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【 CASE REPORT 】

Paraneoplastic Pemphigus Associated with B-cell Chronic Lymphocytic Leukemia Treated with Ibrutinib and Rituximab

Yuta Ito[1], Shinichi Makita[1], Akiko Miyagi Maeshima[2], Shunsuke Hatta[1], Tomotaka Suzuki[1], Sayako Yuda[1], Suguru Fukuhara[1], Wataru Munakata[1,3], Tatsuya Suzuki[1], Dai Maruyama[1] and Koji Izutsu[1]

Abstract:

Paraneoplastic pemphigus (PNP) is a severe autoimmune blistering disease associated with an underlying malignancy, and its prognosis is poor. We herein report the first patient with B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL)-associated PNP successfully treated with the Bruton's tyrosine kinase inhibitor ibrutinib and rituximab. Although his PNP lesions did not improve with ibrutinib monotherapy, the combination of ibrutinib and rituximab was effective against B-CLL/SLL-associated PNP. This case suggests that ibrutinib plus rituximab may be a potent therapeutic option for B-CLL/SLL-associated PNP that is hard to control with ibrutinib alone.

Key words: B-CLL/SLL, paraneoplastic pemphigus, PNP, ibrutinib, rituximab

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Introduction

Paraneoplastic pemphigus (PNP) is a life-threatening autoimmune blistering disease associated with an underlying malignancy. The most common underlying malignancies are mature B-cell neoplasms, such as B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL) (1-3). The prognosis of PNP has been reported to be poor. A recent retrospective study revealed that the PNP mortality rate was 68%, and infection was the most common cause of death (2). High-dose corticosteroids, considered a standard treatment for autoimmune bullous diseases, are also a conventional therapy for PNP (3). However, corticosteroids are not very effective (30%) (3-5), and their long-term use results in severe infection.

We herein report a patient with PNP associated with B-CLL/SLL successfully treated with ibrutinib and rituximab.

Case Report

A 62-year-old man with previously treated B-CLL/SLL presented with severe painful stomatitis extending to the lips and tongue. He had previously received six cycles of bendamustine combined with rituximab (BR) and achieved complete remission (CR) for five years. However, a physical examination revealed extensive lymphadenopathy, suggesting the progression of B-CLL/SLL. A flowcytometric analysis of the peripheral blood revealed the tumor cells to be positive for CD5, CD20, and CD23 and negative for CD3 and CD10. Table summarizes the laboratory findings at presentation.

Initially, we believed the patient to have infectious stomatitis potentially associated with the immunocompromised state caused by B-CLL/SLL. Antimicrobial agents, such as acyclovir, fluconazole, and ampicillin/sulbactam were administered, as empiric therapy for infectious stomatitis.

[1]Department of Hematology, National Cancer Center Hospital, Japan, [2]Department of Pathology, National Cancer Center Hospital, Japan and [3]Rare Cancer Center, National Cancer Center Hospital, Japan
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Correspondence to Dr. Shinichi Makita, smakita@ncc.go.jp

Table. Laboratory Findings at Presentation.

Blood cell count		Biochemistry		Immunology	
WBC	30.6 $\times 10^3$/mcL	TP	6.9 g/dL	IgG	581 mg/dL
Segmented neutrophils	1.0 %	Alb	4.5 g/dL	IgA	39 mg/dL
Stab neutrophils	16.0 %	T-Bil	0.9 mg/dL	IgM	4 mg/dL
Lymphocytes	3.0 %	AST	21 U/L	Beta-D-glucan	<0.6 pg/mL
Monocytes	2.0 %	ALT	21 U/L	Galactomannan antigen	Negative
Eosinophils	78.0 %	LDH	224 U/L	Candida antigen	Negative
Basophils	0 %	Cre	0.8 mg/dL	CMV antigenemia	Negative
Abnormal lymphocytes	78.0 %	Na	142 mmol/L	Anti-desmoglein 1	<3.0 U/mL
RBC	471 $\times 10^4$/mcL	K	5.0 mmol/L	Anti-desmoglein 3	34.1 U/mL
Hemoglobin	13.7 g/dL	Cl	101 mmol/L	Anti-BP180	3.2 U/mL
Platelets	21.7 $\times 10^4$/mcL	CRP	4.01 mg/dL	Anti-envoplakin	Positive
Reticulocytes	2.13 %	Beta-2-microglobulin	5.65 mg/L	Anti-periplakin	Positive

Alb: albumin, ALT: alanine aminotransferase, AST: aspartate transaminase, BUN: blood urea nitrogen, Cl: chlorine, CMV cytomegalovirus, Cre: creatinine, CRP: C-reactive protein, K: potassium, LDH: lactate dehydrogenase, Na: sodium, RBC: red blood cell count, T-Bil: total bilirubin, TP: total protein, WBC: white blood cell count

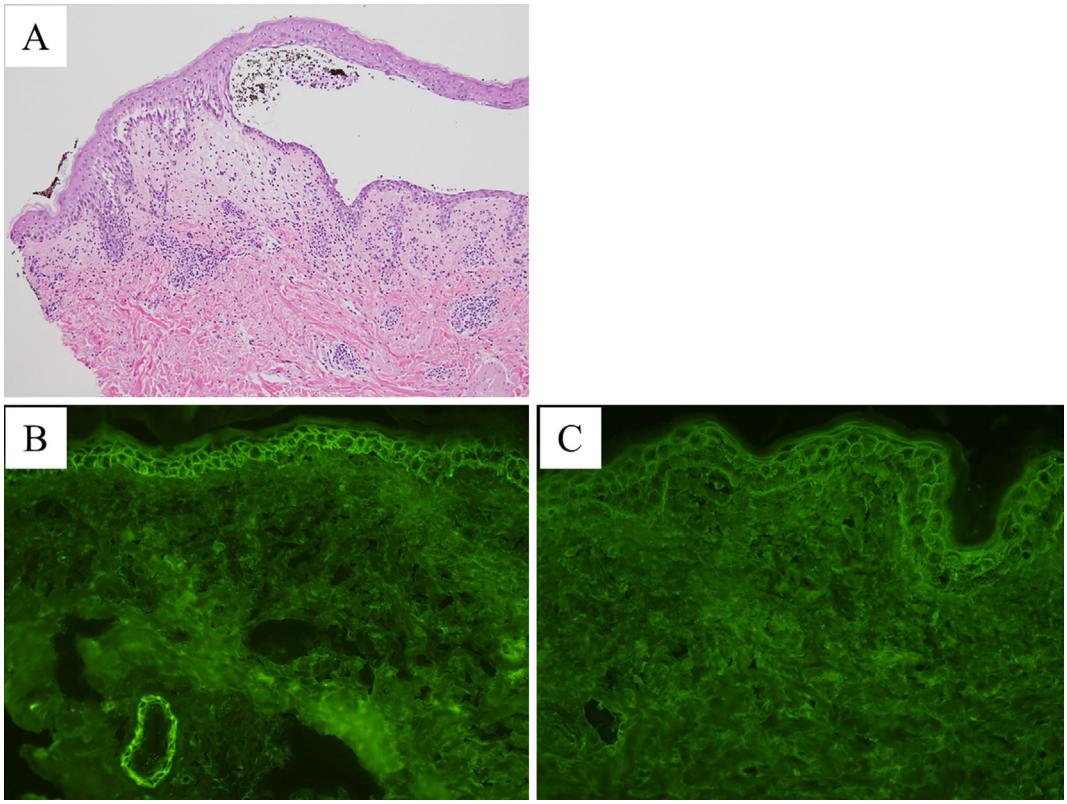

Figure 1. Skin biopsy specimens demonstrating intraepidermal vesicle with acantholysis (A, Hematoxylin and Eosin staining, ×100). Direct immunofluorescence test showing deposition of IgG (B, ×100) and complement C3 (C, ×100) in the epidermal intercellular spaces.

However, the stomatitis did not improve. He was unable to take anything orally because of the painful stomatitis; therefore, total parenteral nutrition was initiated. A biopsy of the oral mucosa revealed non-specific inflammation. No specific findings suggestive of herpes infections or B-CLL/SLL infiltration were observed.

Four weeks later, blistering eruptions developed on his anterior chest. Histopathology of the skin biopsy specimen demonstrated an intraepidermal vesicle with acantholysis (Fig. 1A). Direct immunofluorescence showed the deposition of IgG (Fig. 1B) and complement C3 (Fig. 1C) in the epidermal intercellular spaces. The serum desmoglein 3 autoantibody value was positive at 34.1 U/mL. In an immunoprecipitation assay using the patient's serum, bands of envoplakin and periplakin were detected. Based on these findings, the patient was diagnosed with PNP, probably associated with B-CLL/SLL. PNP was treated with 1 mg/kg/day of prednisolone for 7 days and then tapered. Simultane-

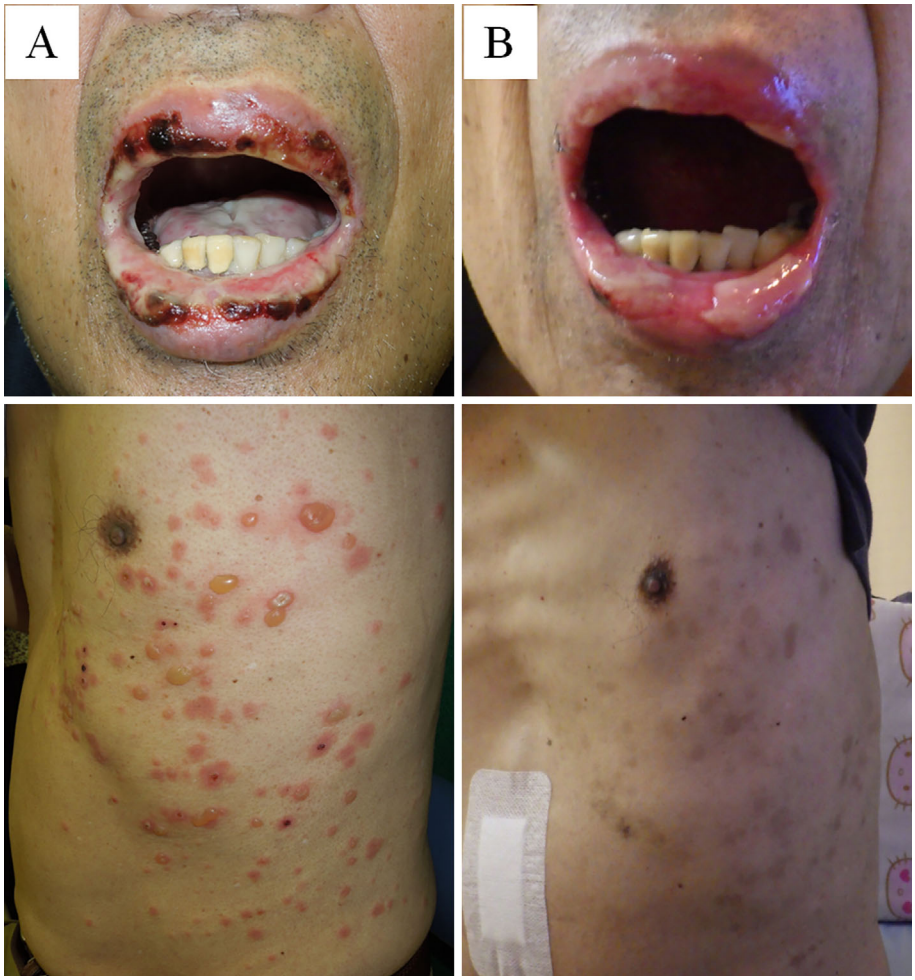

Figure 2. **The pemphigus lesions of the lips, oral cavity, and skin before (A) and after (B) the treatment.**

ously, the underlying B-CLL/SLL was treated with 420 mg/day of ibrutinib. Ibrutinib markedly reduced the B-CLL/SLL, and the lymph node swelling immediately improved. Blistering eruptions in the chest also disappeared. However, the stomatitis remained unimproved and became complicated with mucomembranous infection.

The efficacy of rituximab for pemphigus vulgaris and pemphigus foliaceus was recently demonstrated in a randomized phase III trial (5). Therefore, 375 mg/m^2/week of rituximab was initiated for 8 weeks to control PNP and the anti-tumor effects of B-CLL/SLL, 2 weeks after initiating ibrutinib. The use of rituximab combined with ibrutinib was approved by the pharmaceutical committee of the National Cancer Center Hospital. Written consent was obtained from the patient before initiating rituximab. After the treatment with ibrutinib plus eight doses of rituximab, the patient's stomatitis gradually improved (Fig. 2).

Discussion

To our knowledge, this is the first report of a patient with B-CLL/SLL-associated PNP successfully treated with ibrutinib plus rituximab. Lee et al. reported a case of B-CLL/SLL-associated PNP treated with ibrutinib monotherapy (6). However, PNP was not managed well using ibrutinib alone, and the patient received high-dose steroids, cyclosporine, mycophenolate mofetil, and plasmapheresis.

The most definitive and effective treatment for PNP is the elimination of the underlying neoplasm: surgical removal or effective chemotherapy (1-4). Therefore, obtaining a deep response with systemic chemotherapy seems to be essential in the management of B-CLL/SLL-associated PNP.

Ibrutinib, a Bruton's tyrosine kinase inhibitor, is one of the most promising effective novel agents against B-CLL/SLL (7). Although ibrutinib was extremely effective in this case, the stomatitis caused by PNP remained unimproved. This may have been because the CR rate of ibrutinib was lower than that of the anti-CD20 antibody therapy. A randomized phase III trial comparing ibrutinib and the second-generation anti-CD20 antibody ofatumumab found that ibrutinib significantly improved the progression-free survival rate (88% vs. 65% at 6 months), overall survival rate (90% vs. 81% at 12 months), and overall response rate (ORR) (62.6% vs. 4.1%) in patients with previously treated B-CLL/SLL (8). However, no patient achieved CR with ibrutinib. Although ibrutinib's partial response against B-CLL/SLL

was immediate, residual disease remained able to produce autoantibodies to the desmosomal proteins, which may have resulted in persistent PNP.

To achieve deeper remission, chemoimmunotherapy might be more effective than ibrutinib monotherapy. For example, BR in patients with previously treated B-CLL resulted in an ORR of 59.0% with a 9.0% CR rate. The minimal residual disease levels in the bone marrow were negative in 7.7% of evaluable patients (9). However, cytotoxic regimens were associated with an increased rate of severe infections, even in physically "fit" patients (10). Therefore, more effective novel treatments with lower rates of neutropenia and mucositis are desirable. A phase II study of ibrutinib plus rituximab in patients at high-risk for B-CLL/SLL was recently conducted (11). This combination demonstrated an ORR of 95% with an 8% CR rate. Venetoclax, a BCL2 inhibitor, is also a promising agent. According to a phase Ib study of venetoclax plus rituximab, 86% patients achieved an overall response with a 51% CR rate (12).

Rituximab alone seems an effective treatment for autoimmune blistering diseases. As described, Joly et al. conducted a randomized phase III trial to compare rituximab plus prednisolone and prednisolone alone as a first-line treatment for pemphigus. As a result, rituximab demonstrated a significantly increased CR rate (5). Furthermore, several case reports have shown the efficacy of rituximab in patients with PNP associated with B-cell lymphomas (3, 4, 13). In the present case, rituximab was effective for treating both the underlying malignancy and B-cell that produce autoantibodies causing PNP.

In conclusion, the efficacy of single-agent ibrutinib against B-CLL/SLL-associated PNP may be limited, possibly due to infrequent deep remission. This case may suggest that rituximab combined with ibrutinib might be a potent therapeutic option in patients with B-CLL/SLL-associated PNP, whose mucocutaneous lesions are difficult to control using single-agent ibrutinib.

Author's disclosure of potential Conflicts of Interest (COI).
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