Rituximab Treatment for Paraneoplastic Pemphigus Associated with Follicular B-Cell Lymphoma: A Case Report and Review of Treatment Outcome

Waranaree Winayanuwattikun, M.D., Leena Chularojanamontri, M.D., Papapit Tuchinda, M.D., Penvadee Pattanaprichakul, M.D., Kanokvalai Kulthanan, M.D.

Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To report a case of paraneoplastic pemphigus (PNP), a rare disease, associated with follicular B-cell lymphoma. Treatment outcomes of PNP associated with follicular B-cell lymphoma following rituximab treatment were also reviewed in this article.

Case presentation: We reported a PNP patient presenting with intractable stomatitis and erythema multiforme-like lesions. Skin biopsy from erythema multiforme-liked lesion revealed interface dermatitis and necrotic keratinocytes. Direct immunofluorescence demonstrated immunoglobulin G deposition at intercellular space, as well as complement deposition at dermo-epidermal junction. Indirect immunofluorescence using rat bladder substrate was helpful in confirming the diagnosis of PNP. Further investigations revealed an underlying disease of follicular B-cell lymphoma. He was treated with rituximab and systemic corticosteroids. Improvement of mucocutaneous lesions and lymphoma were noted. Nevertheless, he developed hospital-acquired pneumonia and died from septic shock shortly after receiving conventional chemotherapy. His survival duration was approximately 8 months after diagnosis of PNP.

Conclusion: It seemed that rituximab might provide promising benefits for mucocutaneous lesions in PNP patients associated with follicular B-cell lymphoma.

Keywords: Paraneoplastic pemphigus; rituximab; follicular B-cell lymphoma; therapy; bronchiolitis obliterans (Siriraj Med J 2018;70: 523-528)

INTRODUCTION

Paraneoplastic pemphigus (PNP), a rare disease, is characterized by severe intractable stomatitis and polymorphous skin eruptions in patients with underlying neoplasms.[1] Treatment of neoplasm is the most important, but variable results for mucocutaneous lesions have been demonstrated.[2] To control mucocutaneous lesions, high dose corticosteroids and immunosuppressive drugs are frequently used which can lead to severe infections and other complications. Recently, rituximab (anti-CD20 antibodies) has been used in PNP patients with CD20+ lymphoma.[3-5] Herein, we reported our case and review treatment outcome of rituximab in PNP patients associated with follicular B-cell lymphoma.

CASE REPORT

A 44-year-old man without any underlying disease came to see a rheumatologist due to chronic stomatitis and weight loss of 18 kilograms for 6 months. Prednisolone 20 mg/day, hydroxychloroquine 200 mg/day and colchicine

Correspondence to: Leena Chularojanamontri
E-mail: leenajim@gmail.com
Received 28 December 2017 Revised 8 June 2018 Accepted 10 July 2018
doi:10.14456/smj.2018.84

0.6 mg/day were initiated due to a suspicion of Bechet's disease. After 2 weeks of treatment, a patient had a worsening of his oral lesion and developed erosive erythematous patches and target-like lesions on his genitalia, trunk, and extremities (Fig 1). He was then referred for dermatologic consultation. Steven-Johnsons syndrome and PNP were suspected due to stomatitis and erythema multiforme-like lesions. Possible drugs including colchicine and hydroxychloroquine were discontinued. After stopping the possible drugs for 2 weeks, his mucocutaneous lesions still deteriorated. He developed mild dyspnea and dry cough. Skin biopsy from erythema multiforme-liked lesion revealed interface dermatitis and necrotic keratinocytes. Direct immunofluorescence demonstrated immunoglobulin G deposition at intercellular space, as well as complement deposition at dermo-epidermal junction. Indirect immunofluorescence was positive for rat bladder substrate (Fig 1a-1d). The diagnosis of PNP was established and oral prednisolone 60 mg/day (1 mg/kg/day) was started to control mucocutaneous lesions.

Computed tomography (CT) angiogram of the chest demonstrated diffuse peribronchial wall thickening with bronchiolitis, possibly lymphadenopathy along periaortic region, and a focal ground glass opacity at upper lobe of right lung. CT-guided biopsy showed small to medium sized atypical lymphoid cells with positive immunostaining of CD3, CD20, CD10, CD43 and bcl-2, but negative immunostaining for CD5, CD23, or cyclin D1. For disease staging, abdominal CT scan was performed which revealed enlargement of intraabdominal nodes including paraaortic, retrocaval, aortocaval, common iliac, and celiac-mesenteric regions. Bone marrow biopsy showed no invasion of atypical lymphoid cells. These findings were compatible with follicular B-cell lymphoma stage II. Bronchoscopy and bronchoalveolar lavage (BAL) were undergone due to fever, dyspnea, and abnormal chest imaging at upper lobe of right lung. Polymerase chain reaction and culture of BAL fluid for *Mycobacterium tuberculosis* were negative. However, anti-tuberculous drugs were initiated because smear negative pulmonary tuberculosis could not be excluded. Moreover, antifungal drugs were commenced as BAL fluid revealed positive for galactomannan antigen. To prevent adrenal crisis and control severe infections, prednisolone was gradually decreased from 60 mg to 15 mg resulting in deterioration in mucocutaneous lesions.

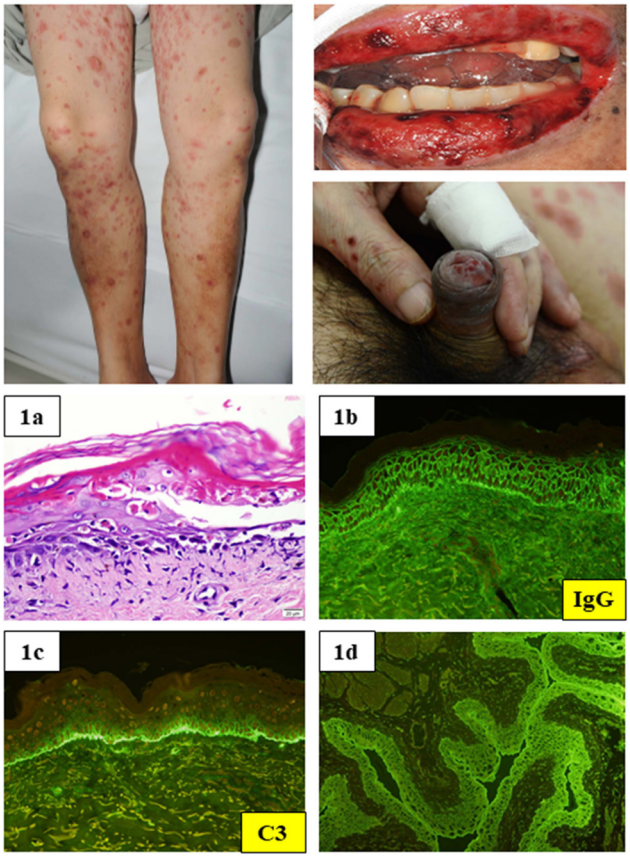


Fig 1. Clinical presentations, histopathology, and immunofluorescent results

One month after tuberculosis and fungal treatment, serious infections were controllable. However, rituximab-based chemotherapy for follicular B-cell lymphoma could not be initiated due to his performance status. Thus, rituximab at the dose of 375 mg/m^2 with prednisolone 45 mg/day every 21-day was used to control both PNP and follicular B-cell lymphoma. After a third cycle of rituximab there was an improvement in mucocutaneous lesions (Fig 2) and CT chest showed a decrease in the size of mediastinal and hilar lymph nodes. However, he had an acute exacerbation of chronic dyspnea after the fifth cycle of rituximab. A repeated CT chest showed pleuroparenchymal fibrosis which led to the suspicion of bronchiolitis obliterans. Nevertheless, lung function test was not able to be performed due to very poor performance status of the patient. After the 8th cycle of rituximab, he received one cycle of CVP (cyclophosphamide, vincristine, prednisolone) regimen. Shortly afterwards, the patient developed hospital-acquired pneumonia and died from septic shock. His survival duration after diagnosis of PNP with follicular B-cell lymphoma was approximately 8 months.

DISCUSSION

Due to a wide range of clinical presentations and complexity in the pathogenesis, the diagnosis and treatment of PNP remains a great challenge. Similar to our patient, severe painful, hemorrhagic, therapy-resistant stomatitis is the earliest complaint and usually precedes cutaneous lesions.[6] The retrospective study in 12 Korean patients with



Fig 2. Mucocutaneous lesions (a) before rituximab initiation, (b) a 3rd cycle of rituximab, (c) a 5th cycle of rituximab

PNP showed that erythema multiforme-like or lichenoid eruptions were more common than blister-like lesion in the East Asian population.[7] Bronchiolitis obliterans, a rare and fatal complication, is characterized by progressive obliteration of small airways and a persistent decline in lung function. The prognosis of PNP is very poor with a mortality rate of 90%. Common causes of death are sepsis, respiratory failure, and underlying neoplasm.[1,2,6]

Corticosteroids are the first-line treatment of mucocutaneous lesions. Steroid sparing agents such as azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil or autoantibody-lowering agents (intravenous immunoglobulin and plasmapheresis) have been used with variable results.[2] Based on our literature review, rituximab has been used in some PNP patients with follicular B-cell lymphoma since 2001. Table 1 shows demographic data and outcomes of reported cases of PNP-related follicular lymphoma patients receiving rituximab treatment.[3-5,9-18] It was shown that neither conventional chemotherapy nor steroid sparing agent yielded satisfactory results in mucocutaneous lesions. On the other hand, rituximab seemed to induce a favorable outcome. Twelve of 14 patients (85.7%), including our patient, had an improvement in mucocutaneous lesions (Table 1).

Bronchiolitis obliterans, an irreversible obstructive lung disease, is a major cause of death in PNP patients.[6], Lee *et al.*, reported a patient who achieved the longest survival (27 months) of PNP-related bronchiolitis obliterans from R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen.[18] However, Lee *et al.*, stated that full dose of chemotherapeutic regimen, not only rituximab, led to this promising result.[18] Some authors stated that rituximab in combination with cyclosporine is one of a few treatment options for PNP that can lead to long-term remission.[19,20] Up to date, it is still difficult to determine a treatment protocol and treatment outcome of rituximab in PNP due to a low prevalence of the disease.[1,2]

Conversely, several protocols including a lymphoma protocol, a rheumatoid arthritis protocol, low-dose rituximab with or without concomitant use of intravenous immunoglobulin and immunoadsorption have been proposed in treating pemphigus vulgaris or pemphigus foliaceous patients. Current evidence suggests that rituximab has a favourable outcome in treating patients with pemphigus vulgaris and pemphigus foliaceous.[21] Complete and clinical remission rates were approximately 65-78%. Mean time to disease control was less than one month. The underlying neoplasm of PNP, rather than an autoimmune process, may be a reason for the difference in clinical outcomes following rituximab treatment between PNP and other variants of pemphigus.[21]

With regards to the patient's primary disease, rituximab seems to change the paradigm of treating follicular B cell lymphoma.[22] Several randomized trials demonstrated improved response rates time to progression and overall survival rate in the rituximab plus chemotherapy patients.[23-27] Rituximab was shown to rapidly deplete CD20+ tumor B-cells and the effect was detected after a few months of treatment.[28] Moreover, using rituximab as a maintenance therapy in patients who already received rituximab-based chemotherapy showed higher disease-free duration.[29]

The most common reported adverse events of rituximab were infusion reactions.[30] Many reactions are dose-dependent and developed within 24 hours of the first infusion. Slow infusion rate, premedication with antihistamine, acetaminophen, and/or corticosteroids can reduce symptoms in non-severe reactions. In patients with severe reactions, infusion would be permanently withdrawn. A minimal risk to develop leukopenia and infection in rituximab maintenance therapy has been reported.[31]

In conclusion, due to PNP is a relatively rare disease, it is difficult to determine the efficacy of rituximab in PNP associated with lymphoproliferative disorders or other neoplasms. Based on limited evidence, it seemed that rituximab may provide promising results of mucocutaneous lesions in PNP associated follicular B-cell lymphoma.

REFERENCES

1. Kaplan I, Hodak E, Ackerman L, Mimouni D, Anhalt GJ, Calderon S. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. Oral Oncol. 2004;40:553-62.
2. Frew JW, Murrell DF. Current management strategies in paraneoplastic pemphigus (paraneoplastic autoimmune

TABLE 1. Reported cases of paraneoplastic pemphigus (PNP) with follicular lymphoma treated with rituximab

Studies	Year	Age (yrs) / Sex	Lymphoma staging	First treatment of PNP and lymphoma	Outcome from previous treatment	Rituximab(R) and other treatment	Mucocutaneous lesions after rituximab treatment	Follow-up time
Borradori [9]	2001	61 / F	IVA	Prednisolone and 6 cycles of CHOP regimen	Slightly improvement in stomatitis	R: 375 mg/m^2 weekly × 4 weeks then every 2 months	1 month: rapidly improved	4 months
Heizmann [3]	2001	73 / F	Not reported	Prednisolone and cyclophosphamide for 4 weeks	No improvement in mucocutaneous lesions	R: 375 mg/m^2 weekly × 4 weeks	1 week: regression of lesions 6 months: completely resolved 1 year: still absent	1 year
Bernadas [4]	2006	77 / F	IIB	Prednisolone and cyclosporine	No improvement in mucocutaneous lesions and lymph nodes	R: 375 mg/m^2 weekly × 4 weeks and methylprednisolone	8 months: completely resolved	3 years: death
Hoque [10]	2006	49 / F	Not reported	-	-	R-CVP chemotherapy × 3 cycles	1 cycle: improved in the rash but briefly recurred	Death
Deborah [11]	2007	71 / F	Not reported	4 cycles of CHOP	Disease remission but briefly recurred	R: 375 mg/m^2 weekly × 4 weeks and this 4-dose was repeated every 6 months, daclizumab, prednisolone	During 2 years of follow-up: less active of mucositis	2 years
Aoi [5]	2013	60 / M	Not reported	Prednisolone	No improvement in mucocutaneous lesions	R: 375 mg/m^2 weekly × 8 weeks and chemotherapy	5 weeks: almost recovery	Not reported
Morikawa [12]	2014	65 / F	IIIA	-	-	R-CHOP, CVP chemotherapy	Improvement in mucocutaneous lesions	5 months
Hirano [13]	2015	60 / M	Not reported	-	-	R: 375 mg/m^2 weekly × 8 weeks	8 weeks: completely resolved of blisters	14 months: death

Abbreviations: CHOP; cyclophosphamide, doxorubicin, vincristine, prednisolone, CVP; cyclophosphamide, vincristine, prednisolone, IVIG; intravenous immunoglobulin, R; Rituximab

TABLE 1. Reported cases of paraneoplastic pemphigus (PNP) with follicular lymphoma treated with rituximab

Studies	Year	Age (yrs) / Sex	Lymphoma staging	First treatment of PNP and lymphoma	Outcome from previous treatment	Rituximab(R) and other treatment	Mucocutaneous lesions after rituximab treatment	Follow-up time
Rossom [14]	2015	70 / M	IVB	Di-Adreson-F aquosum, cyclophosphamide, azathioprine	No improvement	R: 375 mg/m^2 weekly × 4 weeks and prednisolone	8 weeks: slightly improved	9 months: death from heart failure
Kanwar [15]	2015	61 / M	Not reported	Prednisolone	Poor control	R: 375 mg/m^2 every 21 days × 4 cycles and prednisolone	4 cycles: all mucocutaneous lesions healed	3 months
Namba [16]	2016	59 / F	Not reported	Prednisolone and cyclosporine	N/A	R-CHOP × 2 doses, additional 5 cycles of R-375 mg/m^2, prednisolone, IVIG, cyclosporine	No improvement of mucosal lesions	6 months: death
Kikushi [17]	2017	74 / F	Histological grade II	Prednisolone	No improvement	R: 375 mg/m^2 + Bendamustine	2 weeks: began to improve 4 weeks: almost resolved	1 year: no recurrence of PNP
Lee [18]	2017	53 / M	IVA	-	-	7 cycles of R-CHOP regimen and one additional cycle of R-375 mg/m^2	No improvement in mucocutaneous lesions but not progress	27 months: death from respiratory failure
Our case		44 / M	II	-	-	R: 375 mg/m^2 every 21 days × 8 cycles and prednisolone	Improvement in mucocutaneous lesions	8 months: death from septic shock

Abbreviations: CHOP; cyclophosphamide, doxorubicin, vincristine, prednisolone, CVP; cyclophosphamide, vincristine, prednisolone, IVIG; intravenous immunoglobulin, R; Rituximab

multiorgan syndrome). Dermatol Clin. 2011;29:607-12.
3. Heizmann M, Itin P, Wernli M, Borradori L, Bargetzi MJ. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am J Hematol. 2001;66:142-4.
4. Barnadas M, Roe E, Brunet S, Garcia P, Bergua P, Pimentel L, et al. Therapy of paraneoplastic pemphigus with Rituximab: a case report and review of literature. J Eur Acad Dermatol Venereol. 2006;20:69-74.
5. Aoi J, Makino K, Sakai K, Masuguchi S, Fukushima S, Jinnin M, et al. Case of paraneoplastic pemphigus with follicular lymphoma treated with rituximab. J Dermatol. 2013;40:285-6.
6. Kartan S, Shi VY, Clark AK, Chan LS. Paraneoplastic pemphigus and autoimmune blistering diseases associated with neoplasm: characteristics, diagnosis, associated neoplasms, proposed pathogenesis, treatment. Am J Clin Dermatol. 2017;18:105-26.
7. Choi Y, Nam KH, Lee JB, Lee JY, IHM CW, Lee SE, et al. Retrospective analysis of 12 Korean patients with paraneoplastic pemphigus. J Dermatol. 2012;39:973-81.
8. Schmidt E, Goebeler M, Zillikens D. Rituximab in severe pemphigus. Ann N Y Acad Sci. 2009;1173:683-91.
9. Borradori L, Lombardi T, Samson J, Girardet C, Saurat JH, Hügli A. Anti-CD20 monoclonal antibody (rituximab) for refractory erosive stomatitis secondary to CD20(+) follicular lymphoma-associated paraneoplastic pemphigus. Arch Dermatol. 2001;137: 269-72.
10. Hoque SR, Black MM, Cliff S. Paraneoplastic pemphigus associated with CD20-positive follicular non-Hodgkin's lymphoma treated with rituximab: a third case resistant to rituximab therapy. Clin Exp Dermatol. 2007;32:172-5.
11. Cummins DL, Mimouni D, Tzu J, Owens N, Anhalt GJ, Meyerle JH. Lichenoid paraneoplastic pemphigus in the absence of detectable antibodies. J Am Acad Dermatol. 2007;56:153-9.
12. Morikawa K, Tsuji T, Yamasaki H, Egashira S, Kaguchi A, Kido M, et al. Paraneoplastic pemphigus occurs most commonly in indolent B cell lymphoma. Acta Haematol. 2014;132:73-4.
13. Hirano T, Higuchi Y, Yuki H, Hirata S, Nosaka K, Ishii N, et al. Rituximab monotherapy and rituximab-containing chemotherapy were effective for paraneoplastic pemphigus accompanying follicular lymphoma, but not for subsequent bronchiolitis obliterans. J Clin Exp Hematop. 2015;55:83-8.
14. Rossum MM, Verhaegen NT, Jonkman MF, Mackenzie MA, Koster A, Valk PV, et al. Follicular non-Hodgkin's lymphoma with refractory paraneoplastic pemphigus: case report with review of novel treatment modalities. Leuk Lymphoma. 2004;45:2327-32.
15. Kanwar AJ, Vinay K, Varma S, Koga H, Ishii N, Hashimoto T. Anti-desmoglein antibody-negative paraneoplastic pemphigus successfully treated with rituximab. Int J Dermatol. 2015;54:576-9.
16. Namba C, Tohyama M, Hanakawa Y, Murakami M, Shirakata Y, Matsumoto T, et al. Paraneoplastic pemphigus associated with fatal bronchiolitis obliterans and intractable mucosal erosions: Treatment with cyclosporin in addition to steroid, rituximab and intravenous immunoglobulin. J Dermatol. 2016;43:419-22.
17. Kikuchi T, Mori T, Shimizu T, Koda Y, Abe R, Kurihara Y, et al. Successful treatment with bendamustine and rituximab for paraneoplastic pemphigus. Ann Hematol. 2017;96:1221-2.
18. Lee S, Yamauchi T, Ishii N, Hashimoto T, Kinoshita K, Imamura S, et al. Achievement of the longest survival of paraneoplastic pemphigus with bronchiolitis obliterans associated with follicular lymphoma using R-CHOP chemotherapy. Int J Hematol. 2017:1-8.
19. Perniciaro C, Kuechle MK, Colon-Otero G, Raymond MG, Spear KL, Pittelkow MR. Paraneoplastic pemphigus: a case of prolonged survival. Mayo Clin Proc. 1994;69: 851–55.
20. Gergely L, Varoczy L, Vadasz G, Remenyik E, Illés A. Successful treatment of B-cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporine A. Acta Haematol. 2003;109:202–5.
21. Wang HH, Liu CW, Li YC, Huang YC. Efficacy of Rituximab for Pemphigus: A Systematic Review and Meta-analysis of Different Regimens. Acta Derm Venereol. 2015;95:928–32.
22. Freedman A. Follicular lymphoma: 2018 update on diagnosis and management. Am J Hematol. 2018;93:296-305.
23. Herold M, Haas A, Srock S, Neser S, Al-Ali KH, Neubauer A, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol. 2007;25:1986–92.
24. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106:3725–32.
25. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood. 2005;105:1417–23.
26. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26:4579–586.
27. Salles G, Mounier N, de Guibert S, Morschhauser F, Doyen C, Rossi JF, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. Blood. 2008;112:4824–31.
28. Maloney DG, Liles TM, Czerwinski DK, Waldichuk C, Rosenberg J, Grillo-Lopez A, et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood. 1994;84:2457-66.
29. Schneider T, Rosta A, Losonczy H, Radvanyi G, Ujj G, Egyed M, et al. Efficacy and Tolerability of a 2-Year Rituximab Maintenance Therapy in Patients with Advanced Follicular Lymphoma after Induction of Response with Rituximab-Containing First Line-Regimens (HUSOM Study). Pathol Oncol Res. 2018;24:199-205.
30. Maloney DG, Grillo-Lopez AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol. 1997;15:3266-74.
31. Zhou X, Ma T, Zhang Y, Zhou N, Li J. Rituximab maintenance therapy for patients with diffuse large B-cell lymphoma: A meta-analysis. PLoS One. 2017;12:e0174648.