. In conclusion, the majority of patients with HMLD are expected to favorable response to corticosteroid treatment, whereas chest CT findings such as fibrotic changes may be predictive of the resistance of corticosteroid treatment. Lastly, proper prevention of hard metal exposure is most important as the first step.

Keywords: corticosteroid; hard metal lung disease; hard metals; interstitial pneumonia; treatment
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Introduction

Exposure to hard metals may lead to the development of occupational asthma and hypersensitivity pneumonitis (HP)-like interstitial lung diseases, recognized as hard metal lung disease (HMLD) (Rehfisch et al. 2012; Tanaka et al. 2014). HMLD, first reported in 1940 in Germany, is a type of pneumoconiosis caused by occupational exposure to hard metals, with a substantially shorter exposure time than silicosis (Jobs and Ballhausen 1940; Coates and Watson 1971). The main components of hard metals are tungsten carbide and cobalt, with small quantities of other materials, such as chromium, nickel, titanium, and tantalum, also present in varying degrees. Because of their extreme hardness, hard metals are widely used for cutting and sharpening metals, drilling wells, polishing diamonds, and dental prostheses (Mizutani et al. 2016). The diagnosis of HMLD is essentially given by occupational exposure history to hard metals, the clinical, radiological, and pathological findings of interstitial lung diseases, although the diagnostic criteria of HMLD used in each report show some differences (Coates and Watson 1971; Tanaka et al. 2014).

The radiological and pathological characteristics of HMLD partially resemble HP (Coates and Watson 1971; Gotway et al. 2002; Tanaka et al. 2014; Mizutani et al. 2016), and giant cell interstitial pneumonia (GIP), multinucleated giant cells in the airspaces with interstitial pneumonia with centrilobular fibrosis, is the common pathological finding; however, other pathological fibrotic patterns, such as the usual interstitial pneumonia (UIP) pattern, can also be seen (Ohori et al. 1989; Akira 1995; Moriyama et al. 2007; Tanaka et al. 2014). The pathological patterns of HMLD consist of both GIP and UIP, and the UIP pattern is thought to be a prominent feature in advanced cases of the disease. Appropriate treatment strategies for HMLD have not yet been established. We herein report a case of HMLD

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that responded to corticosteroid treatment, and review reported cases of HMLD treated with corticosteroids.

Clinical Report

A 68-year-old Japanese man was referred to our hospital because of persistent dry cough and progressive dyspnea. He worked as a grinder of hard metals for 18 years between the ages of 49 and 67, and had been an ex-smoker since he was 45 years old, with a previous smoking history of 25 pack-years. On admission, the subject's body temperature, pulse rate, and respiratory rate were 36.5°C, 75 beats/min, and 16 breaths/min, respectively. Modified Medical Research Council dyspnea scale (mMRC) grade was three, and the six-minute walk test (6MWT) revealed that the distance in six minutes walkable was 270 m, and the minimum arterial oxygen saturation of pulse oximetry (SpO_2) (room air) during 6MWT was 86%. On chest auscultation, fine crackles were audible in the bilateral lower lung fields. Clubbed fingers were not observed.

The laboratory data on admission revealed elevated levels of KL-6 (807 U/mL, cutoff level: 500 U/mL) and surfactant protein D (SP-D) (199 ng/mL, cutoff level: 110 ng/mL). His peripheral blood white blood cell count was 8,500/mm^3 (eosinophils, 6.0%). The representative tests for collagen disease-related autoantibodies were all negative. The pulmonary function test results were as follows: total lung capacity, 2.78 L (69.0% of the predicted value); forced vital capacity, 1.38 L (47.0% of the predicted value); forced expiratory volume in 1 s, 91.0%; and carbon monoxide diffusion capacity (DL_{CO}) of the lung, 7.51 mL/min/mmHg (67.0% of the predicted value). A chest radiograph (Fig. 1) showed ground-glass opacities (GGOs) and reticular opacities in bilateral lung fields. High-resolution computed tomography (CT) (Fig. 2A, B) revealed GGOs and consoli-

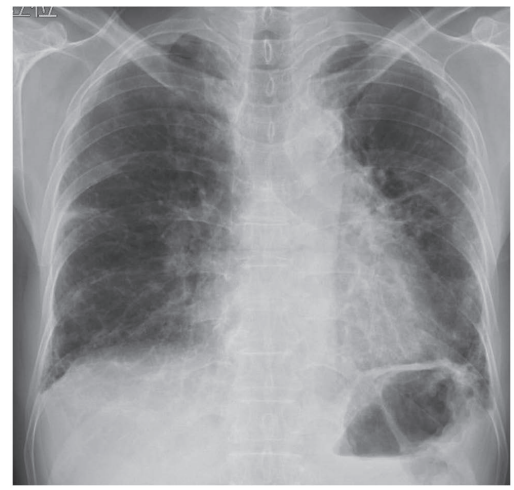

Fig. 1. A chest radiograph on admission.
Chest radiograph on admission, showing ground-glass opacities and reticular opacities with the reduction in lung volume.

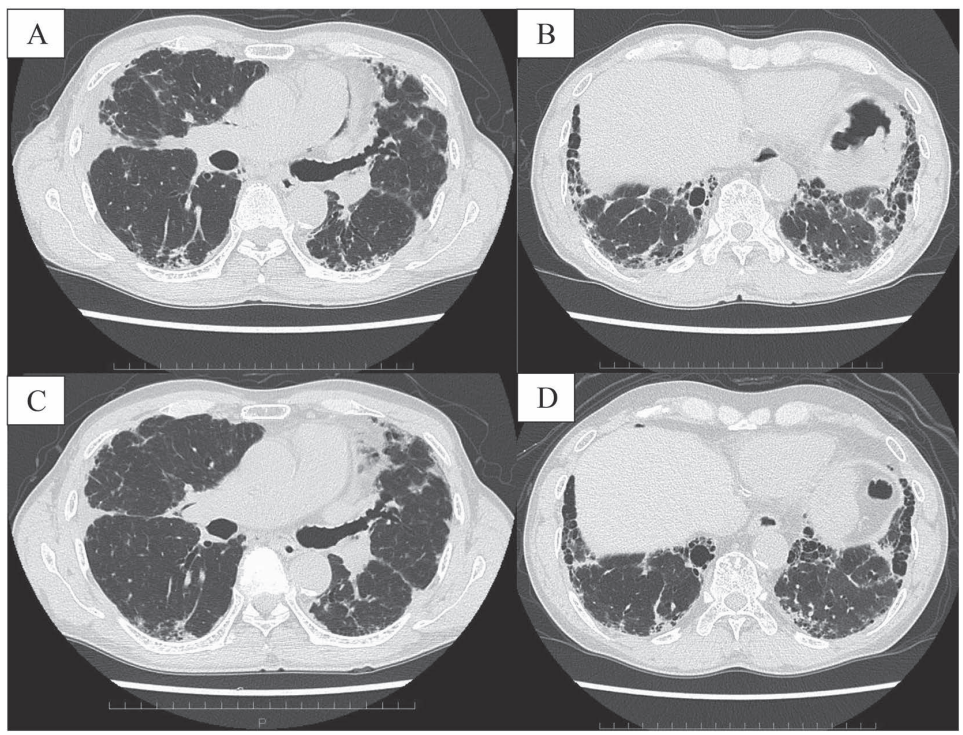

Fig. 2. A chest CT scan on admission.
Chest computed tomography (CT) on admission (A and B) and 2 months after starting corticosteroid therapy (C and D), showing micronodules, ground-glass opacities, consolidations, reticular opacities, and traction bronchiectasis, predominantly in both peripheral lung areas with a reduction of lung volume (A-D). Micronodules and ground-glass opacities were partially improved by corticosteroid treatment (C and D).

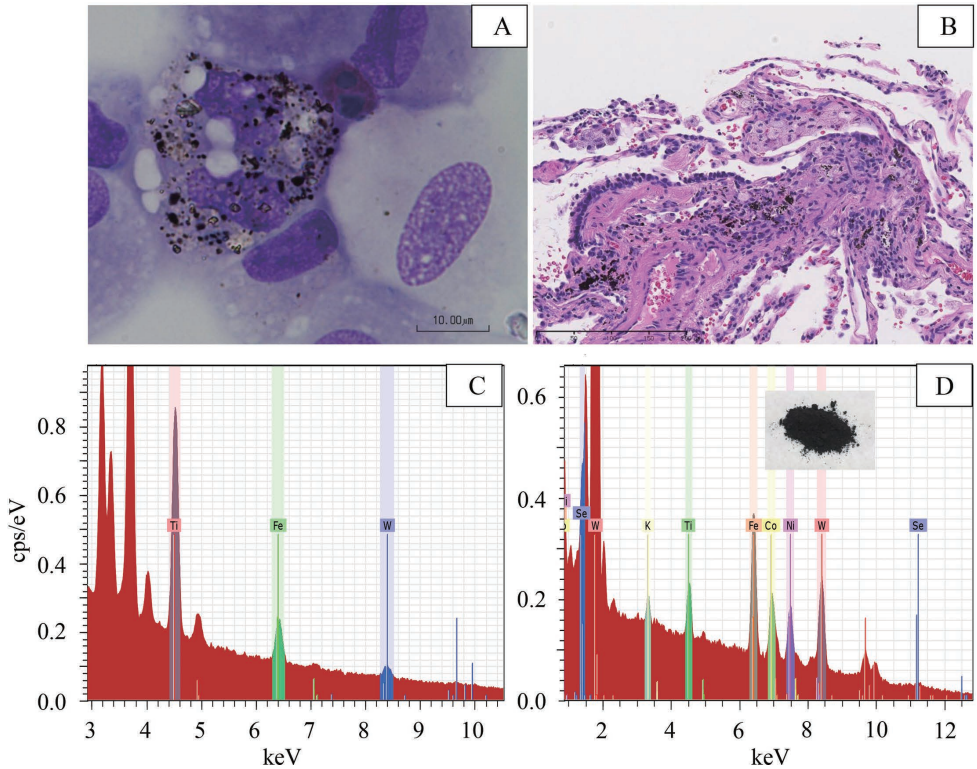

Fig. 3. Pathological findings and X-ray microanalysis of lung specimen or dust sample.
Bronchoalveolar lavage fluid revealed phagocytosis of particles by macrophages (A). Pathological specimens obtained by transbronchial lung biopsy (TBLB) showed chronic inflammation, fibrotic change, and the deposition of particles (B). In the field of TBLB sample, X-ray analytical electron microscopy (S-4500 Hitachi, Japan) detected peaks of hard metal components such as tungsten (W), titanium (Ti) and iron (Fe) (C). In addition to these components, other hard metal components, including cobalt (Co) and nickel (Ni), were detected in the sample of the dust obtained from the workplace of the present patient (D).
Co, cobalt; Fe, iron; K, potassium; Ni, nickel; Se, selenium; TBLB, transbronchial lung biopsy; Ti, titanium; W, tungsten.

dations with centrilobular micronodules, reticular opacities, and traction bronchiectasis, predominantly in the peripheral zone of both lungs with the reduction of the lung volume.

An analysis of bronchoalveolar lavage fluid (BALF) obtained from the middle lobe (right B5a) yielded 1.5×10^5 cells/mL (77% macrophages, 10% lymphocytes, 5% neutrophils, and 8% eosinophils) with a normal CD4/CD8 ratio of 1.3, and phagocytic findings in particles of alveolar macrophages were observed (Fig. 3A). Pathological specimens obtained by transbronchial lung biopsy (TBLB) exhibited chronic inflammatory and fibrotic changes with particle deposition, but multinucleated giant cells with cannibalism (cell engulfment) were not observed (Fig. 3B). X-ray analytical electron microscopy (S-4500 Hitachi, Japan) of TBLB tissue detected diffusely distributed hard metal components such as tungsten, titanium and iron (Fig. 3C). In addition to these components, other components of hard metal, including cobalt and nickel, were detected in the dust obtained from his work place (Fig. 3D).

The patient was diagnosed with HMLD based on the history of occupational exposure to hard metals, the clinical, radiological, and pathological findings of interstitial lung disease, and the detection of components of hard metals, including tungsten from his lung tissues and the dust from his workplace (Coates and Watson 1971).

Because his respiratory symptoms such as dry cough and shortness of breath continued in spite of retiring from work, corticosteroid therapy (prednisolone [25 mg/day]) was initiated, which resulted in partial improvements in the symptoms of dry cough and shortness of breath, mMRC, 6MWT, radiological findings, and the findings of pulmonary function tests; subsequently, prednisolone was gradually tapered (Figs. 3C, D and 4). He was discharged from our hospital after being advised not to perform similar work again.

Discussion

The present patient with HMLD was successfully treated with corticosteroids. We searched for reports of patients with HMLD treated with corticosteroids in English and Japanese articles, and their references in PubMed, and reviewed a total of 18 cases, including our patient (Tables 1 and 2). Fourteen patients (77.8%), including our patient, responded to corticosteroid treatment, whereas the remaining four patients (22.2%) did not show improvement. As seen in our patient, these observations suggest that many

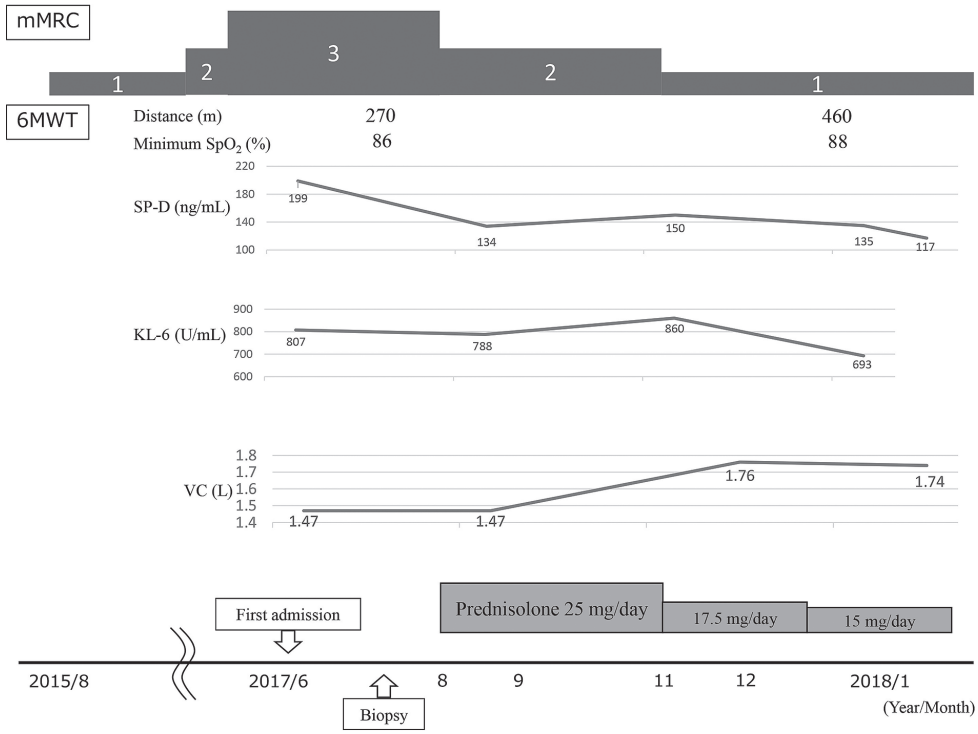

Fig. 4. The clinical course of the patient.
mMRC, modified medical research council dyspnea scale; 6MWT, six-minute walk test.

Table 1. Clinical characteristics of hard metal lung disease treated with corticosteroids.

Case	Age / Sex	Smoking History	Exposure period (y)	Chest Computed Tomography						Pulmonary Function Test		
				GGO	MNO	CD	RO	BE	HCM	%VC	%FEV1	%DLCO
Responders to corticosteroid therapy												
Mizutani et al.	30 / M	Never	6	+			+	+		63	65	72
Mizutani et al.	30 / M	Never	8		+					63	60	107
Nakamura et al.	63 / M	Former	40	+		+		+		76.1	89.1	N/A
Nureki et al.	46 / M	Never	5	+	+					106.7	71.8	90.3
Kim et al.	32 / F	Never	10	+	+					N/A	N/A	N/A
Sakai et al.	21 / M	Never	3	+	+					N/A	N/A	N/A
Moreira et al.	27 / M	Former	8	+	+					34	N/A	60
Bezerra et al.	50 / M	Former	9	+				+	+	51.2	46.9	N/A
Sakamoto et al.	35 / M	Current	17	+	+		+	+		67.4	79.3	34
Enriquez et al.	58 / M	Former	38	+						N/A	N/A	N/A
Yokota et al.	32 / F	N/A	4		+					39.7	80.7	16
Schwarz et al.	51 / M	Never	N/A		+					44.2	55.8	51.3
Dunlop et al.	34 / M	Never	15	+	+			+		35	N/A	24
Present case	68 / M	Former	18	+	+	+	+	+		49	53.3	67
Non-responders to corticosteroid therapy												
Mizutani et al.	44 /M	Never	25	+	+					79	83	N/A
Mizutani et al.	43 /M	Former	6	+			+	+		49	56	20
Mizutani et al.	63 /M	Never	12	+			+	+		83	86	67
Kaneko et al.	54 /M	Never	21			+	+			30.1	29.8	9.2

BALF, bronchoalveolar lavage fluid; BE, Traction bronchiectasis; CD, consolidation; DLco, carbon monoxide diffusion capacity; FEV1, forced expiratory volume in one second; GGO, ground-glass opacities; HCM, honeycomb; MNO, micronodular opacities; N/A, not available; RO, reticular opacities; VC, vital capacity.

Table 2. Pathological characteristics of hard metal lung disease in patients treated with corticosteroids.

Case	BALF				Pathology		Elements detected	
	Giant cell	Eos.(%)	Lymph.(%)	CD 4/8	Biopsy	Findings	W	Co
Responders to corticosteroid therapy								
Mizutani et al.	+	N/A	N/A	N/A	Surgical	GIP	+	+
Mizutani et al.	+	N/A	N/A	N/A	TBLB	GIP	NA	NA
Nakamura et al.		25	50	0.5	TBLB	Fibrotic change with small black deposits	+	–
Nureki et al.		N/A	74.3	0.16	Surgical	Bronchocentric interstitial pneumonia	+	–
Kim et al.	+	N/A	80	7.82	TBLB	GIP, HP	NA	NA
Sakai et al.	+	21	28.5	0.57	Surgical	GIP	+	+
Moreira et al.	N/A	N/A	N/A	N/A	Surgical	GIP	–	–
Bezerra et al.	N/A	N/A	N/A	N/A	Surgical	DIP,GIP	NA	NA
Sakamoto et al.	+	10	6	0.87	TBLB	GIP, OP	+	–
Enriquez et al.	N/A	N/A	N/A	N/A	Surgical	GIP	NA	NA
Yokota et al.		4.3	32.8	N/A	TBLB	Centrilobular fibrosis	+	+
Schwarz et al.		61.6	24	0.4	TBLB	GIP	–	–
Dunlop et al.	N/A	N/A	N/A	N/A	Surgical	GIP	NA	NA
Present case		8	10	1.3	TBLB	Chronic inflammatory cell infiltration	+	–
Non-responders to corticosteroid therapy								
Mizutani et al.	+	N/A	N/A	N/A	Surgical	DIP and cellular bronchiolitis	+	+
Mizutani et al.	+	N/A	N/A	N/A	Surgical	GIP	NA	NA
Mizutani et al.		N/A	Elevation	N/A	Surgical	HP	NA	NA
Kaneko et al.		N/A	N/A	N/A	Surgical	Apital cap-like subpleural dense fibrosis	+	–

Co, cobalt; DIP, desquamative interstitial pneumonia; GIP, giant cell interstitial pneumonia; HP, hypersensitivity pneumonitis; OP, organizing pneumonia; TBLB, transbronchial lung biopsy; W, tungsten.

patients with HMLD are expected to show favorable response to corticosteroid treatment, although one patient died due to an aggravation of HMLD (Mizutani et al. 2016).

The characteristics in the clinical and laboratory findings of the responders and non-responders to corticosteroid treatment among HMLD patients are shown in Table 3. In the summary of a total of 18 cases of HMLD, the median age was 43.5 years (21-68), 88.8% of the patients were male and the median exposure duration was 10.0 years (1.8-40). The comparison of the pulmonary function test results of responders (n = 14) and non-responders (n = 4) to corticosteroids revealed that the median %DLco values of responders and non-responders were 60.0% (16.0-107.0) and 20.0% (9.2-67.0), respectively. On chest CT, GGOs and/or micronodular opacities were often observed in the responders, whereas reticular opacities were often observed in addition to GGOs in the non-responders (Table 3).

The radiological findings of HMLD are similar to those of HP (Sakamoto et al. 2008; Okuno et al. 2010; Tanaka et al. 2014). In a review of 19 patients with HMLD (Tanaka et al. 2014), centrilobular nodules, GGO, reticular opacity, and traction bronchiectasis were observed in 16 (84.2%), 16 (84.2%), 5 (26.3%), and 4 (21.0%) cases, similar to the findings in Table 3. Fibrotic changes, such as reticular opacity and traction bronchiectasis, were predictive of treatment resistance and poor prognosis of patients with interstitial lung diseases (Ichikado et al. 2002, 2006; Best et al. 2008; Shin et al. 2008; Oda et al. 2014), and fibrotic findings, such as reticular opacity, were associated with poorer prognosis in patients with HP (Churg et al. 2009; Wang et al. 2017). In our review, reticular opacities in chest CT may be also predictive of treatment resistance. Taken together with previous reports, we suggest that 20% to 30% of patients with HMLD exhibit fibrotic findings and that these fibrotic changes appear to be associated with resistance with corticosteroid treatment. In a majority of patients, especially those with centrilobular nodules and GGO, it is expected that improvements in HMLD will occur if further exposure to hard metals is avoided and corticosteroid treatment is applied.

It is recommended that a multidisciplinary approach is considered, with surgical biopsy used to diagnose interstitial lung diseases in the relevant guidelines (Travis et al. 2013). The rates of surgical lung biopsy were 46.7% in the responders to corticosteroids and 100% in the non-responders (Table 3). The response to corticosteroid in interstitial lung diseases is related to a definite diagnosis of interstitial lung diseases, and may also be related to chest CT findings, such as GGO and centrilobular opacities indicating transrespiratory tract distribution. In addition, the UIP pattern in chest CT may indicate a clinical need to differentiate idiopathic pulmonary fibrosis with pathological UIP from other non-idiopathic interstitial pneumonias. Surgical lung biopsy is very helpful for a definite diagnosis of HMLD,

Table 3. Characteristics of responders and non-responders to corticosteroid treatment.

	Total	Corticosteroid	
		Responders	Non-responders
Number of patients	18	14	4
Age	43.5 (21-68)	34.5 (21-68)	49.0 (43-63)
Sex (Male)	16 of 18 (88.8)	12 of 14 (85.7)	4 of 4 (100)
Smoking history			
Former or current	7 of 17 (41.2)	6 of 13 (46.2)	1 of 4 (25.0)
Former	6 of 17 (35.3)	5 of 13 (38.5)	1 of 4 (25.0)
Current	1 of 17 (5.9)	1 of 13 (7.7)	0 of 4 (0.0)
Never	10 of 17 (58.9)	7 of 13 (53.8)	3 of 4 (75.0)
Duration of exposure (years)	10.0 (1.8-40)	8.5 (3-40)	16.5 (6-25)
Pulmonary function test			
%VC	51.2 (30.1-106.7)	51.2 (34.0-106.7)	64.0 (30.1-83.0)
$\%FEV_1$	65.0 (29.8-89.1)	65.0 (46.9-89.1)	69.5 (29.8-88.9)
%DLco	55.7 (9.2-107.0)	60.0 (16.0-107.0)	20.0 (9.2-67.0)
Chest CT findings			
Ground-glass opacities	14 of 18 (77.8)	11 of 14 (78.6)	3 of 4 (75.0)
Micronodular opacities	11 of 18 (61.1)	10 of 14 (71.4)	1 of 4 (25.0)
Consolidation	3 of 18 (16.7)	2 of 14 (14.3)	1 of 4 (25.0)
Reticular opacities	6 of 18 (33.3)	3 of 14 (21.4)	3 of 4 (75.0)
Traction bronchiectasis	8 of 18 (44.4)	6 of 14 (42.9)	2 of 4 (50.0)
Honeycomb	1 of 18 (5.6)	1 of 14 (7.1)	0 of 4 (0.0)
Bronchoalveolar lavage fluid			
Giant cell (+)	7 of 14 (50.0)	5 of 10 (50.0)	2 of 4 (50.0)
Eosinophils (%)	15.5 (4.3-61.6)	15.5 (4.3-61.6)	N/A
Lymphocytes (%)	30.7 (6.0-80.0)	30.7 (6.0-80.0)	N/A
Surgical lung biopsy	11 of 18 (61.1)	7 of 14 (50.0)	4 of 4 (100)
Pathological findings of the lung			
Giant cell interstitial pneumonia	11 of 18 (61.1)	10 of 14 (71.4)	1 of 4 (25.0)
Others	7 of 18 (38.9)	4 of 14 (28.6)	3 of 4 (75.0)
Electron microanalysis			
Tungsten	10 of 11 (90.9)	8 of 9 (88.9)	2 of 2 (100)
Cobalt	4 of 11 (36.4)	3 of 9 (33.3)	1 of 2 (50.0)
Combination of immunosuppressants	3 of 18 (16.7)	1 of 14 (7.1)	2 of 4 (50.0)

Data are presented as median (range) or number of total number (%), unless otherwise stated.

but physicians should also consider proper combination of the occupational history of hard metal exposure, radiological findings, the detection of hard metals by elemental analyses in lung biopsy specimens, and BALF analysis in suspected patients with HMLD.

The detection of tungsten and/or cobalt in BALF or lung specimens may lead to a definite diagnosis of HMLD (Tanaka et al. 2014). In the present case, the components of hard metals, including tungsten, titanium, and iron, were detected, but cobalt, chromium, nickel, and tantalum were not detected. Cobalt was detected in only 4 of 9 (44.4%) patients with HMLD in whom tungsten was detected in the lung tissues, possibly because of the highly soluble nature of cobalt in protein fluid (Harding 1950; Moriyama et al. 2007); therefore, tungsten appears to be one of the most important components for the diagnosis of HMLD. In addition, some metal components, such as iron and titanium, were detected in both dust and TBLB samples by electron microscopy, but cobalt and nickel were only detected in the dust, not in the lung. The difference in the detection of each metal component is influenced by the biopersistence of each metal component in the lung; for example, biological half-life of titanium, nickel and cobalt in the lung are 1.8-2.2 months, 4.9-9.5 months and 2.0-44.0 hours, respectively (Apostoli et al. 1994; Mosconi et al. 1994; Oyabu et al. 2017). In our patient, we could compare the mineral component of both TBLB sample and the exposed dust in the work place, and confirm the different biopersistence in each metal component. There are no reports compared the results of metal components between the lung and the dust

samples so far.

The association between the duration of exposure to hard metals and the response of HMLD to corticosteroids is currently unknown. A shorter duration of exposure in the GIP group than in fibrosis group (median 6.1 versus 23.8 years, respectively) was reported, suggesting that different immune responses of the hosts to hard metals (Tanaka et al. 2014). In the present review of the literature, the duration of exposure in the responders and non-responders to corticosteroids was 8.5 years (3-40) and 16.5 years (9.2-67.0), respectively. Seven of 17 patients (41.2%) had over 15 years of exposure (Table 1), and among them, two patients responded to corticosteroid treatment despite having 40 and 38 years of exposure, respectively (Enriquez et al. 2007; Nakamura et al. 2014).

Increased proportions of lymphocytes, eosinophils, and giant cells in BALF in patients with HMLD have been shown (Forni 1994; Kinoshita et al. 1999; Tanaka et al. 2014), and an increase of any of lymphocytes, eosinophils, and giant cells is seen in BALF in all responders to corticosteroids with BALF data (Table 1), although the data were insufficient to compare the findings in the responders and the non-responders to corticosteroids. Pathologically, the GIP pattern was common, but other fibrotic patterns, such as the UIP pattern, could also be seen in patients with HMLD (Ohori et al. 1989; Akira 1995; Moriyama et al. 2007; Tanaka et al. 2014). In our review, the GIP pattern was frequently observed in responders (71.4%) compared with non-responders (25%) (Table 3), and the proportion of patients with the GIP pattern may be associated with the favorable response to corticosteroids. In general, the proportion of BALF cells and pathological findings may predict the response to corticosteroid treatment; however, the further accumulation of these findings is required to confirm this in patients with HMLD.

In the present review, only HMLD patients treated with corticosteroids were included (Table 1). Among the 18 patients, six cases, including our patient, were treated with corticosteroids (Yokota et al. 1996; Enriquez et al. 2007; Bezerra et al. 2009; Kim et al. 2013; Nakamura et al. 2014), because the symptoms and/or radiological findings did not show improvement even after avoiding dust exposure before corticosteroid therapy. However, the detailed information of remaining 12 cases were unknown (Schwarz et al. 1994; Dunlop et al. 2005; Sakamoto et al. 2008; Moreira et al. 2010; Kaneko et al. 2010; Sakai et al. 2010; Nureki et al. 2013; Mizutani et al. 2016). On the other hand, Huang et al. (2012) reported that proper prevention of dust exposure (change of workplace, proper wearing of mask, maintenance of better exhaust ventilation and air condition monitoring in the workplace) was effective in patients with HMLD. Furthermore, Okuno et al. (2010) and Terui et al. (2015) reported cases, in which avoiding dust exposure alone improved the chest CT findings. Thus, physicians should consider proper prevention of dust exposure to be the first step in treating HMLD patients. The further accumulation of clinical data is needed to elucidate the factors in HMLD patients that are associated with the improvement of lung involvement by the avoidance of inhalation exposure alone.

In conclusion, the present case and our review of case reports suggest that HMLD is expected to exhibit a favorable response to corticosteroid treatment in a majority of the cases, but fibrotic findings appear to be a risk factor for treatment resistance. Therefore, the accumulation of evidence to find the other key factors for the prediction of the response to corticosteroid treatment is expected to help establish a treatment strategy for HMLD. In addition, the result of our patient may be helpful to understand the pathogenicity of HMLD including an influence of different biopersistence of each metal component in the lung of a patient with HMLD.

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Conflict of Interest

The authors declare no conflict of interest.

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