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

Yuya Kurihara, Kazuki Taoka, Eri Takagi, Kazuhiro Toyama, Kumi Nakazaki and Mineo Kurokawa

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

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.

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

1Department of Hematology and Oncology, Graduate School of Medicine, The University of Tokyo, Japan, 2General Education Center, The University of Tokyo Hospital, Japan and 3Department of Cell Therapy and Transplantation Medicine, The University of Tokyo Hospital, Japan

Received for publication June 14, 2020; Accepted for publication October 4, 2020

Correspondence to Dr. Mineo Kurokawa, kurokawa-tky@umin.ac.jp
Table 1. Laboratory Findings at Diagnosis with Automated Blood Cell Counter.

| Test  | Value                  |
|-------|------------------------|
| RBC   | 4.65 x 10^12 /µL       |
| MCV   | (83.6-98.2)            |
| Hb    | 15.1 g/dL              |
| Hct   | 44.5 %                 |
| PLT   | 1.1 x 10^4 /µL         |
| Reti  | 1.5 %                  |
| IPF   | 11.9 %                 |
| MPV   | 14.6 fl                |
| PDW   | 14.3 %                 |

WBC: white blood cell, Pro: promyelocyte, Myelo: myelocyte, Meta: metamyelocyte, Seg: segment, Lym: lymphocyte, Mono: mononucleosis, Baso: basophil, 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-bil: 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, D-dimer: 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.
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/m²) 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/m² days 1, 4, 8, and 11; rituximab 375 mg/m² day 0; cyclophosphamide 500 mg/m² day 1; doxorubicin 33 mg/m² day 1; and prednisolone 60 mg/m² 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 (<1.0×10⁴/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 0.3×10⁴/μL. However, there were no severe adverse events, including bleeding. After the second course of VR-CAP, his platelet count increased sharply.
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/m² day 0; bendamustine 90 mg/m² 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 1.0×10⁵/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
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).

Acknowledgement
We thank Ryan Chastain-Gross, Ph.D., for editing a draft of this manuscript.

References
1. González-López TJ, Sánchez-González B, Jarque I, et al. Use of eltrombopag for patients 65 years old or older with immune thrombocytopenia. Eur J Haematol 104: 259-270, 2020.
2. Cines DB, Bussel JB, Lieberman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood 113: 6511-6521, 2009.
3. Ono K, Onishi Y, Kobayashi M, et al. Successful treatment of aggressive mature B-cell lymphoma mimicking immune thrombocytopenic purpura. Intern Med 57: 2019-2025, 2018.
4. Ogata T, Shimomura Y, Yamashita D, Imai Y, Ishikawa T. Substantial improvement in immune thrombocytopenic purpura associated with T-cell/histiocyte-rich B-cell lymphoma treated with chemotherapy: a case report. Mol Clin Oncol 10: 441-445, 2019.
5. Al-Nawakil C, Park S, Chapuis N, et al. Salvage therapy of autoimmune thrombocytopenic purpura revealing non-Hodgkin lymphoma by the thrombopoietin receptor agonist romiplostim. Br J Haematol 156: 129-152, 2011.
6. Wu B, Cheng Y. Upregulation of innate immune responses in a T cell/histiocyte-rich large B cell lymphoma patient with significant autoimmune disorders mimicking systemic lupus erythematosus. Ann Hematol 93: 353-354, 2014.
7. Berrang T, Holloway C, Hart J, Yee A, Berry B, Kob R. Successful treatment of non-Hodgkin lymphoma associated immune thrombocytopenia with involved field radiotherapy. Hematol Oncol 31: 218-220, 2013.
8. Park SY, Kim S, Kim ES, et al. A case of non-Hodgkin’s lymphoma in patient with Coombs’ negative hemolytic anemia and

| Case | Diagnosis | Disease location | Treatment | References |
|------|-----------|-----------------|-----------|------------|
| 1    | MCL       | Spleen and BM   | ×         | Current patient |
| 2    | AMBCL     | Spleen, lung, bone, and BM | × × | (3) |
| 3    | THRBLCL   | LN              | ×         | (4) |
| 4    | MCL       | LN              | × ×       | (5) |
| 5    | DLBCL     | No information  | ×         | (5) |
| 6    | MZL       | No information  | × ×       | (5) |
| 7    | MZL       | No information  | × ×       | (5) |
| 8    | THRBLCL   | 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, aR: 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, THRBLCL: T-cell/histiocyte-rich B-cell lymphoma, DLBCL: diffuse large B-cell lymphoma, MZL: marginal zone lymphoma, HSTL: hepatosplenic T-cell lymphoma, MAL: mucosa-associated lymphoid tissue lymphoma, CD5BCL: CD5-positive B-cell lymphoma, THRBLCL: T-cell/histiocyte-rich large B-cell lymphoma, EXBCL: extranodal B-cell lymphoma, LN: lymph node, BM: bone marrow.
idiopathic thrombocytopenic purpura. Cancer Res Treat 44: 69-72, 2012.

9. Kuonen F, Bucher M, Leval DL, et al. Purpura of the face and neck: an atypical clinical presentation revealing a hepatosplenic T cell lymphoma. Case Rep Dermatol 6: 37-42, 2014.

10. Harada S, Yamazaki S, Nakamura F, et al. Autoimmune neutropenia preceding Helicobacter pylori-negative MALT lymphoma with nodal dissemination. Int J Clin Exp Pathol 7: 6386-6390, 2014.

11. Uchiyama M, Sato K, Ikeda T. Diffuse large B-cell lymphoma complicated with autoimmune thrombocytopenia. Intern Med 50: 1215-1218, 2011.

12. Takahashi T, Maruyama Y, Saitoh M, et al. Synchronous occurrence of diffuse large B-cell lymphoma of the duodenum and gastrointestinal stromal tumor of the ileum in a patient with immune thrombocytopenic purpura. Intern Med 55: 2951-2956, 2016.

13. Hosoda Y, Hagino H, Hino N, Motokura T. Efficacy of bendamustine on thrombocytopenia and hemolytic anemia secondary to CD5-positive B-cell lymphoma with massive splenomegaly in a patient with rheumatoid arthritis. Mol Clin Oncol 7: 855-858, 2017.

14. Elsayed H, Hassan M, Nash J, Lyall M, Poullis M. Lung resection for treatment of idiopathic thrombocytopenic purpura associated with a pulmonary lymphoma. Ann Thorac Surg 88: e37-e38, 2009.

15. Watanabe T, Kurihara H, Magarisawa S, Shimoda S, Yoshida K, Ishiuichi S. Resolution of immune thrombocytopenic purpura associated with extranodal B-cell lymphoma of the petroclival region after radiotherapy. Surg Neurol Int 1: 76, 2010.

16. Alexander WH, Cathrin S, Christian S, et al. Autoimmune thrombocytopenia in non-Hodgkin’s lymphomas. Haematologica 93: 447-450, 2008.

17. Fehr J, Hofmann V, Kappeler V. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high dose intravenous gammaglobulin. N Engl J Med 306: 1254-1258, 1982.

18. Clarkson SC, Bussel JB, Kimberly RP, Valinsky JE, Nachman RN, Unkeless JC. Treatment of refractory immune thrombocytopenic purpura with an anti-Fcy-receptor antibody. N Engl J Med 314: 1236-1239, 1986.

19. Anthony RM, Kobayashi T, Wermeling F, Ravetch JV. Intravenous gammaglobulin suppresses inflammation through a novel TH2 pathway. Nature 475: 110-113, 2011.

20. Yuan YC, Yan QZ, Ning Z, Yao Z, Wei QX, Yong MT. Evaluation of IVIG response in relation to Th1/Th2 cytokines in pediatric immune thrombocytopenia. Cytokine 120: 234-241, 2019.

21. Semple JW, Miley Y, Cosgrave D, et al. Differences in serum cytokine levels in acute and chronic autoimmune thrombocytopenic purpura; relationship to platelet phenotype and antiplatelet T-cell reactivity. Blood 87: 4245-4254, 1996.

22. Kessel A, Ammuri H, Peri R, et al. Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function. J Immunol 179: 5571-5575, 2007.

23. Ephrem A, Chamat S, Miquel C, et al. Expansion of CD4+CD25+ regulatory T cells by intravenous immunoglobulin: a critical factor in controlling experimental autoimmune encephalomyelitis. Blood 111: 715-722, 2008.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).