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【 CASE REPORT 】

Granulomatous Lymphocytic Interstitial Lung Disease in Multiple Myeloma

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Abstract:

An 82-year-old woman complained of recurring cough and shortness of breath and was diagnosed with progressive multiple myeloma (MM). Chest computed tomography (CT) revealed bilateral ground-glass opacity and interlobular septal thickening predominantly in the lower lung zones. Histopathologic findings obtained by a transbronchial lung cryobiopsy (TBLC) revealed alveolitis and granulomas consistent with granulomatous-lymphocytic interstitial lung disease (GLILD). Aggressive chemotherapy for MM contributed to the improvement in respiratory symptoms and abnormal chest CT findings. In cases of MM with lung abnormalities, the possibility of GLILD must be ruled out, and a TBLC should be considered to attain an accurate diagnosis.

Key words: granulomatous lymphocytic interstitial lung disease, multiple myeloma, transbronchial lung cryobiopsy, computed tomography

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Introduction

Granulomatous-lymphocytic interstitial lung disease (GLILD) is a rare disease characterized by lymphocytic infiltration and the presence of granulomas in the lungs (1). It is also a complication of common variable immunodeficiency (CVID), which is associated with a reduced survival (2). Recently, GLILD has also been reported as a complication in other primary immunodeficiencies (PID) and acquired immunodeficiency syndrome (AIDS) (3, 4). Nevertheless, no cases of GLILD in multiple myeloma (MM) have been reported.

The diagnosis of GLILD requires a surgical lung biopsy (SLB) because a transbronchial lung biopsy (TBLB) specimen is usually insufficient for attaining a definitive diagnosis (1). Only one case report has diagnosed GLILD by a transbronchial lung cryobiopsy (TBLC) in a CVID patient (5).

We herein report the first documented case of GLILD accompanied by MM that was diagnosed by a TBLC.

Case Report

An 82-year-old woman with MM was admitted to our hospital due to cough and shortness of breath over the past month prior to consultation. She had been diagnosed with monoclonal gammopathy of undetermined significance (MGUS) 22 years ago, which progressed to stage III IgG-lambda MM 4 years ago. The diagnosis was made when she presented with progressed anemia but did not show any other rational symptoms. Staging was done based on the re-

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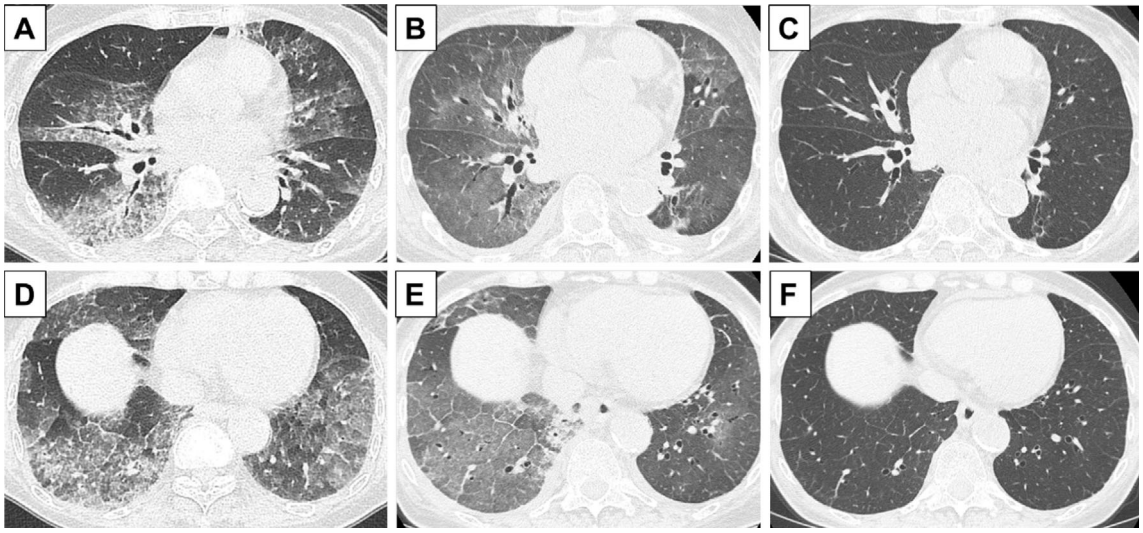

Figure 1. Chest computed tomography two years ago (A, D), on admission (B, E) and eight months after initiation of MM treatment (C, F). GGO, reticulation and interlobular septal thickening were seen predominantly in the bilateral lower lung zones (A, D), with similar features but decreased reticulation (B, E). These findings remarkably improved after MM treatment (C, F). GGO: ground-glass opacity, MM: multiple myeloma

vised international staging system (R-ISS) for MM. She had had similar respiratory symptoms two years ago. Chest high-resolution computed tomography (HRCT) at the time had shown bilateral ground-glass opacity (GGO), reticulation and interlobular septal thickening, predominantly in the lower lung zones (Fig. 1A, D). Bronchoalveolar lavage (BAL) and a TBLB were performed to rule out secondary pulmonary alveolar proteinosis (PAP). However, a final diagnosis was not established.

The patient's symptoms and radiological findings improved spontaneously after two weeks. One month after BAL and the TBLB, an immunomodulatory agent, such as lenalidomide, along with steroid dexamethasone was initiated to combat her symptomatic MM. However, this treatment was discontinued after a month due to drug-induced liver injury, and the patient was placed on follow-up without any MM treatment. She developed cough and shortness of breath one month prior to her most recent admission.

On admission, a physical examination revealed a body temperature of 36.2°C, heart rate of 109 beats/min, respiratory rate of 20 breaths/min, SpO_2 of 93% on 2 L/min oxygen by nasal cannula, and fine crackles in the bilateral lower lung fields. She had no clubbed fingers, dilation of the jugular veins, edema of the feet, or episodes of irritant gas inhalation. Laboratory data demonstrated a normal white blood cell count (6,500 cells/μL) and cell differentiation with slightly increased neutrophils (79.2%), decreased lymphocytes (12.3%), and normal values for monocytes (6.6%), eosinophils (1.7%), and basophils (0.2%). There were also increased levels of total protein (11.3 g/dL), IgG (8,482 mg/dL), Krebs von den Lungen-6 (544 U/mL), and surfactant protein-D (282 ng/mL) and decreased levels of hemoglobin (8.8 g/dL) and albumin (1.8 g/dL). Antinuclear antibodies, antineutrophil cytoplasmic antibodies, cytomegalovirus, HIV antigen, and antibodies were negative, while β-D-glucan was immeasurable (Table 1). HRCT revealed bilateral GGO and interlobular septal thickening predominantly in the lower lung zones (Fig. 1B, E), features that were similar to the findings from two years ago, although reticulations had decreased.

The BAL fluid (BALF) showed an increased total cell count (16.75×10^5/mL), lymphocyte ratio (63.0%), CD4/8 ratio of 2.21, without a milky appearance or hemorrhaging. Microorganisms, including *Mycobacterium* and fungi, were also not seen in the BALF culture or on Grocott's staining. A TBLC specimen obtained from the right lower lobe segments B8 and B9 revealed interstitial lymphoid infiltration, predominantly in the alveolar septae. The alveolar space exhibited several eosinophilic granulomatous aggregations of macrophages in a polypoid arrangement, which are atypical in the interstitium (Fig. 2A, B). The eosinophilic substance in the alveolar space had no granular features suggestive of PAP. Amorphous eosinophilic material seen in amyloidosis was also not found. Ziehl-Neelsen and Grocott stains did not show *Mycobacterium* infection or pneumocystis pneumonia (PCP). Immunohistochemical staining revealed predominantly T lymphocytes (Fig. 3A, B), with a higher number of CD4-positive T cells (Fig. 3C) than CD8-positive T cells (Fig. 3D).

Based on the laboratory and radiological findings as well as the underlying MM, the differential diagnoses included PAP, hypersensitivity pneumonitis (HP), lymphoproliferative disease (e.g. lymphocytic interstitial lung disease), Sjögren's syndrome, secondary nonspecific interstitial pneumonia, drug-induced pneumonia, amyloidosis, and infections, such as tuberculosis and PCP.

Table 1. Laboratory Data and Blood Gas Analysis on 2L/min Oxygen at the Time of Admission.

Characteristics	Patient's data	Unit	Normal range	Characteristics	Patient's data	Unit	Normal range
WBC	6,500	/μL	33-86	SP-D	282	ng/mL	<110.0
RBC	271	$\times10^4$/μL	386-492	ACE	6.3	U/L	8.3-21.4
Hemoglobin	8.8	g/dL	11.6-14.8	RF	25	IU/mL	≤15
Hematocrit	26.1	%	35.1-44.4	ANA	(-)		(-)
Platelet	15.4	$\times10^4$/μL	15.8-34.8	MPO-ANCA	<1.0	U/mL	<3.5
TP	11.3	g/dL	6.6-8.1	PR3-ANCA	<1.0	U/mL	<3.5
Albumin	1.8	g/dL	4.1-5.1	β-D-glucan	nd	pg/mL	<11.0
BUN	18	mg/dL	8-20	CMV-Ag	(-)		(-)
Creatinine	0.63	mg/dL	0.46-0.79	HIV-Ag/Ab	(-)		(-)
CRP	0.36	mg/dL	≤0.14	pH	7.454		7.350-7.450
IgG	8482	mg/dL	861-1,747	PaCO2	22.8	mmHg	35.0-45.0
IgA	13	mg/dL	93-393	PaO2	65.9	mmHg	80.0-100.0
IgM	11	mg/dL	50-269	HCO3	15.6	mmol/L	22.0-26.0
KL-6	544	U/mL	<500	BE	-6.9	mmol/L	-2.0-2.0

ACE: angiotensin converting enzyme, ANA: antinuclear antibodies, BE: base excess, BUN: blood urea nitrogen, CMV-Ag: cytomegalovirus antigenemia, CRP: C-reactive protein, HCO3: bicarbonate ion, HIV-Ag/Ab: human immunodeficiency virus antigen/antibody, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, KL-6: Krebs von den Lungen-6, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibodies, nd: not detected, PaCO2: partial pressure of carbon dioxide in arterial blood, PaO2: partial pressure of carbon oxygen in arterial blood, pH: potential of hydrogen, PR3-ANCA: proteinase3-antineutrophil cytoplasmic antibodies, RBC: red blood cell count, RF: rheumatoid factor, SP-D: surfactant protein-D, TP: total protein, WBC: white blood cell count

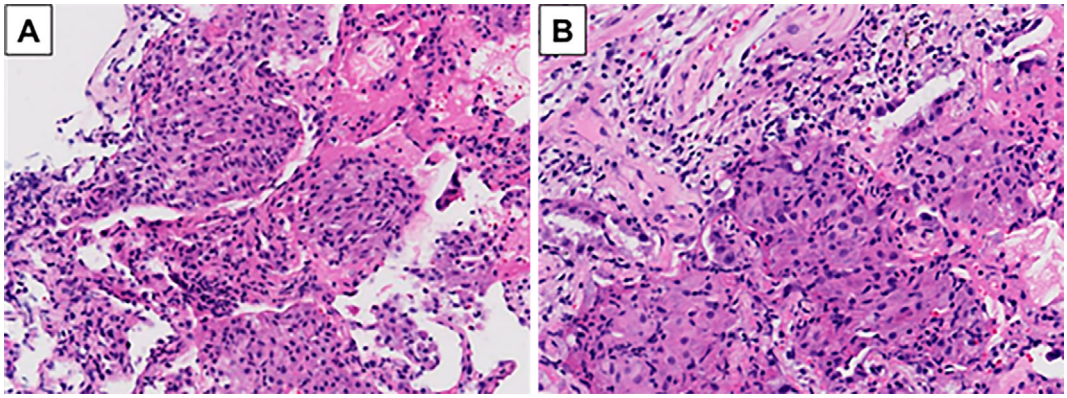

Figure 2. Histopathological features from the right lower lobe transbronchial lung cryobiopsy showing (A) interstitial lymphoid infiltration predominantly in the alveolar septa and filling of the alveolar space with non-granular eosinophilic substance, thus ruling out pulmonary alveolar proteinosis [Hematoxylin and Eosin (H&E) staining, magnification ×200], and (B) granulomatous aggregation of macrophages (H&E staining, magnification ×400).

Some granulomatous diseases were excluded; for example, IgG4-related disease and multicentric Castleman disease were ruled out as there were no plasma cell infiltration. Sarcoidosis was ruled out as granulomas were seen mainly in the alveolar space, but not in the interstitium. In addition, in this case, there was too much alveolitis, while hilar adenopathy or the upper lobe predominance of an abnormal lung shadow was absent. As a result, these findings did not correspond to sarcoidosis.

Non-fibrotic HP was also ruled out because she had no history of inhaled antigen exposure and granulomas were not located within the peribronchiolar interstitium. Lymphomatoid granulomatosis was also deemed unlikely as there were no pulmonary nodular lesions or lymphocytic invasion of the vascular wall, and Epstein-Barr virus-encoded small RNA *in situ* hybridization for CD20-positive lymphocytes was negative.

A multidisciplinary discussion led to a diagnosis of GLILD associated with MM because of the main pathophysiology of both alveolitis and granulomatous aggregation of macrophages.

Treatment with bortezomib, cyclophosphamide, and dexamethasone for MM was initiated on day 34 of admission. Her shortness of breath gradually decreased, and her chest

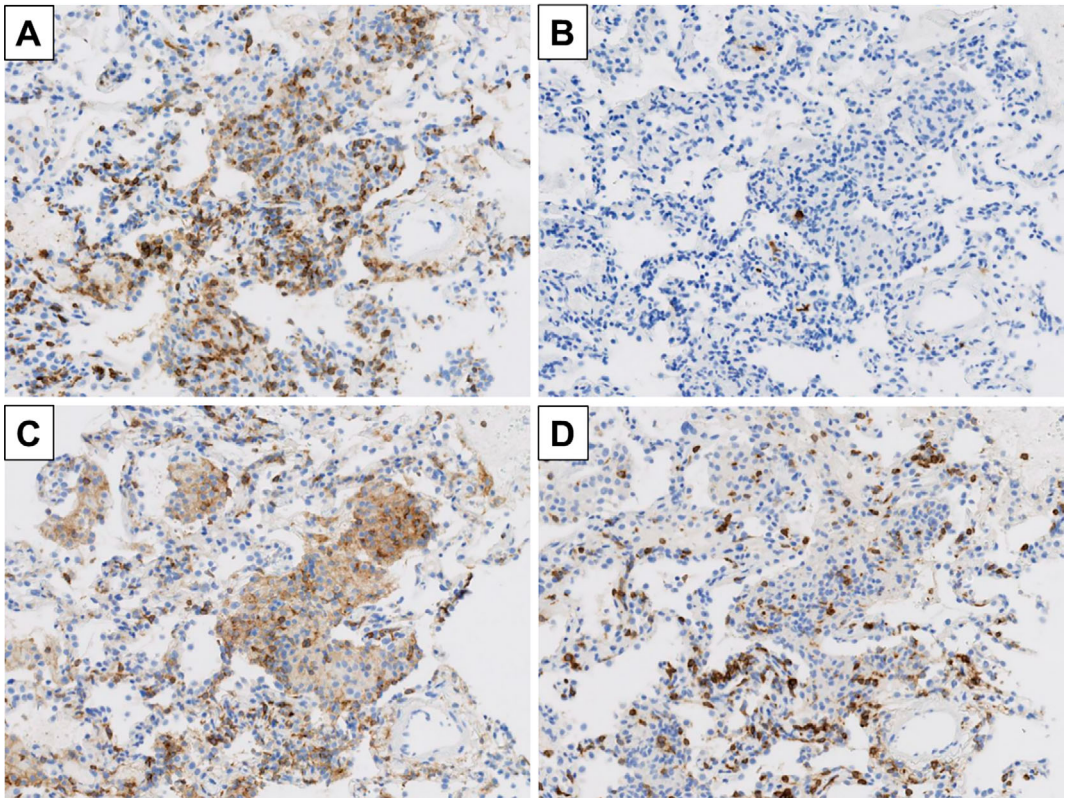

Figure 3. **Immunohistochemical features from the right lower lobe transbronchial lung cryobiopsy showing (A) lymphocytes, predominantly CD3-positive T cells with (B) a few CD20-positive B cells, magnification ×200 (both). (C) There were more CD4-positive T cells than (D) CD8-positive T cells, magnification ×200 (both).**

Table 2. **Lung Function Tests at 2 Years Prior to Admission and 8 Months after Initiation of Multiple Myeloma Treatment.**

Characteristics	2 years prior to admission	8 months after treatment
VC, L	2.10	2.41
%VC predicted, %	100.5	118.7
FVC, L	2.12	2.40
%FVC predicted, %	109.8	127.7
FEV1, L	1.66	1.78
FEV1/FVC ratio, %	78.3	74.17
%FEV1 predicted, %	112.9	127.1
%DLCO predicted, %	84.4	98.3
%DLCO/VA predicted, %	92.0	90.8

FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, VC: vital capacity, DLCO: diffusing capacity for carbon monoxide, VA: alveolar volume

CT findings remarkably improved after eight months of treatment (Fig. 1C, F), in accordance with the improvement of MM. Lung function test findings also improved in terms of the vital capacity and gas transfer (Table 2).

Discussion

This case report reveals two points of clinical significance: GLILD can be associated with MM, and a TBLC is a useful procedure for its diagnosis.

GLILD can be a complication of MM. The British Lung Foundation and United Kingdom Primary Immunodeficiency Network (BLF/UK PIN) suggested the following consensus definition: "GLILD is a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, in whom other conditions have been suspected and, where possible, excluded" (1). GLILD has been recognized as a complication in other PIDs and AIDS (3, 4). The clinical features of GLILD range from major symptoms of breathlessness and cough to being asymptomatic (1). Both chest CT and histopathological findings are important for its diagnosis (1). Diffuse pulmonary nodules surrounded by GGO with lower lobe predominance, interlobular septal thickening predominantly in mid-to-lower lung fields, and a natural course of waxing and waning of radiological findings is seen in GLILD (3, 6). These radiological findings and clinical course were also seen in our case. The histopathological features of GLILD obtained from an SLB in 16 patients with CVID included granulomas, peribronchiolar and interstitial lymphoid infiltration, and organizing pneumonia in most cases (7). Our patients' histopathological findings on a TBLC were also compatible with GLILD. The respiratory symptoms and abnormal chest shadows worsened with MM progression and gradually improved with MM treatment. Therefore, a diagnosis of GLILD associated with MM was

made.

A TBLC was useful for diagnosing this condition. The BLF/UK PIN consensus statement declared that the diagnosis of GLILD required an SLB because procedures that collect small samples, such as a conventional TBLB, may be insufficient for an accurate diagnosis (1, 7). A TBLC was considered superior to a conventional TBLB but slightly inferior to video-assisted thoracic surgery in terms of the diagnostic yield, with an acceptable safety profile (8, 9). High levels of concordance between a TBLC and SLB were shown with regard to histopathological agreement and the multidisciplinary discussion (MDD) diagnosis (10). Doan et al. reported a case of GLILD diagnosed by a cryobiopsy in a CVID patient (5). We selected a TBLC in this case because a previous TBLB had not allowed a sufficiently sized specimen to be collected for a diagnosis and owing to the patient's poor physical state. Consequently, we accurately made an MDD-based diagnosis of GLILD by a cryobiopsy with only minimal oozing after the procedure. Thus, a TBLC may be a useful procedure for the diagnosis of GLILD.

Although the etiology of GLILD is unclear, T-cell function disorder results in abnormal antigen handling and/or responses to viral infection (1). MM causes hypogammaglobulinemia as plasma cells overrun monoclonal non-efficient paraproteins and inhibit polyclonal B lymphocytes, similar to CVID (11). In addition, MM-related immunodeficiency presents with B cell dysfunction and quantitative and functional T-cell abnormalities, which may induce GLILD (12). However, the presence of such findings in the present case remains unclear because we did not assess the T or B cell functions in this patient. GLILD may remain latent in MM and other immunodeficiency diseases and states, since this disorder is uncommon and difficult to diagnose by a forceps biopsy. Infections in case of MM with lung abnormalities should be ruled out, as they are a significant cause of morbidity and mortality in patients with MM (13-15). Both bacterial and viral infections are possible (13). The BLF/UK PIN consensus statements state that immunoglobulin substitution and corticosteroids are acceptable therapies for GLILD in CVID, although treatment responses and prognoses vary (1, 2, 3, 16). We believe that the treatment of the underlying GLILD-associated disease should be prioritized.

In conclusion, GLILD can be a complication of MM, and a TBLC is a useful procedure for its diagnosis. Patients with MM and diffuse lung abnormalities require a further examination, and a TBLC should be considered for obtaining a definitive diagnosis.

The publication of the case report was approved by the patient and the local ethics board of Kurume University Hospital. We obtained permission to publish this case report from the patient (in Japanese).

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

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