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Case Study

Rituximab Monotherapy and Rituximab-Containing Chemotherapy Were Effective for Paraneoplastic Pemphigus Accompanying Follicular Lymphoma, but not for Subsequent Bronchiolitis Obliterans

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A 60-year-old male patient suffered from mild exertional dyspnea, wheezing, and systemic blisters. He was diagnosed with paraneoplastic pemphigus (PNP) with follicular lymphoma in the pancreas head and pelvic cavity. He was first treated with eight cycles of rituximab; his blisters and erosions gradually improved and highly elevated levels of auto-antibodies related to PNP gradually decreased to normal levels. However, obstructive and restrictive respiratory failure still progressed. Computed tomography of the inspiratory and expiratory phases revealed obstructive pulmonary disorder, leading to a diagnosis of bronchiolitis obliterans (BO). The patient underwent plasma exchange and was repeatedly treated with rituximab monotherapy and rituximab-containing chemotherapies, but died 7 months after the diagnosis of BO. Early introduction of rituximab-containing regimens may be necessary to prevent the development of BO accompanying PNP. However, when a diagnosis of PNP-related BO is made, lung transplantation may also be considered for patients in whom rituximab-containing regimens are effective for PNP. 〔*J Clin Exp Hematop 55(2) :* 83-88*, 2015*〕

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INTRODUCTION

Paraneoplastic pemphigus (PNP) is a systemic autoimmune bullous disease that accompanies malignant neoplastic diseases.[1] Primary malignant neoplasms include many hematological malignancies, such as non-Hodgkin's lymphoma and B lymphocytic leukemia. PNP is associated with the production of IgG autoantibodies to desmogleins-1 and -3, bullous pemphigoid 180 (BP180), and plakins, and shows histopathologically acantholytic changes in the epidermis and clinically extensive blisters and erosions on the skin and various mucosae.[2,3] Skin blisters result in epidermal defects and cause severe infections, similar to massive skin burns. Without control of the malignant neoplasms, resolution of the skin blisters is difficult and requires high doses of corticosteroids and immunosuppressive drugs. Therefore, approximately 90% of PNP cases result in death with severe infections and other complications. However, it was previously reported that an anti-CD20 antibody, rituximab, successfully induced remission in many patients with pemphigus accompanying follicular lymphoma.[4-6]

Bronchiolitis obliterans (BO) is an irreversible and lethal lung disease that occurs in chronic graft-versus-host disease patients after allogeneic hematopoietic stem cell transplantation. It was also reported that 30-40% of patients with PNP progress to BO, which represents the major cause of death.[7,8] The use of corticosteroids and/or immunosuppressant drugs failed to induce remission of BO. Thus, only lung transplantation may rescue patients with PNP-related BO.

Herein, we report a 60-year-old male patient who suffered from BO accompanying PNP with follicular lymphoma. This case has already been reported as PNP with follicular lymphoma successfully treated with rituximab treatment, mainly from a dermatological point of view.[6] However, the patient subsequently developed BO and died 7 months later.

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CASE REPORT

In May 2012, a 60-year-old man presented at the Department of Dermatology, Kumamoto University Hospital. As already reported,[6] he showed massive blisters on both arms and hands that subsequently spread to the whole body, as well as extensive erosive lesions in the oral cavity. He also had a mild fever and mild dyspnea and wheezing. He exhibited high titers of anti-desmogleins-1 and -3 and BP180 antibodies and direct immunofluorescence showed IgG deposits to the keratinocyte cell surface in the epidermis. Western blotting of normal human epidermal extracts using the patient's serum revealed protein bands corresponding to 190-kDa periplakin and 210-kDa envoplakin.[9-12] On the basis of these findings, he was diagnosed with PNP.

To identify the primary malignancy that had induced PNP, he underwent ^{18}fluorine-labeled fluorodeoxyglucose positron emission tomography-computed tomography, which detected tumors in the pancreas and left intrapelvic region, as well as infiltrating tumor cells in the bone marrow regions (Fig. 1a). A computed tomography-guided needle biopsy from the pancreas revealed the infiltration of relatively small lymphoma cells that were positive for CD20, CD79a, and CD10 (Fig. 1b). Fluorescence *in situ* hybridization analysis of bone marrow aspirates indicated an *IgH-Bcl2* translocation, suggesting follicular lymphoma (Fig. 1c). Taking these findings together, he was diagnosed with PNP accompanying follicular lymphoma.

For chemotherapy for the follicular lymphoma, he was moved to the Department of Hematology, Rheumatology, and Infectious Disease. At this time, most of the blisters had already changed to erosions. The skin lesions emitted a bad odor, and bacterial cultures of the skin specimens revealed the existence of methicillin-resistant *Staphylococcus aureus*.

Initially, we decided not to use chemotherapeutic agents. We treated him with eight cycles of weekly rituximab because rituximab does not induce leukopenia or myelosuppression and instead should reduce the B cells that are responsible for

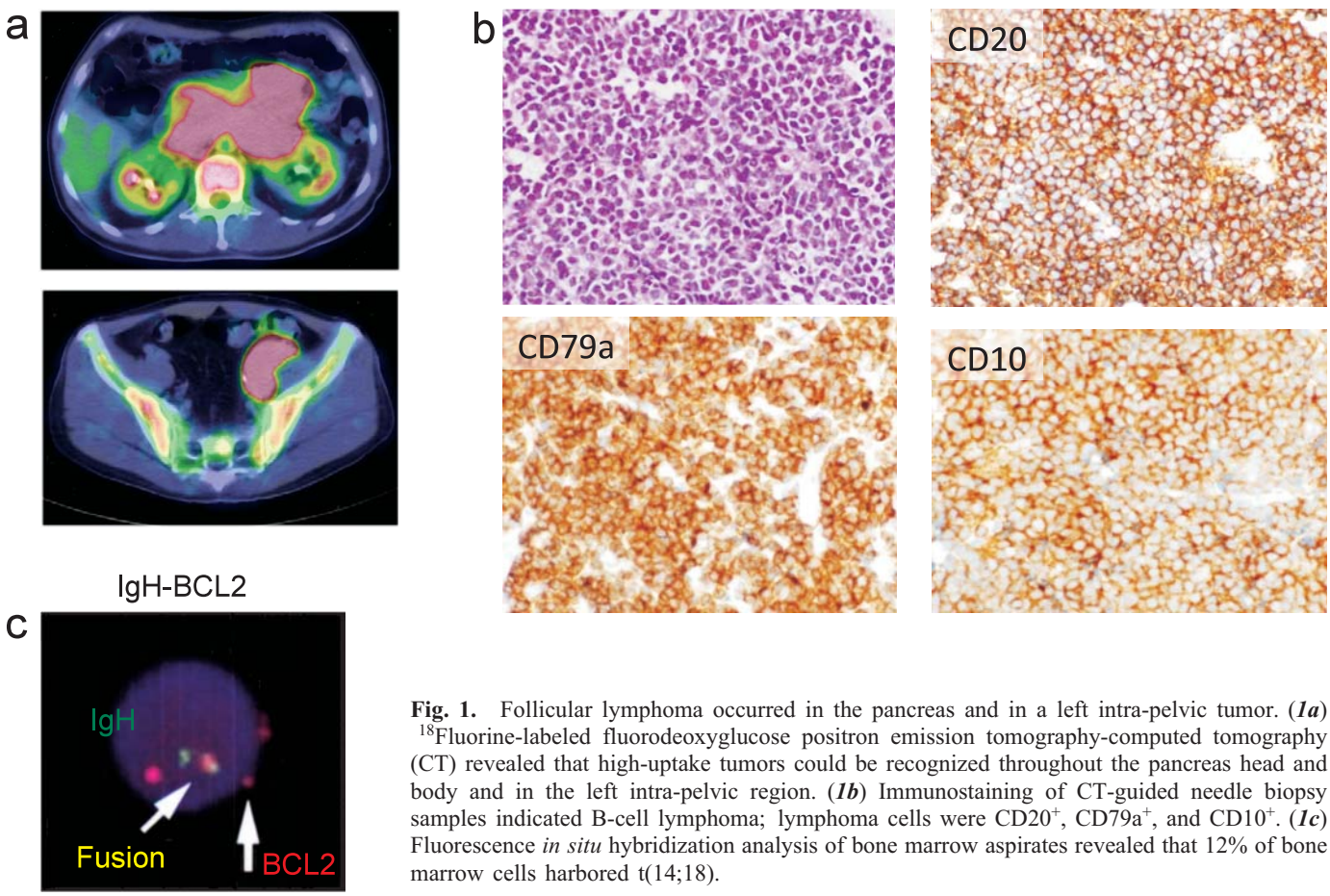

Fig. 1. Follicular lymphoma occurred in the pancreas and in a left intra-pelvic tumor. (***1a***) ^{18}Fluorine-labeled fluorodeoxyglucose positron emission tomography-computed tomography (CT) revealed that high-uptake tumors could be recognized throughout the pancreas head and body and in the left intra-pelvic region. (***1b***) Immunostaining of CT-guided needle biopsy samples indicated B-cell lymphoma; lymphoma cells were CD20$^+$, CD79a$^+$, and CD10$^+$. (***1c***) Fluorescence *in situ* hybridization analysis of bone marrow aspirates revealed that 12% of bone marrow cells harbored t(14;18).

the production of anti-desmogleins-1 and -3 and BP180 antibodies. After eight cycles of rituximab treatment, the blisters completely resolved and the titers of all autoantibodies were reduced to normal levels.[6] The dose of corticosteroids was tapered to less than 20 mg daily. The pancreatic tumor became smaller, as did the left pelvic tumor. The soluble interleukin-2 receptor level was initially 1,870 mg/L, but then decreased to 263 mg/L after rituximab treatment (Fig. 2a).

Soon after discharge, the patient had exertional dyspnea and was returned to the hospital by ambulance. Chest X-ray did not show any abnormalities, the SpO_2 was 97%, and there was no evidence of infection (C-reactive protein level was

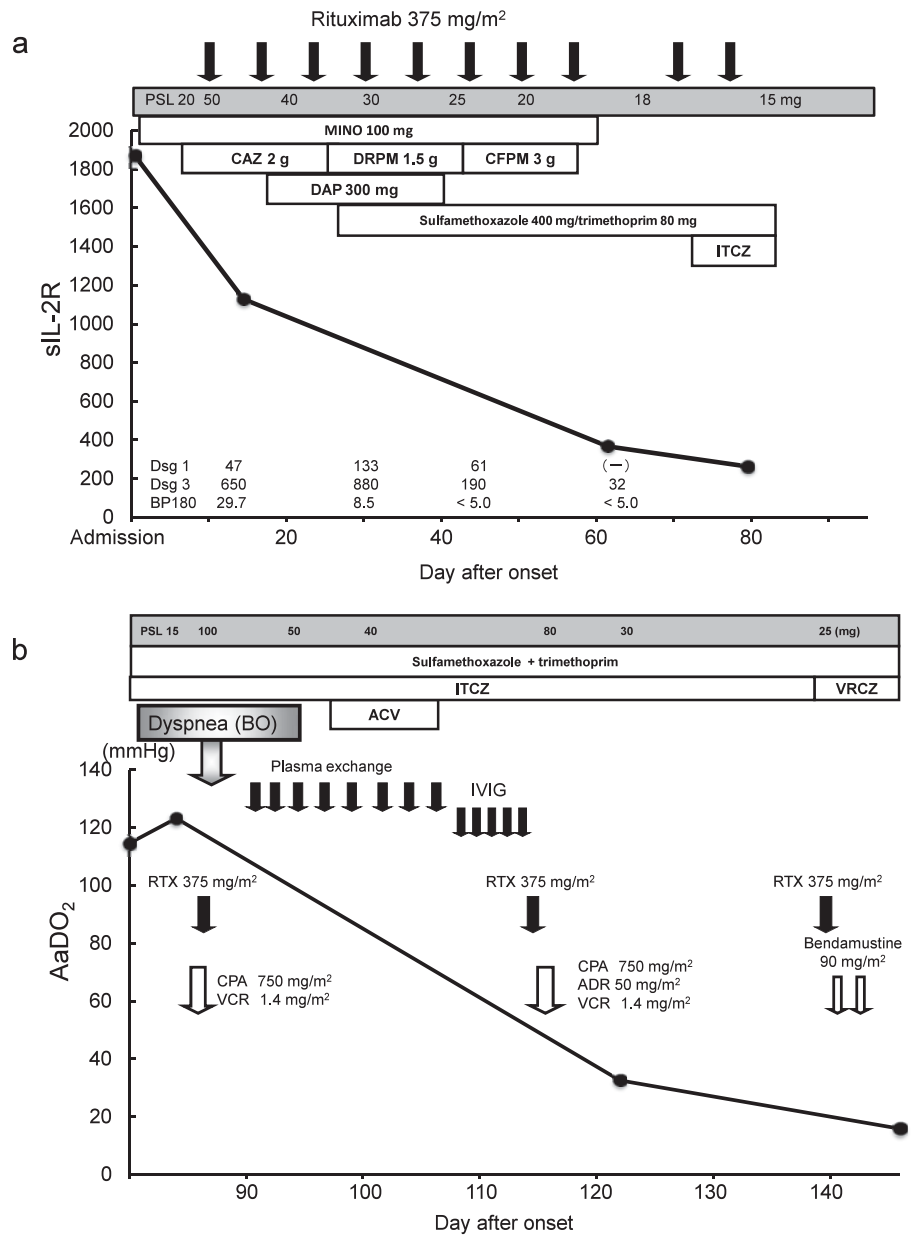

Fig. 2. Clinical course of this case. (***2a***) The clinical course before the diagnosis of bronchiolitis obliterans (BO). Eight cycles of rituximab treatment decreased serum soluble interleukin-2 receptor levels. (***2b***) The clinical course after the diagnosis of BO. Eight cycles of plasma exchange, IVIG, 1 cycle of rituximab, cyclophosphamide, vincristine, and prednisolone, and 2 cycles of rituximab-bendamustine could not stop the progression of BO. sIL-2R, soluble interleukin-2 receptor; PSL, prednisolone; MINO, minomycin; CAZ, ceftazidime; DRPM, doripenem; CFPM, cefepime; ITCZ, itraconazole; DAP, daptomycin; Dsg 1, anti-desmoglein 1 antibody; Dsg 3, anti-desmoglein 3 antibody; BP180, anti-BP180 antibody; VRCZ, voriconazole; ACV, acyclovir; IVIG, intravenous immunoglobulin; RTX, rituximab; CPA, cyclophosphamide; ADR, adriamycin; VCR, vincristine.

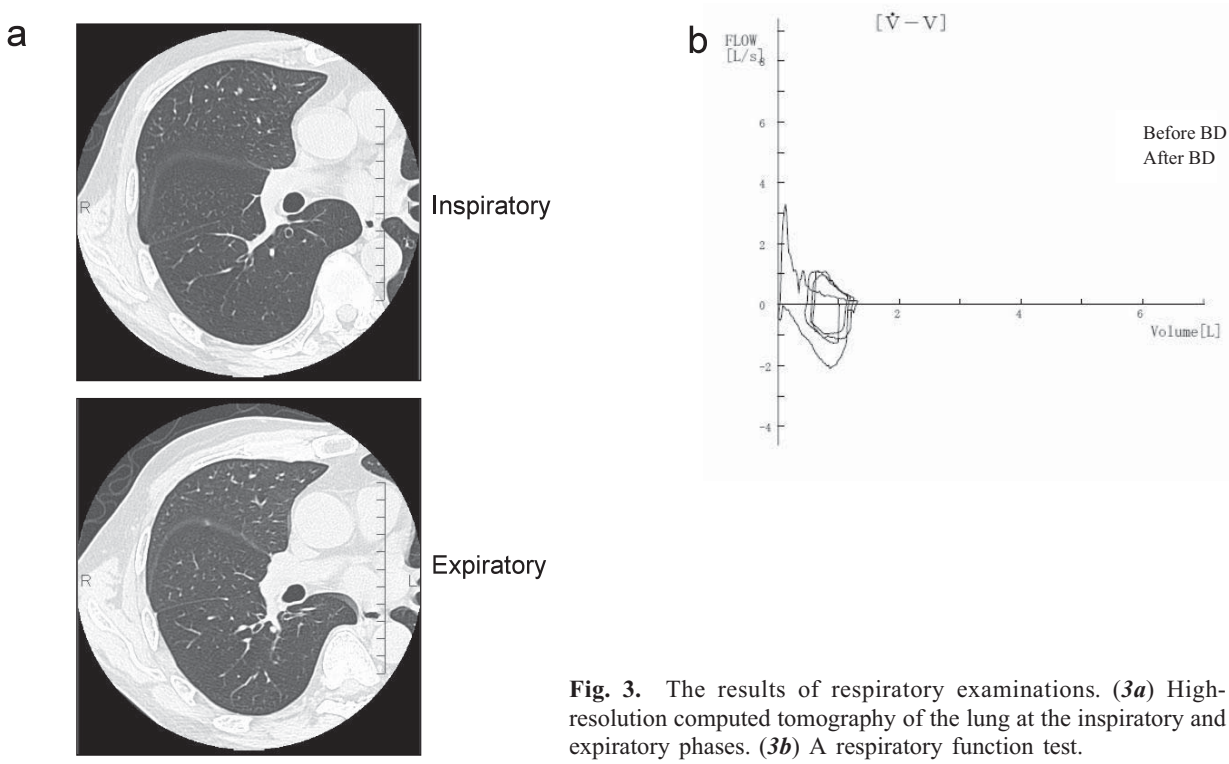

Fig. 3. The results of respiratory examinations. (***3a***) High-resolution computed tomography of the lung at the inspiratory and expiratory phases. (***3b***) A respiratory function test.

Table 1. Respiratory function test and arterial blood gas analysis at the onset of bronchiolitis obliterans

Tidal volume	1.46 L
Vital capacity	44%
Forced inspiratory flow rate	30.9%
pH	7.395
$PaCO_2$	34.9 mmHg
PaO_2	74.2 mmHg
HCO_3^-	20.9 mmol/L
Base excess	− 2.8 mmol/L
SaO_2	94.6%
Alveolar-arterial oxygen difference	114.6 mmHg

0.51). The exertional dyspnea did not improve and high-resolution computed tomography revealed air trapping at the end-expiratory phase and a respiratory function test showed obstructive and restrictive pulmonary failure (Fig. 3, Table 1). He was diagnosed with BO. Plasma exchange was performed as a standard therapy for BO. To prevent further reductions in lung function, we expected that further eradication of follicular lymphoma cells would be necessary for the suppression of abnormal autoimmune reaction to lung. The patient was thus treated with one cycle of rituximab, cyclophosphamide, vincristine, and prednisolone and two cycles of rituximab with bendamustine (Fig. 2b). The anti-desmoglein-1 and -3 and BP180 antibodies remained within normal ranges. However, the exertional dyspnea progressed, and the patient finally exhibited CO_2 narcosis and became dependent on mechanical ventilation. He survived for 7 months after the development of BO but then died, 14 months after the onset of PNP.

DISCUSSION

In this report, we describe that 8 cycles of rituximab regimen and rituximab-containing regimens could not improve BO that occurred in a patient with PNP accompanied by follicular lymphoma, although they were very effective for PNP.

PNP is a disease that generally has a poor prognosis because treatment of the associated malignancies is difficult in most cases. Pemphigus is usually treated with systemic corticosteroids and immunosuppressive agents, which frequently induce severe infections. Therefore, chemotherapies for associated malignancies with cytotoxic agents, which induce neutropenia, are often impossible. Indeed, our case had a *Staphylococcus aureus* infection in pemphigus-related erosions, and could not be treated with cytotoxic agents.

Several reports have shown the effectiveness of rituximab in PNP, particularly in patients associated with follicular lymphoma.[4-6] Because our patient had follicular lymphoma, we performed eight cycles of rituximab treatment.[13] The rituximab treatment reduced B cells that produced anti-

desmogleins-1 and -3, and BP180 antibodies, leading to the remission of PNP. Because B-cell malignant lymphomas are the most common malignant neoplasms in PNP, rituximab therapy without cytotoxic agents should be one of the possible therapeutic options for PNP. Additionally, rituximab may show high effectiveness in PNP associated with other types of malignant neoplasm.

Our patient developed lethal BO. Almost all PNP cases that develop BO, except for some patients with Castleman disease, result in a fatal outcome.[7] The mechanisms of development of BO in PNP have not yet been elucidated. IgG deposits were shown in bronchial epithelial cells, suggesting that autoreactive antibodies might be responsible for the development of BO. However, our case was extensively treated with rituximab and the levels of anti-desmoglein-1 and -3 and BP180 antibodies decreased to within normal ranges, suggesting that the mechanisms of development may differ between PNP and BO. The patient had anti-periplakin and anti-envoplakin autoantibodies, in addition to anti-desmogleins and anti-BP180 antibodies. Recently, it was reported that anti-periplakin antibodies can be detected in 40% of idiopathic pulmonary fibrosis cases.[14] Therefore, anti-periplakin antibody could have been involved in the development of BO in our patient. However, after eight cycles of rituximab treatment, the anti-periplakin and anti-envoplakin autoantibodies also became negative. In addition, after he was treated with plasma exchange and high doses of intravenous immunoglobulin, the lymphocytes decreased to 4.2%. Then, both $CD10^+$ and $CD20^+$ lymphocytes disappeared after two cycles of rituximab and bendamustine therapy. These findings suggested that IgG autoantibodies may not be involved in BO. Accordingly, it has been reported that $CD8^+$ T cells infiltrated into bronchioli in BO associated with Castleman disease, suggesting that cell-mediated immunity, particularly cytotoxic T cells, might be involved in BO.[15]

Our case already had exertional dyspnea and wheeze at the first presentation. Therefore, BO might already have existed at disease onset and gradually became apparent as obstructive and restrictive respiratory failure during the disease course of PNP. This patient could not survive for more than 7 months, even though he was treated with eight cycles of weekly rituximab that eliminated the serum autoantibodies involved in pemphigus. In this case, lung damage might have existed before treatment with rituximab for 3 months, and the damage in the lungs might have become more severe and irreversible prior to starting rituximab treatment. Therefore, the patient may have required lung transplantation in order to survive. Indeed, in Western countries, lung transplantation is thought to be the only way to rescue patients with BO. Even in Japan, it has recently been reported that lung transplantation for a patient with BO after allogeneic stem cell transplantation was successful.[16,17] However, it is difficult to find donors for lung transplantation because only a few are available and lung transplantation for cancer patients is not generally accepted in Japan. Therefore, living-donor lobar lung transplantation from family members might be the best choice for rescuing Japanese patients with BO accompanied by PNP.

In conclusion, rituximab-containing regimens may not be effective for BO associated with PNP, although early rituximab treatment is likely to be necessary for preventing the development of BO.

DISCLOSURE/CONFLICT OF INTEREST

The authors have no financial or competing interests to declare.

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