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【 CASE REPORT 】

Acute Pulmonary Graft-Versus-Host Disease in a Patient with Adult T-cell Leukemia-Lymphoma Diagnosed by a Cryobiopsy

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Abstract:
A 51-year-old woman with adult T-cell leukemia-lymphoma was hospitalized in order to undergo allogeneic hematopoietic stem-cell transplantation. On day 29 after transplantation, she began to experience hypoxia upon exertion. Chest computed tomography revealed centrilobular granular shadows, and pulmonary function tests revealed a remarkable obstructive ventilatory impairment compared to before transplantation. A histopathological analysis following a transbronchial lung cryobiopsy revealed acute graft-versus-host disease (GVHD). We herein report a rare case of histopathologically diagnosed acute pulmonary GVHD with spontaneous remission.

Key words: adult T-cell leukemia-lymphoma, transbronchial lung cryobiopsy, acute graft-versus-host disease, spontaneous remission

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Introduction

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a life-prolonging or curative treatment option for patients with hematologic malignancies (1). However, graft-versus-host disease (GVHD), an adverse immunological reaction, remains the leading cause of death following allo-HSCT. The skin, gastrointestinal tract, and liver are well described target organs of GVHD (2). In contrast, pulmonary GVHD is discussed less often in this setting (3). Moreover, post-transplantation patients often have a poor general condition, and performing a sufficient lung biopsy for an accurate diagnosis is difficult. We encountered the present pulmonary GVHD case after allo-HSCT for adult T-cell leukemia-lymphoma (ATLL). A histological diagnosis allowed us to observe the progress and not perform any unnecessary treatment.

Case Report

A 51-year-old woman was referred to the department of hematology with abnormal lymphocyte levels 4 years previously. Human T-cell leukemia virus type-1 was positive. Laboratory tests and computed tomography (CT) led to a diagnosis of smoldering-type ATLL, and she underwent a follow-up examination. This time, abnormal lymphocytes were increased (about 74% of white blood cells), and we concluded that the smoldering type of ATLL had transitioned to the chronic type. Chemotherapy was scheduled.

She started treatment with the CHOP regimen (C: cyclophosphamide, H: hydroxydaunorubicin, O: oncovin, P: prednisone). Mogamulizumab (MOG) was added because of an inadequate response to two courses of CHOP treatment. She finally received four courses of CHOP and a single dose of MOG (1 mg/kg), resulting in a partial remission. She was also administered triple IT (methotrexate, cytarabine, predni-

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solone) 5 times for prophylaxis of central nervous system involvement. She subsequently underwent allo-HSCT from a human leukocyte antigen (HLA)-matched unrelated female bone marrow donor after fludarabine and melphalan as the conditioning regimen.

GVHD prevention consisted of tacrolimus and methotrexate. Bone marrow engraftment was achieved on day 16 after allo-HSCT. On day 29, she began to experience hypoxia upon exertion. During exertion, she needed 3.0 L/min of nasal cannula oxygen. On day 36, pulmonary function tests (PFTs) revealed a remarkable obstructive ventilation disorder compared to her condition before undergoing allo-HSCT (Table 1).

On chest CT scans, diffuse thickening of the bronchial walls and worsening of the centrilobular granular shadow were noted, and air trapping was observed (Fig. 1).

Pulmonary GVHD was suspected, and thus, bronchoalveolar lavage and a cryobiopsy were performed.

The total cell counts were 6.0×10^6/mL, lymphocytes were 60%, macrophages 38%, neutrophil 2%. Lymphocytes were predominant in bronchoalveolar lavage fluid. A bacterial culture was negative, and Pneumocystis jirovecii and Cytomegalovirus PCR were also negative (Table 2). A histopathological analysis of lung tissues revealed acute pulmonary GVHD (Fig. 2).

After bronchoscopy, her respiratory status gradually improved with the continuation of tacrolimus without any additional treatments such as steroids. On day 51, a clinical diagnosis of gastrointestinal GVHD stage 0 was made, and the condition spontaneously improved (Fig. 3). On day 80, a clinical diagnosis of skin GVHD stage 2 was made, and steroids were applied to her skin. On day 97, PFTs improved (Table 1). On day 110, she was discharged, and her respiratory condition has since remained stable. On day 189, the diffuse thickening of the bronchial walls and the centrilobular granular shadow disappeared on chest CT scans (Fig. 4).

Table 1. Pulmonary Function Tests.

	Before remission induction therapy	On the Day 36	On the Day 97
VC(L)	2.97	1.76	2.32
%VC(%)	101	60.7	79.7
FEV_1(L)	2.21	0.86	1.46
%FEV_1(%)	94.4	37.2	63.2
FEV_1%(%)	74.4	48.9	62.9
%DLCO(%)	85.4	46.3	46.8
RV/TLC(%)	99.2	160.8	113.6

DLCO: diffusing capacity for carbon monoxide, VC: vital capacity, FEV1: forced expiratory volume in 1 second, TLC: total lung capacity, RV: residual volume

Discussion

Acute pulmonary GVHD in the first 120 days after allo-HSCT has been reported in from 3-15% of all patients (4). The clinical symptoms include fever, cough, dyspnea, and hypoxemia. Radiographic findings include bilateral interstitial infiltrate. PFTs show obstructive findings. Mortality rates range from 60% to 80% overall, while they are greater than 95% for patients requiring mechanical ventilation.

The patient in our case had a cough, dyspnea, and hypoxemia. According to PFTs and chest CT, remarkable obstructive findings, diffuse thickening of the bronchial walls, and a worsening of the centrilobular granular shadow compared to that before allo-HSCT were all observed. Pulmonary GVHD was suspected and then positively diagnosed following a cryobiopsy. Because her oxygen demand had improved to normal, the day after the cryobiopsy, we chose to carefully follow her and to not use steroids.

Lauren Xu et al. reported the histological findings in lung biopsies in 17 biopsies from 14 patients with suspected pulmonary GVHD (5). The histopathological features are increased intraepithelial bronchiolar T cells, reactive bronchiolar cells showing atypia, and apoptotic bodies in the bronchiolar mucosa. In our case, T cells infiltrated the intraepithelial bronchiolar tissue, and apoptosis was seen.

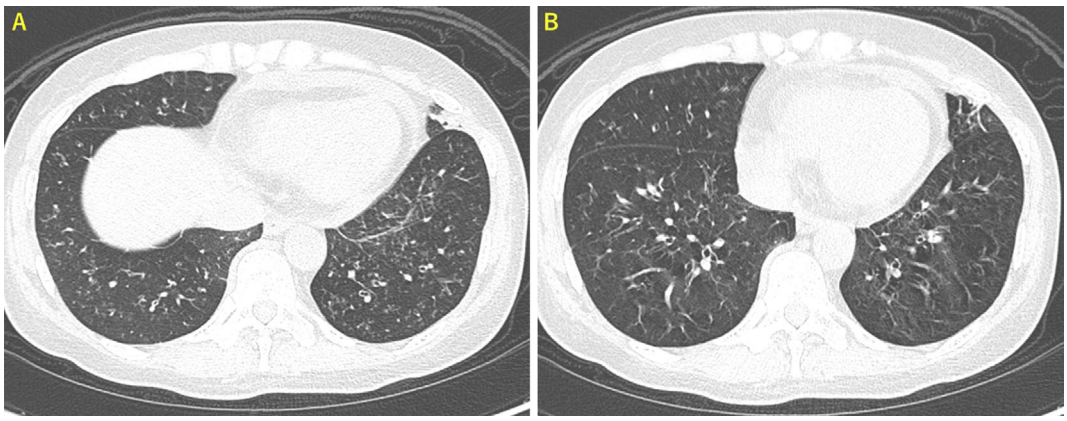

Figure 1. On chest CT scans, diffuse thickening of the bronchial walls and worsening of the centrilobular granular shadow and air trapping were seen. The respiratory phase (A). The exhalation phase (B).

Table 2. Laboratory Data before Remission Induction Therapy and in Bronchoalveolar Lavage Fluid.

WBC(/μL)	18,100	CRP(mg/dL)	0.05
Neutro(%)	8	AMY(U/L)	48
Eos(%)	1	CPK(U/L)	48
Lymph(%)	13	CH50(U/mL)	48
Mono(%)	4	BNP(pg/mL)	<5.8
Abnormal cell(%)	74	ANA	<40
Hb(g/dL)	14.4	IgG(mg/dL)	1,551
PLT(/μL)	27.1×10^4	βD-glucan(pg/mL)	7.2
Alb(g/dL)	4.4	HTLV-1 DNA	positive
AST(U/L)	17		
ALT(U/L)	14	Urinary protein	negative
LDH(U/L)	211	Urinary occult blood	negative
BUN(mg/dL)	19	Urinary sugar	negative
CRE(mg/dL)	0.71		
eGFR(mL/min/1.73m^2)	67.9		
Na(mmol/L)	140		
K(mmol/L)	4.4		
Ca(mg/dL)	10.2		

WBC: white blood cell, Neutro: neutrophil, Eos: eosinophil, Mono: monocyte, Hb: hemoglobin, PLT: platelet, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CRE: creatinine, eGFR: estimated glomerular filtration rate, Na: sodium, K: potassium, Ca: calcium, CRP: C-reactive protein, AMY: amylase, CPK: creatine phosphokinase, CH50: complement activities, BNP: brain natriuretic peptide, ANA: antinuclear antibody, IgG: immunoglobulin G, HTLV-1 DNA: human T-cell leukemia virus type 1 deoxyribonucleic acid, PCR: polymerase chain reaction

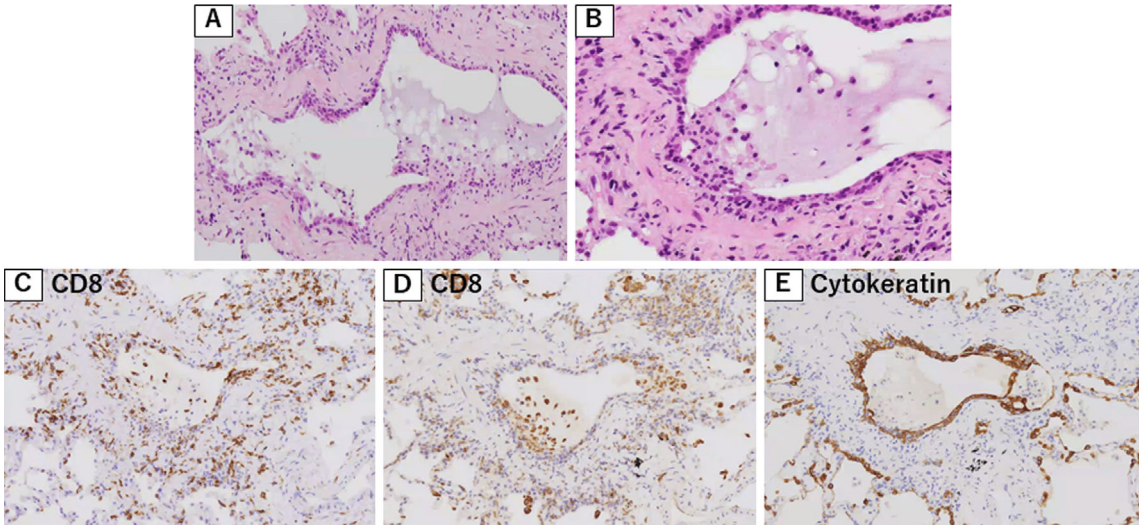

Figure 2. Photomicrograph of a histopathological pulmonary specimen obtained by a cryobiopsy. Hematoxylin and Eosin staining (A), (B). Lymphocytic infiltration into the bronchial walls and prolapse of the bronchial epithelium (A). Erosions in the bronchiole epithelium (B). Immunohistochemistry for CD8 shows T-cell infiltration (C) and agglomeration of histiocytes on the erosive surface (D). Immunohistochemistry for cytokeratin shows erosions in the bronchiole epithelium (E).

Usually, almost all patients had a pathological or clinical diagnosis of extrapulmonary GVHD when pulmonary GVHD was diagnosed. Generally, gastrointestinal and skin GVHD also progress when pulmonary GVHD progresses, but in this case, pulmonary GVHD preceded the gastrointestinal and skin GVHD, and thus, a histological diagnosis was very important in this case.

Systemic steroid therapy is the standard first-line treatment for acute GVHD (6). However, in 35-50% of patients, acute GVHD becomes refractory to systemic steroid therapy. These patients need alternative therapies including extracorporeal photopheresis, anti-tumor necrosis factor-α antibod-

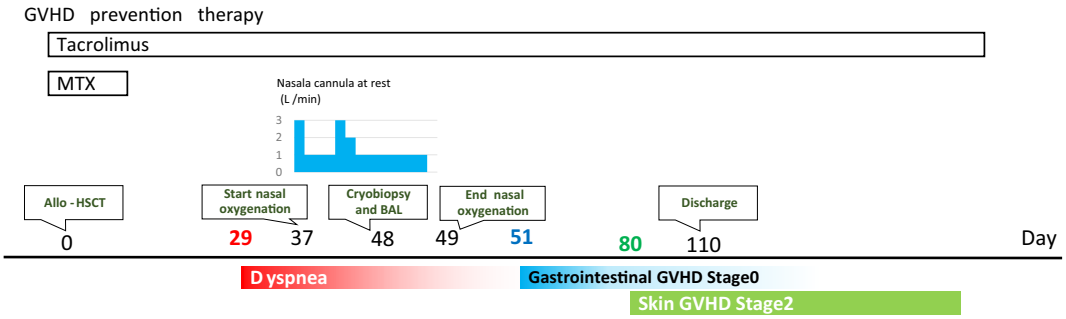

Figure 3. **The clinical course of our patient.**

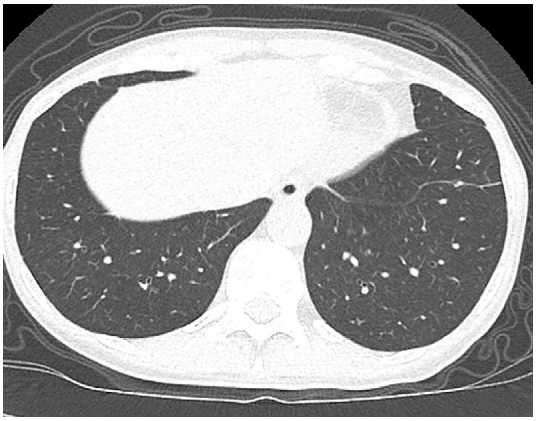

Figure 4. **Chest CT scans on day 189 showed the disappearance of the diffuse thickening of the bronchial walls and the absence of the centrilobular granular shadow.**

ies, mammalian target of rapamycin kinase inhibitors, mycophenolate mofetil, methotrexate, or anti-interleukin-2 receptor antibodies (7).

Zeiser R et al. reported that the established risk factors for acute GVHD are HLA mismatch, unrelated donor/recipient, a female donor for a male recipient, the use of a peripheral blood stem cell graft, and not using a reduced-intensity conditioning regimen (2). Our case was HLA matched and involved a female recipient who received a reduced-intensity conditioning regimen (fludarabine and melphalan) and did not receive a peripheral blood stem cell graft. The only one of these risk factors in our patient was the unrelated donor/recipient, which may explain the spontaneous remission in our case.

MOG, a humanized anti-CC chemokine receptor 4 monoclonal antibody that is usually administered at 1 mg/kg 8 times at weekly intervals, has recently become an important treatment option for ATLL in Japan. On the other hand, MOG is significantly associated with an increase in transplantation-related mortality due to severe GVHD (8, 9). MOG treatment at shorter intervals [<50 days (8), <3 months (9)] between the last administration and allo-HSCT is strongly associated with the development of severe GVHD, because the plasma concentration of MOG is sufficient to deplete regulatory T cells and may be maintained for 2 to 3 months (9). Shigeo Fuji et al. reported that patients with a pretransplantation disease status of stable disease or progressive disease have a worse clinical outcome after allo-HSCT (8), and these chemorefractory ATLL patients could thus be candidates for the addition of MOG. In our case, CHOP did not sufficiently reduce the tumor volume, and we used MOG as an additional treatment. Considering the increased risk of GVHD, only one dose was given, with a 3-month interval between MOG and allo-HSCT. We therefore believe that the administration of MOG in our case was reasonable and sufficiently safe.

Some reports show that a cryobiopsy has a higher diagnostic yield than conventional forceps (10), and high levels of agreement are present between a cryobiopsy and surgical lung biopsy for both histopathological interpretation and multidisciplinary discussion (11). Moreover, a cryobiopsy may make it possible to make a histopathological assessment, even in patients who cannot undergo a surgical lung biopsy (12).

Pulmonary GVHD is a rare disease compared to gastrointestinal, liver, and skin GVHD, but it can be fatal and requires careful identification to avoid problems such as pulmonary infection diseases. The benefits of avoiding steroids, which increase the risk of infection in post-transplant patients, are enormous.

In our case, we established an accurate treatment plan for pulmonary GVHD following a cryobiopsy. A cryobiopsy is an appropriate technique for post-transplant patients with a poor general condition, and further knowledge of this technique in these types of patients is needed in the future.

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

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