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

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.
Table. Laboratory Findings at Presentation.

<table>
<thead>
<tr>
<th>Blood cell count</th>
<th>Biochemistry</th>
<th>Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 30.6 ×10^3/mcL</td>
<td>TP 6.9 g/dL</td>
<td>IgG 581 mg/dL</td>
</tr>
<tr>
<td>Segmented neutrophils 1.0 %</td>
<td>Alb 4.5 g/dL</td>
<td>IgA 39 mg/dL</td>
</tr>
<tr>
<td>Stab neutrophils 16.0 %</td>
<td>T-Bil 0.9 mg/dL</td>
<td>IgM 4 mg/dL</td>
</tr>
<tr>
<td>Lymphocytes 3.0 %</td>
<td>AST 21 U/L</td>
<td>Beta-D-glucan &lt;0.6 pg/mL</td>
</tr>
<tr>
<td>Monocytes 2.0 %</td>
<td>ALT 21 U/L</td>
<td>Galactomannan antigen Negative</td>
</tr>
<tr>
<td>Eosinophils 78.0 %</td>
<td>LDH 224 U/L</td>
<td>Candida antigen Negative</td>
</tr>
<tr>
<td>Basophils 0 %</td>
<td>Cre 0.8 mg/dL</td>
<td>CMV antigenemia Negative</td>
</tr>
<tr>
<td>Abnormal lymphocytes 78.0 %</td>
<td>Na 142 mmol/L</td>
<td>Anti-desmoglein 1 &lt;3.0 U/mL</td>
</tr>
<tr>
<td>RBC 471 ×10^6/mcL</td>
<td>K 5.0 mmol/L</td>
<td>Anti-desmoglein 3 34.1 U/mL</td>
</tr>
<tr>
<td>Hemoglobin 13.7 g/dL</td>
<td>Cl 101 mmol/L</td>
<td>Anti-BP180 3.2 U/mL</td>
</tr>
<tr>
<td>Platelets 21.7 ×10^9/mcL</td>
<td>CRP 4.01 mg/dL</td>
<td>Anti-envelopalin Positive</td>
</tr>
<tr>
<td>Reticulocytes 2.13 %</td>
<td>Beta-2-microglobulin 5.65 mg/dL</td>
<td>Anti-periplakin Positive</td>
</tr>
</tbody>
</table>


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.

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.
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 mucormembranous infection.

The efficacy of rituximab for pemphigus vulgaris and pemphigus foliaceus was recently demonstrated in a randomized phase III trial (5). Therefore, 375 mg/m²/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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References


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