Case Report

Case Report of Paraneoplastic Pemphigus-Related Bronchiolitis Obliterans in a Follicular Lymphoma Patient undergoing a CHOP with Azathioprine Regimen

Manassamon Navinpipat, MD[1], Rasthawathana Desomchoke, MD[1], Taksa Luasiripanthu, MD[1]

[1] Division of Medicine, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

Paraneoplastic pemphigus (PNP) is a rare, lethal, paraneoplastic autoimmune mucocutaneous blistering disease commonly associated with lymphoproliferative disorders including malignant lymphomas. Lymphoproliferative disorders associated with PNP are sometimes associated with serious lung complications such as bronchiolitis obliterans (BO). Because of its rarity, guidelines have not been established for management of PNP. Furthermore, most patients die within 1 year. We report treatment of lymphoma-associated PNP and BO using CHOP chemotherapy with azathioprine. A 57-year-old Thai woman suffered from systemic blisters, severe erosive stomatitis, and abdominal distension. Computed tomography revealed multiple lymphadenopathies. She was diagnosed with follicular lymphoma grade 1 (Ann Arbor stage IVA) and PNP-related BO. The patient underwent four cycles of CHOP and azathioprine. The erosive stomatitis and systemic blisters resolved completely. The lymph nodes became smaller with a partial response of the underlying follicular lymphoma. However, the bronchiolitis obliterans persisted. The patient achieved 15 months of survival. The present case suggests that intensive chemotherapy with immunosuppressive improves the prognosis of patients with PNP-related BO associated with lymphoma.

Keywords: Follicular lymphoma, Paraneoplastic pemphigus, Bronchiolitis obliterans

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Paraneoplastic pemphigus (PNP), which was first described in 1990, is a systemic autoimmune bullous disease characterized by severe stomatitis and polymorphous skin eruptions. Primary malignant neoplasms include many hematological malignancies such as non-Hodgkin's lymphoma and B lymphocytic leukemia[1,2]. PNP is associated with production of immunoglobulin G (IgG) autoantibodies against desmoglein-1 and -3, bullous pemphigoid 180, and plakin family proteins, and demonstrates pathologically acantholytic changes in the epidermis and clinically extensive blisters and erosions on the skin and various mucosae[3,4]. Initial treatment of PNP with systemic corticosteroids is often attempted and other immunosuppressive agents are also used in combination with systemic corticosteroids. However, most patients with PNP have a very poor prognosis that depends on the status of the underlying neoplasms[6] with mortality at 75% to 90%[7]. Although treatment of the underlying neoplasms is effective, especially for Castleman's disease patients, in patients with PNP associated with malignant neoplasms, the response of PNP to treatment of the underlying malignancy appears to be unfavorable[8].

Bronchiolitis obliterans (BO) is an irreversible and lethal obstructive lung disease that occurs in chronic graft-versus-host disease patients after allogeneic hematopoietic stem cell transplantation, which is associated with PNP[9]. The frequency of BO, a major cause of PNP patient death, with PNP was reported to be 18% to 93%[10,11]. The use of corticosteroids and/or immunosuppressant does not induce remission of BO. Thus, only lung transplantation may cure patients with PNP-related BO. PNP-related BO has an extremely poor prognosis despite complete remission (CR) of the accompanying neoplasms[10,11].

Owing to the rarity of PNP, definitive guidelines have not been established for management of PNP, and efficacy data are primarily limited to case reports[5]. We report a 57-year-old female patient with PNP and BO associated with follicular lymphoma. This patient survived for 15 months after the diagnosis. This case was treated with the CHOP regimen and immunosuppressive therapy, azathioprine. However, the patients subsequently developed BO and died 11 months later.

Case Report

In November 2016, a 57-year-old Thai woman presented at Chulabhorn Hospital. The protocol of this research was reviewed and approved by the Human research ethics committee Chulabhorn Research Institute No. 030/

Correspondence to:

Navinpipat M.

Department of Medicine, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok 10210, Thailand.

Phone: +66-2-5766000

Email: manassamon.hir@pccms.ac.th

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2562. She was admitted for severe erosive stomatitis (Figure 1) and massive blisters on both arms and hands, which subsequently spread to the whole body (Figure 2 and 3). In addition to the mucosal lesions, she had an abdominal distension and weight loss of about 10 kg. She also had an abdominal mass of about 6×8 cm detected by physical examination. Her temperature was 37.1°C, heart rate was 106 beats per minute, and blood pressure was 135/74 mmHg. The patient had an oxygen saturation of 96% in ambient air. Clinical laboratory data were as follows. White blood cell count: 8,190/µL; neutrophils, 88%; lymphocytes: 9%; hemoglobin: 13.3 g/dL; platelet count: 510,000/µL; serum total protein: 6.5 g/dL; albumin: 3.9 g/dL; liver functions (42 IU/L aspartate aminotransferase and 82 IU/L) alanine aminotransferase. However, there were no other abnormalities including 324IU/L lactate dehydrogenase and renal functions (0.83 mg/dL Cr). A skin biopsy showed suprabasal acantholysis with dyskeratosis, and lymphocytic exocytosis, epidermal spongiosis, and intradermal vesicle were also observed. On the basis of these findings (Figure 4), she was diagnosed with PNP. To identify the primary malignancy that had induced PNP, she underwent computed tomography of the chest and whole abdomen, which detected tumors in bilateral supraclavicular, para-tracheal, bilateral axillary para-aortic, mesenteric, bilateral common iliac, and external iliac regions and inguinal lymph nodes. The largest lymph nodes were para-aortic lymph nodes up to 8.1×6.1 cm (Figure 5). Infiltrating tumor cells in the kidney and pulmonary region were also observed. A computed tomography-guided needle biopsy from the para-aortic lymph node revealed infiltration

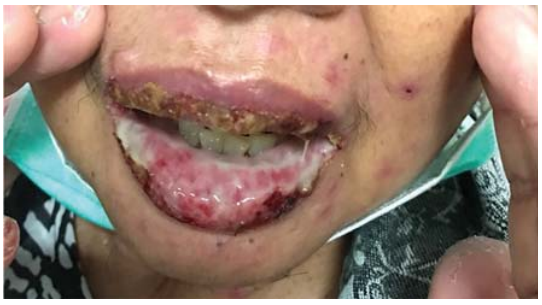

Figure 1. Severe erosive stomatitis of the oral mucosa.

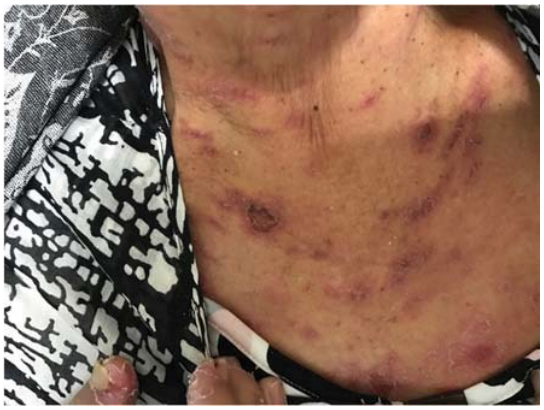

Figure 2. Massive blisters spread to the whole body.

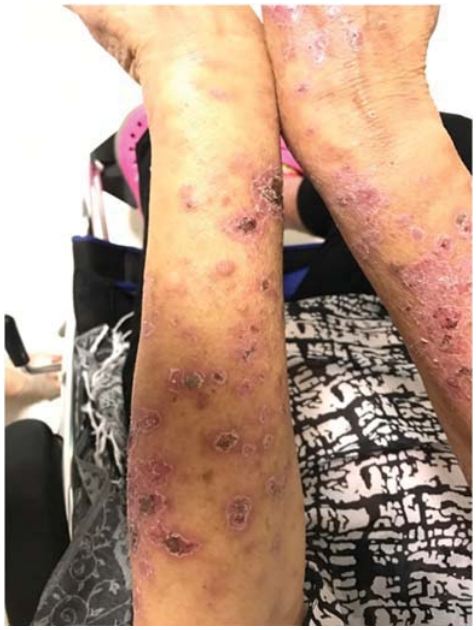

Figure 3. Massive blisters on both arms.

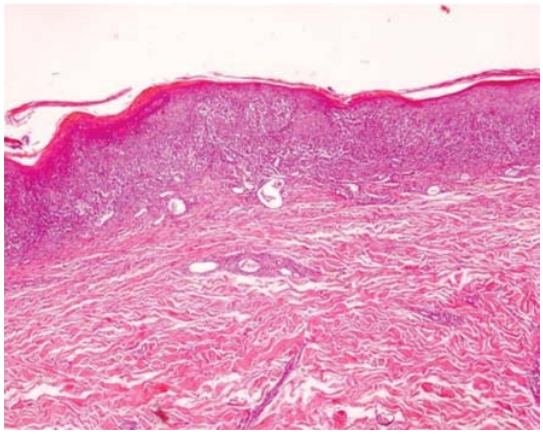

Figure 4. Skin sections revealed acantholysis with dense inflammatory cell infiltrates

of relatively small lymphoma cells that were positive for CD20, CD10, and BCL-2 (Figure 6 to 9), which suggested follicular lymphoma grade 1. Considering these findings, she was diagnosed with PNP accompanying follicular lymphoma. A diagnosis of stage IV AE follicular lymphoma grade 1 was made. The follicular lymphoma international prognostic index (FLIPI) score was calculated as 2 (Ann Arbor stage IV and more than three nodal sites). The present patient was diagnosed with high tumor burden FL because of more than three nodal sites over 3 cm in accordance with both British National lymphoma Investigation and Groupe d'Etude des lymphomesfolliculaires criteria for a high tumor burden[14,29,30].

For chemotherapy of follicular lymphoma, we planned to treat her with six cycles of rituximab combined with CHOP (R-CHOP) every 3 weeks. Because of financial issues, she was treated with four cycles of CHOP every 3 weeks and immunosuppressive agent azathioprine without rituximab, including 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m^2 vincristine, maximum 2 mg/body on day 1, 100 mg/body prednisolone (PSL) on days 1 to 5 of each cycle, and azathioprine 100 mg/day. After four cycles of chemotherapy and azathioprine, the blisters had resolved completely. The para-aortic lymph became smaller

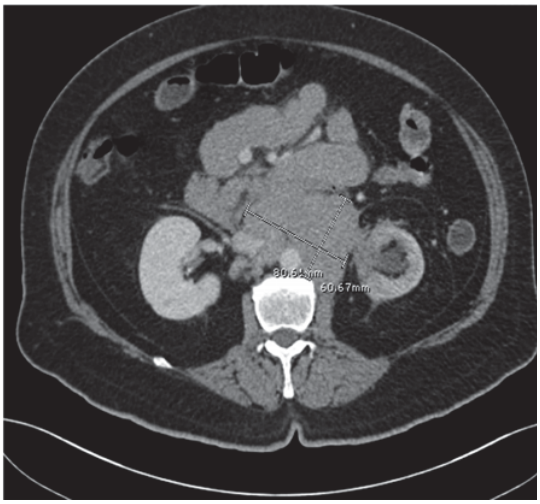

Figure 5. CT whole abdomen showed multiple lymphadenopathies. The largest lymph nodes were para-aortic lymph nodes sized up to 8.1×6.1 cm.

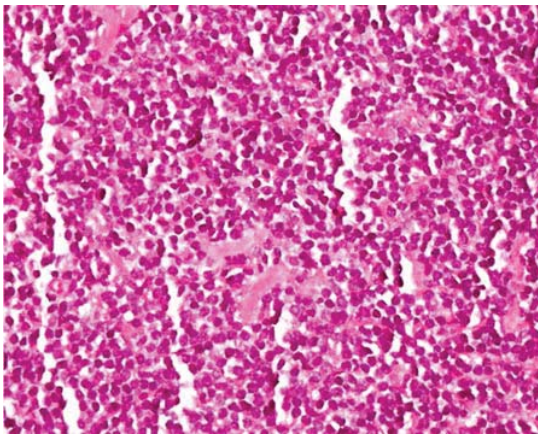

Figure 6. Lymph node biopsy showed small lymphoid cells with small round hyperchromatic nuclei, an irregular nuclear contour, inconspicuous nucleoli, and a small amount of cytoplasm.

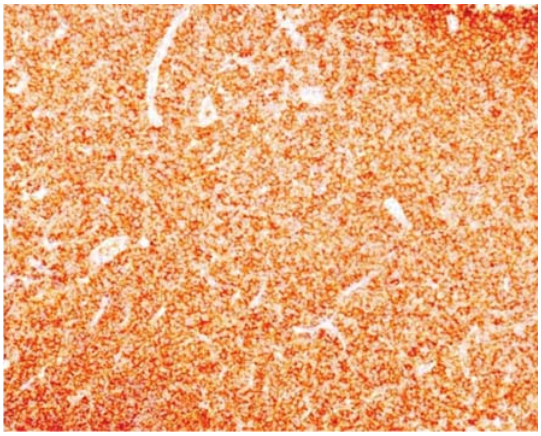

Figure 7. Atypical small lymphoid cells were CD20+.

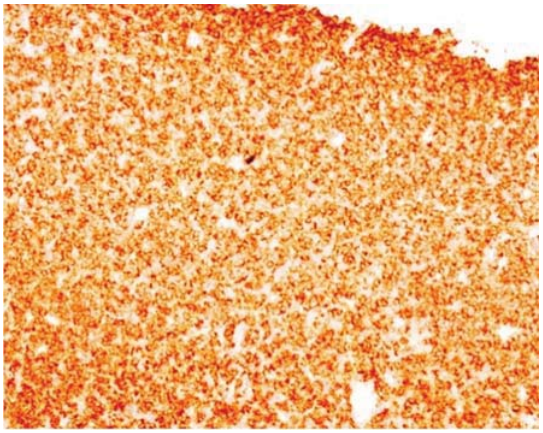

Figure 8. Atypical small lymphoid cells were Bcl-2+.

with PR of the underlying FL. After two cycles of chemotherapy, she suffered from dyspnea with respiratory failure. She was admitted for 7 days with antibiotic treatment, but the dyspnea remained. Computed tomography of the chest showed bronchial dilatation, bronchiolar wall thickening, and air trapping at the end-expiratory phase, and arterial blood gas analysis indicated hypoxemia. A surgical lung biopsy for diagnosis of BO was not performed because of her poor performance status PS=3 and risk of serious respiratory failure caused by the surgical procedure. Clinically, other diseases, such as chronic obstructive pulmonary disease, bronchial asthma, interstitial pneumonia, and other autoimmune pulmonary disease, which caused dyspnea, could be excluded. In accordance with these findings, the present patient was diagnosed with probable BO[13]. On the basis of these findings, the patient was diagnosed as having PNP associated with BO. Therefore, we treated her with systemic corticosteroids, and she improved with home oxygen therapy. The patient was thus treated with fours cycles of cyclophosphamide, vincristine, doxorubicin, and prednisolone, and azathioprine at 100 mg/day for 10 months. Long-term oxygenation therapy was continued to improve dyspnea and quality of life. Although she died from progressive respiratory failure at 15 months after the diagnosis of BO associated with PNP, there was no recurrence of FL.

Discussion

In this case report, we describe that four cycles of chemotherapy and azathioprine did not improve BO that occurred in a patient with PNP accompanied by follicular lymphoma, although they were very effective for PNP.

PNP generally occurs after non-Hodgkin's lymphoma[17,18], and patients with PNP have a poor prognosis. Survival is usually less than 1 year regardless of the status of the underlying neoplasm[7]. Although PNP patients usually have associated lymphoproliferative disorders, there has been little attention focused on the relationship between the intensity of immunochemotherapy against malignant lymphoma and survival. This is because most PNP cases have been published in journals in the fields of dermatology and respiratory medicine. At present, approximately 80 PNP-related BO patients have been reported. Nevertheless, only one patient was reported in a journal in the field of hematology[19]. Although most of these patients have extremely poor outcomes, this patient achieved 15 months of survival from PNP-related BO associated with a lymphoproliferative disorder without rituximab treatment.

Pemphigus is usually treated with systemic corticosteroids and immunosuppressive agents that frequently induce severe infections. Several reports have shown the effectiveness of rituximab for PNP treatment, particularly in patients with follicular lymphoma[17]. This patient with PNP-related BO associated with FL was treated with the CHOP regimen and azathioprine without rituximab because of financial issues. The chemotherapy and azathioprine treatment reduced tumor cells as well as B lymphocytes and their production of antibodies, including autoantibodies against envoplakin and periplakin, which lead to remission of PNP and a partial response of the follicular lymphoma. This case showed efficacy of intensive chemotherapy to improve survival of PNP-related BO associated with lymphoma. Despite a report that described antibodies deposited in bronchial epithelial cells of patients with PNP-related BO[9], no report has shown the efficacy of immunochemotherapy. Hoffman et al reported that CD8+ T lymphocytes might play a major role in pulmonary involvement[18], but the mechanism through which PNP-related BO occurs is not well understood.

Although BO is an inflammatory disease, FDG-PET at follow-up after four cycles of chemotherapy did not show any FDG uptake in this case. To the best of our knowledge, no reports have mentioned the relationship between BO and FDG uptake. However, carcinomas with abundant mucin and/or fibrosis often exhibit low FDG uptake because of their low cellularity[19]. Airway inflammation and fibrosis are the main pathological features of BO[20]. Consequently, relative FDG uptake in BO patients may tend to be low because of fibrosis and low cellularity. Furthermore, a previous study has demonstrated that enhanced FDG accumulation reflects the degree of disease activity ofbronchiolitis obliterans organizing pneumonia[21]. Accordingly, we presume the reason for why not any uptake of FDG was detected in the present patient was because the cellularity of BO was low owing to its fibrosis and disease activity, which was not severe enough for uptake of FDG at the follow-up.

After achievement of CR from PNP and PR of the underlying FL in the present patient, symptoms of BO remained stable without progression. This finding suggests that the intensive chemotherapy prevented progression of BO. CHOP therapy with azathioprine was effective to treat PNP-associated FL. Furthermore, it might have acted as a strong immunosuppressor of PNP-related BO.

All previously reported patients died within approximately 1 year and received insufficient immuno-chemotherapy because of severe infections, poor PS, respiratory failure, and the low grade of the underlying lymphoma (Table 1). In the present case, although respiratory disease had persisted after PR of FL, chemotherapy was continued. Because of the severe infections and poor PS, dose intensity of CHOP was reduced in cycles three and four until completion of four cycles. Granulocyte colony-stimulating factor and antibiotics enabled delivery of chemotherapy in this patient.

The present patient received chemotherapy and azathioprine, who achieved PR of FL and CR of PNP. Hematologist should also be aware of PNP-related BO, because it is a rare but lethal complication of lymphoproliferative disorders, which can be treated by immunochemotherapy. Thus, PNP-related BO associated with underlying lymphoma should be treated by multidisciplinary professionals including a hematologist.

Table 1. Reported cases of BO-related PNP with lymphoma, which required CHOP for treatment

Number	Age (years)	Sex	Diagnosis	Lymphoma treatment	Treatment BO and PNP	Survival from onset of BO (months)	Cause of death	Authors	Years	References
1	36	F	FL	MTX, MIT, CPA, VCR, VP-16, MCNU, BH-AC, CBDCA, PSL+RT	PSL 50 mg/body	10	BO	Takahashi et al	2000	[22]
2	63	F	FL	CB, VCR, PSL	No	1	BO	Gudi et al	2004	[23]
3	44	F	Splenic B-cell lymphoma	R-COP[A] 3 cycles	No	11	BO	Wang et al	2007	[24]
4	56	M	TCL	CHOP[B]	PSL, RIT	13	BO	Maldanado et al	2009	[10]
5	47	M	DLBCL (diagnosed by autopsy)	No	mPSL 1,000 mg/body for 3 days, then PSL 120 mg/body	3	BO	Park et al	2013	[25]
6	64	F	FL	No	PSL1 mg/kg and mPSL 500 mg/body for 3 days, PE, IVIG, and CyA 2 mg/kg	7	BO	Kanaoka et al	2014	[26]
7	65	F	FL	R-CHOP[c] 1 cycle, RIT, R-CVP[D] 1 cycle	No	Unknown	BO	Morikawa et al	2014	[27]
8	60	M	FL	R-CVP 1 cycle, R-CHOP 1 cycle, BR[E] 1 cycle	RIT 375 mg/m^2 and PSL, PE, IVIG	7	BO	Hirano et al	2015	[17]
9	53	M	FL	R-CHOP 6 cycles	PSL and RIT 37 5 mg/m^2	27	BO	Shin et al	2017	[28]

F = Female; M = Male; FL = follicular lymphoma; DLBCL = diffuse large B cell lymphoma; MTX = methotrexate; MIT = mitocanthrone; CPA = cyclophosphamide; VCR = vincristine; VP-16 = etoposide; MCNU = ranimustine; BH-AC = enocitabine; RIT = rituximab; CSDCA = carboplatin; PSL = prednisolone; RT = radiotherapy; CB = chlorambucil; ADR = doxorubicin; mPSL = methylprednisolone; IVIG = intravenous immunoglobulin; PE = plasma exchange; CyA = cyclosporin A

[A] R-COP regimen: rituximab, cyclophosphamide, vincristine, and prednisolone

[B] CHOP regimen: cyclophosphamide, doxorubicin, vincristine, and prednisolone

[C] R-CHOP regimen: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

[D] R-CVP: rituximab, cyclophosphamide, vincristine, and prednisolone

[E] BR regimen: rituximab, and bendamusti

Indeed, intensive immunochemotherapy such as R-CHOP for underlying lymphoma markedly improved the prognosis of the patient with PNP-related BO and achieved longer survival, but it was not sufficient to prevent lethal respiratory failure. Further studies are needed to elucidate the mechanism of BO in PNP patients, and more cases are needed to determine new treatment options for PNP-related BO associated with lymphoproliferative disorders.

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Potential conflicts of interest

The authors declare no conflict of interest.

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