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【 CASE REPORT 】

Treatment of Secondary Immune Thrombocytopenia with Non-Hodgkin Lymphoma: A Case Report and Literature Review

Yuya Kurihara[1], Kazuki Taoka[1], Eri Takagi[2], Kazuhiro Toyama[1], Kumi Nakazaki[1] and Mineo Kurokawa[1,3]

Abstract:
Secondary immune thrombocytopenic purpura (ITP) with non-Hodgkin lymphoma (NHL) is a rare disease. Although some treatment regimens are available for primary ITP, the treatment strategy for secondary ITP remains unconfirmed. We herein report a 79-year-old man who was diagnosed with secondary ITP with mantle cell lymphoma. Although intravenous immunoglobulin (IVIG) has been considered an effective option for secondary ITP, similar to the treatment of primary ITP, our patient did not benefit from IVIG. A literature review including the current report revealed that IVIG was ineffective in all treated patients. Secondary ITP with NHL should be treated differently from primary ITP.

Key words: secondary immune thrombocytopenia, intravenous immunoglobulin, chemotherapy, non-Hodgkin lymphoma

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Introduction

Secondary immune thrombocytopenic purpura (ITP) with hematological malignancies, including non-Hodgkin lymphoma (NHL), is a rare disease. Treatments for primary ITP include steroids, intravenous immunoglobulin (IVIG) in the event of severe thrombocytopenia, and the anti-CD20 monoclonal antibody rituximab. Splenectomy is also effective but is burdensome for patients. Thrombopoietin receptor agonists, such as romiplostim and eltrombopag, are also expected to be effective in patients with refractory ITP (1).

The optimal treatment for secondary ITP with NHL has not yet been established (1, 2). Although IVIG is considered an effective option for primary ITP, its role in the treatment of secondary ITP has not been determined.

We herein report a patient with secondary ITP who responded to lymphoma treatment with the VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone) and R-B (rituximab and bendamustine) regimens. We also conducted a literature review of treatments for secondary ITP with NHL over the last decade.

Case Report

A 79-year-old man came to the hospital with severe thrombocytopenia. Complete blood tests revealed severe thrombocytopenia, with a platelet count of 1.0×10^4/μL and reticulated platelets elevated to 11.9%. His white blood cell count (with a normal differentiation count) and hemoglobin level were normal. His lactate dehydrogenase level was 200 U/L (Table 1). Immunohistochemistry of the pathological bone marrow tissue revealed cyclin D1 and CD20-positive lymphocytes infiltrating a small amount of bone marrow (Fig. 1A-C). G-banded karyotyping demonstrated 48, XY, add (9) (q13), t(11;14)(q13; q32), +21, +22 in 3 of 20 metaphases. Fluorescence *in situ* hybridization with a bone marrow analysis for BCL1/IgH fusion signals showed signals in only 3.5% of normal nuclei (Fig. 1D). A flow cytometric analysis of the bone marrow showed a small number of cells

[1]Department of Hematology and Oncology, Graduate School of Medicine, The University of Tokyo, Japan, [2]General Education Center, The University of Tokyo Hospital, Japan and [3]Department of Cell Therapy and Transplantation Medicine, The University of Tokyo Hospital, Japan
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Correspondence to Dr. Mineo Kurokawa, kurokawa-tky@umin.ac.jp

Table 1. Laboratory Findings at Diagnosis with Automated Blood Cell Counter.

WBC	6,700 /μL	TP	6.6 g/dL	IgG	977 mg/dL
Blast	0.0 %	Alb	4.2 g/dL	IgA	102 mg/dL
Pro	0.0 %	BUN	18.4 mg/dL	IgM	277 mg/dL
Myelo	0.5 %	Cre	1.12 mg/dL	PT(%)	100 %
Meta	0.5 %	T-Bil	0.7 mg/dL	PT (INR)	0.94
Band	2.0 %	GOT	26 IU/L	APTT	30.7 s
Seg	70.0 %	GPT	21 IU/L	Fib	312 mg/dL
Lym	18.0 %	LDH	200 IU/L	D-dimer	0.5 μg/mL
Mono	5.5 %	γ-GTP	19 IU/L	FDP	5.3 μg/mL
Baso	0.5 %	ALP	297 IU/L	IL2R	1,627 U/mL
Eosino	3.0 %			PA-IgG	145.9 ng/10^7cells
RBC	465×10^4 /μL	(Reference range)		Direct Coombs test	(-)
MCV	95.7 fL	(83.6-98.2)		Indirect Coombs test	(-)
Hb	15.1 g/dL	(13.7-16.8)		Na	139 mEq/L
Hct	44.5 %	(40.7-50.1)		K	4.4 mEq/L
PLT	1.1×10^4 /μL	(15.8-34.8×10^4)		Cl	103 mEq/L
Reti	1.5 ‰	(0.8-2)			
IPF	11.9 %	(2-10)			
MPV	14.6 fL	(6.5-11.7)			
PDW	14.3 %	(9.8-16.2)			

WBC: white blood cell, Pro: promylocyte, Myelo: myelocyte, Meta: metamyelocyte, Seg: segment, Lym: lymphocytosis, Mono: mononucleosis, Baso: basophils, Eosino: eosinophil, RBC: red blood cell, MCV: mean corpuscular volume, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, Reti: reticulocyte, IPF: idiopathic pulmonary fibrosis, MPV: mean platelet volume, PDW: platelet distribution width, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, T-bill: total bilirubin, GOT: glutamic oxaloacetic acid transaminase, GPT: glutamic pyruvate transaminase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrinogen degradation product, IL2R: interleukin-2 receptor, PA-IgG: platelet-associated IgG, Na: natrium, K: kalium, Cl: chlorine

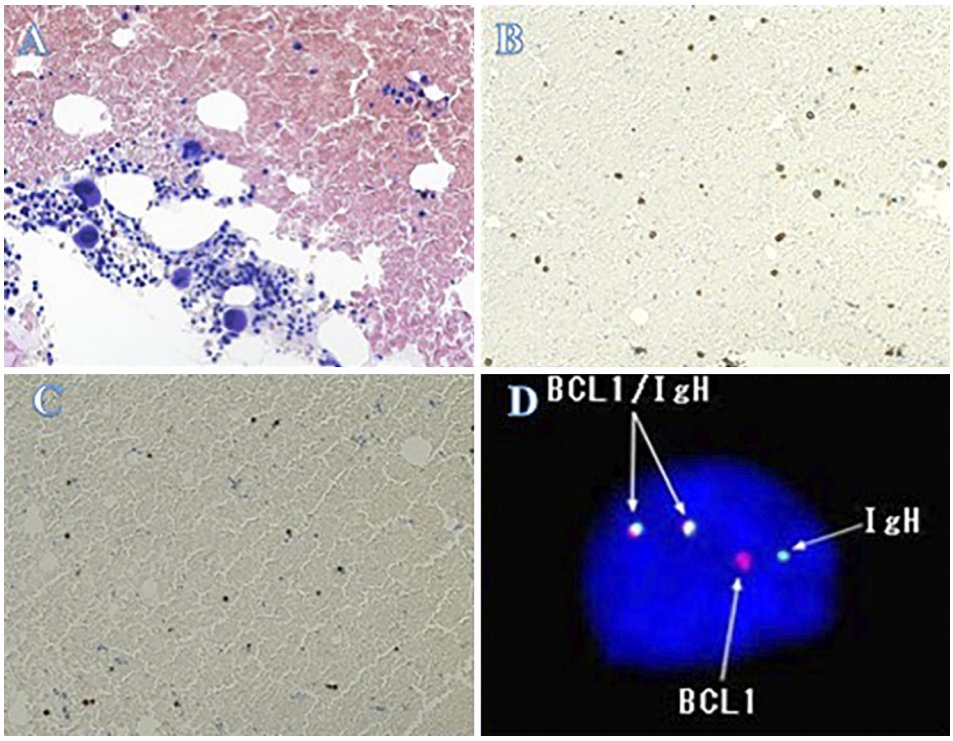

Figure 1. Bone marrow biopsy specimens. A: Wright-Giemsa stain; magnification, ×40. B: Immunostaining for CD20; magnification, ×40. C: Immunostaining for cyclin D1; magnification, ×40. Sporadic cyclin D1-positive cells were observed. D: Fluorescence *in situ* hybridization with a bone marrow analysis for BCL1/IgH fusion signals.

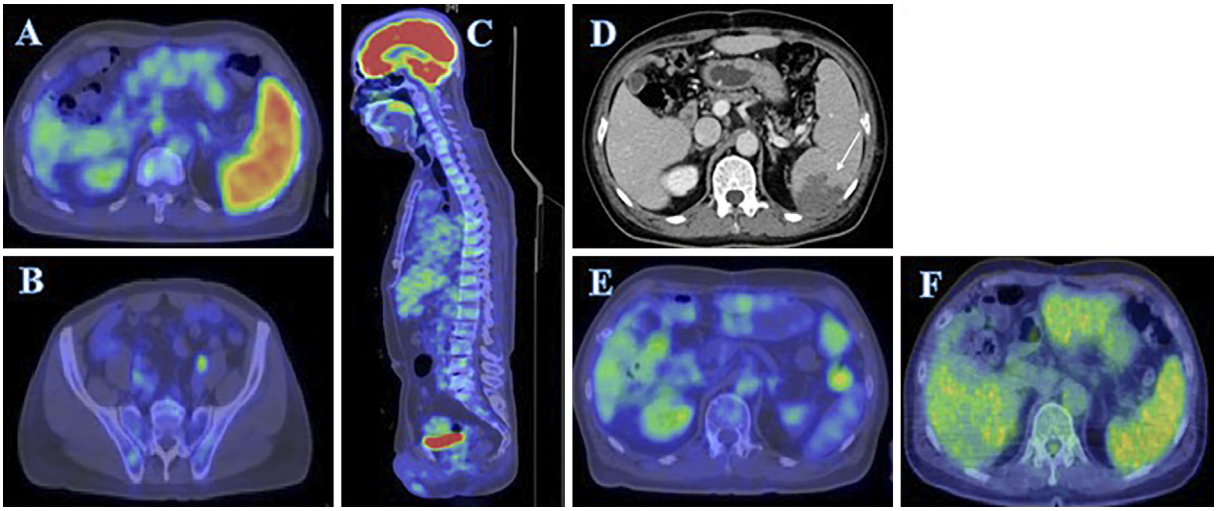

Figure 2. **A: Positron emission tomography-computed tomography image acquired prior to treatment. The spleen showed an abnormal uptake. B and C: Positron emission tomography-computed tomography image acquired prior to treatment. Although the pelvis and vertebral bodies showed a weakly abnormal uptake, maximum standardized uptake values could not be determined; we were thus unable to confirm the presence of malignant lymphoma cells in these regions. D: Contrast-enhanced computed tomography revealed infarction of a portion of the spleen (indicated by white arrow). E: Positron emission tomography-computed tomography image acquired after treatment. An abnormal uptake was absent. F: Positron emission tomography-computed tomography image acquired during recurrence of severe thrombocytopenia. The spleen showed an abnormal uptake and regrowth.**

that expressed CD19, CD20, CD5, and light chain κ; they did not express CD10. The invasion of the bone marrow by a small number of lymphoma cells was presumed not to have affected hematopoiesis in the patient.

Positron emission tomography-computed tomography revealed splenomegaly with a maximum standardized uptake value of 9. Furthermore, no lymphadenopathy or abnormal uptake was observed, except in the spleen (Fig. 2A-C). Myelodysplastic syndrome and other hematological malignancies were initially considered, but there were no signs of neutrophil or erythroid dysplasia or other abnormal findings. Antinuclear antibody, anticardiolipin antibody, lupus anticoagulant, antiplatelet antibody, and *Helicobacter pylori* IgG antibody test results were all negative. A bone marrow specimen showed some megakaryocytes and few malignant lymphoma cells.

Platelet transfusion was ineffective based on 1-hour and 24-hour corrected count increments of 5,000/μL and 0/μL, respectively, and a high reticulated platelet score; these findings indicated that the patient was refractory to platelet infusion due to an immune mechanism. Based on the results of the above examinations, we ruled out other diseases, such as myelodysplastic syndrome, anaplastic anemia, and connective tissue disease; the patient was ultimately diagnosed with secondary ITP with mantle cell lymphoma (MCL).

The patient's clinical course is shown in Fig. 3. We were unable to perform splenectomy because of severe thrombocytopenia, and chemotherapy was difficult for the same reason. IVIG (400 mg/kg/day) was administered for 5 days, but the patient's platelet count was not elevated. Prednisone (0.5 mg/day) was then administered continuously for 2 weeks but failed, and third-line rituximab (375 mg/m^2) monotherapy was also ineffective. During third-line treatment, the patient reported abdominal pain; therefore, we performed contrast-enhanced computed tomography, which revealed splenic infarction (Fig. 2D). The cause of the splenic infarction was unclear, but its presence prevented the use of eltrombopag-based treatment. Therefore, MCL was diagnosed after the first administration of rituximab, so we changed the primary disease target to MCL and administered VR-CAP chemotherapy (bortezomib 1.3 mg/m^2 days 1, 4, 8, and 11; rituximab 375 mg/m^2 day 0; cyclophosphamide 500 mg/m^2 day 1; doxorubicin 33 mg/m^2 day 1; and prednisolone 60 mg/m^2 days 1-5); we modified the dose based on the patient's age. A review of the related literature (3-15) over the past decade confirmed that chemotherapy did not result in severe bleeding in any patients with ITP secondary to NHL. We explained to the patient that previous reports had shown no critical adverse events associated with this chemotherapy but noted that his platelet count was already low (<1.0×10^4/μL) and might be further reduced as a result of chemotherapy-related bone marrow suppression. After considering all of the information, the patient agreed to receive chemotherapy.

During chemotherapy, he developed cytopenia, and his platelet count decreased to 0.3×10^4/μL. However, there were no severe adverse events, including bleeding. After the second course of VR-CAP, his platelet count increased sharply

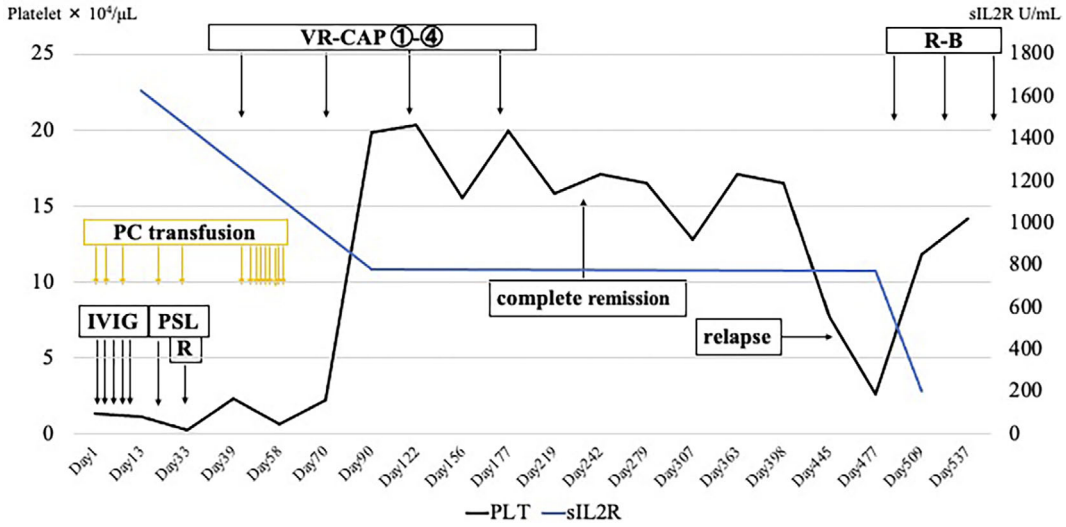

Figure 3. **Clinical course. IVIG: intravenous immunoglobulin, PSL: prednisone, R: rituximab, VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone, R-B: rituximab and bendamustine, PC: platelet concentrate**

and improved to normal levels following an MCL response. The patient exhibited complete remission of his MCL (Fig. 2E) after four courses of VR-CAP, and his platelet count remained normal. However, approximately nine months after he developed complete remission, the patient's platelet count began to decrease again. Positron emission tomography-computed tomography again revealed splenomegaly, with a maximum standardized uptake value of 6 (Fig. 2F). We diagnosed him with a relapse of secondary ITP with MCL. The patient then received second-line R-B therapy (rituximab 375 mg/m^2 day 0; bendamustine 90 mg/m^2 days 0 and 1), and his platelet count began to increase smoothly.

Discussion

We noted two important clinical issues in the present and previous case reports of secondary ITP with NHL over the last 10 years: IVIG was ineffective in all patients with secondary ITP with NHL, whereas chemotherapy was highly efficacious in terms of the recovery of both severe thrombocytopenia and malignant lymphoma.

First, IVIG did not increase the platelet counts. Initially, when we diagnosed the patient's disease, there was a delay of several days prior to the receipt of the results of the bone marrow biopsy and fluorescence *in situ* hybridization. Until that point, we were unable to confirm whether or not the patient had malignant lymphoma. If we had used steroid treatment, it would have eradicated the malignant lymphoma cells. Thus, the use of steroid treatment would have prevented the diagnosis of malignant lymphoma if the bone marrow biopsy had been unable to validate a diagnosis of malignant lymphoma, as positron emission tomography (PET) did not clearly show an abnormal uptake except in the patient's spleen. Furthermore, considering that the platelet count was below 1.0×10^4/μL, the patient was at risk of bleeding; the performance of chemotherapy might thus have led to a more severe reduction in the platelet count. Therefore, we considered it reasonable to select IVIG. IVIG is commonly used for the treatment of primary ITP with severe thrombocytopenia. Over the last decade, 16 patients with NHL-associated ITP have been described, excluding patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (Table 2) (3-15). In these case reports, severe thrombocytopenia in patients with secondary ITP and NHL was also treated with IVIG; this approach was ineffective in eight patients. Although IVIG is usually recommended for primary ITP when the platelet count is reduced, patients with secondary ITP with NHL do not benefit from IVIG.

Second, chemotherapy was effective in shrinking the tumor and restoring the platelet count, even in patients with severe thrombocytopenia, with no significant adverse events. Considering these findings, secondary ITP with NHL should be treated differently from primary ITP.

The reason for the failure of IVIG to increase the platelet count was not clear (3-5, 13, 15) but might be related to the etiology of the reduction in the platelet count (2). IVIG is only intended to provide a temporary increase in the platelet count, as it does not treat the primary disease mimicking thrombocytopenia. Therefore, chemotherapy for the primary disease may be the optimal treatment (16). The mechanisms of action of IVIG are not entirely clear in patients with primary and secondary ITP. The blockade of Fcγ receptors on macrophages, Kupffer cells, and immunoglobulins is a widely recognized mechanism (17, 18), but it is not the only one. Cytokines and T cells may also be involved in the effects of IVIG (19-23). Patients with secondary ITP with malignant lymphoma might have different outcomes regarding those cells and proteins as well as other factors that may

Table 2. Summary of Treatment Responses for Secondary ITP with NHL.

Case	Diagnosis	Disease location	Treatment							References
			IVIG (0/8)	PSL or DEX (3/11)	Rituximab (2/7)	TPO (3/7)	Chemo (±R) (10/10)	Surgery (3/3)	Radiation (2/2)	
1	MCL	Spleen and BM	×	×	×		○			Current patient
2	AMBCL	Spleen, lung, bone, and BM	×	×	×	×	○			(3)
3	THRBCL	LN	×	×			○			(4)
4	MCL	LN	×	×	○	○	○			(5)
5	DLBCL	No information	×			○	○			(5)
6	MZL	No information	×	×	×	×				(5)
7	MZL	No information		×	○	○				(5)
8	THRLBCL	LN					○			(6)
9	DLBCL	Nasopharynx							○	(7)
10	DLBCL	LN		○				○		(8)
11	HSTL	Skin, spleen, and BM					○			(9)
12	MALT	Submandibular glands and LN		○						(10)
13	DLBCL	LN and colon	×	×	×		○			(11)
14	DLBCL	Duodenum and LN				×	○	○		(12)
15	CD5BCL	Spleen, lung, and BM	×	×	×	×	○			(13)
16	MALT	Lung						○		(14)
17	EXBCL	Bone		○					○	(15)

Most patients were treated with several therapies at the same time, so it was difficult to determine which was the most effective therapy. ○ or × indicates treatment that was successful or failed, respectively. The definition of success in this table is that the selected treatments may have contributed to the recovery of platelet counts, according to the patients' clinical courses, whereas failed treatments did not contribute. Empty rows with neither ○ nor × indicate that these treatments were not selected. ITP: immune thrombocytopenic purpura, NHL, non-Hodgkin lymphoma, chemo.: chemotherapy, ±R: with or without rituximab, IVIG: intravenous immunoglobulin, PSL: prednisolone, DEX: dexamethasone, R: rituximab, TPO: thrombopoietin receptor agonist, MCL: mantle cell lymphoma, AMBCL: aggressive mature B-cell lymphoma, THRBCL: T-cell/histiocyte-rich B-cell lymphoma, DLBCL: diffuse large B-cell lymphoma, MZL: marginal zone lymphoma, HSTL: hepatosplenic T-cell lymphoma, MALT: mucosa-associated lymphoid tissue lymphoma, CD5BCL: CD5-positive B-cell lymphoma, THRLBCL: T-cell/histiocyte-rich large B-cell lymphoma, EXBCL: extranodal B-cell lymphoma, LN: lymph node, BM: bone marrow

cause thrombocytopenia compared with patients who have primary ITP. Malignant lymphoma cells might elicit the production of specific antibodies. Given the above factors, a complex network might be involved.

IVIG was not effective against secondary ITP with NHL, while chemotherapy provided a beneficial effect. These observations are of great clinical importance in terms of medical expenditure, given that IVIG is an expensive treatment; therefore, adjusting the treatment strategy might improve patient outcomes and reduce costs.

The findings described in our case report and previous literature indicate that the implementation of chemotherapy should take priority over the use of IVIG in patients with secondary ITP with NHL.

Informed consent was obtained from the patient for publication of this case report.

The authors state that they have no Conflict of Interest (COI).

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