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【 CASE REPORT 】

Monoclonal B-cell Lymphocytosis Exacerbated by Prednisolone Therapy for Dermatomyositis

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Abstract:
Lymphoproliferative diseases have been associated with various autoimmune diseases. We experienced a case of non-chronic lymphocytic leukemia type monoclonal B-cell lymphocytosis (MBL) that was exacerbated by increasing prednisolone for dermatomyositis and then improved by decreasing the dosage. Because MBL is difficult to diagnose, cases like ours may not be rare. These findings will facilitate our understanding of the mechanism underlying lymphoproliferative diseases and autoimmune diseases.

Key words: monoclonal B-cell lymphocytosis, dermatomyositis, monoclonal gammopathy, tumor immunity

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Introduction

Monoclonal B-cell lymphocytosis (MBL) is a lymphoproliferative disease newly classified in the 2017 World Health Organization criteria for the classification of lymphoid neoplasm (1). It is defined by a monoclonal B-cell count $<5\times10^9$/L in the peripheral blood in patients with no associated lymphadenopathy, organomegaly, other extramedullary involvement, or any other feature of a B-cell lymphoproliferative disorder (1).

More than 4% of the general population over 40 years old harbor MBL, and the frequency of MBL in the general population progressively increases with age (2, 3). Some cases with MBL progress to chronic lymphocytic leukemia (CLL) or other B-cell lymphoma. MBL is classified into three categories based on the phenotype: CLL-type, atypical CLL-type, and non-CLL-type (1). A total of 75% of MBLs are CLL-type MBL; in contrast, non-CLL type MBL is rare, so little information is available concerning this entity. Patients with MBL carry a significantly higher risk of serious infections (4) and nonhematologic cancers than those without MBL (5).

Dermatomyositis is an inflammatory myopathy with a characteristic rash. In recent years, disease-specific autoantibodies of this disease, such as anti-Mi-2 antibody, anti-MDA 5 antibody, and anti-TIF1-γ antibody, have been reported. This disease is known to be strongly associated with a wide range of malignant disease, particularly ovarian, lung, pancreatic, stomach, and colorectal cancers, as well as non-Hodgkin lymphoma (6). In particular, 65% of anti-TIF1-γ antibody-positive patients have malignant disease (7).

We herein report a case of non-CLL type MBL that presented with marked lymphocytosis after receiving prednisolone (PSL) therapy for dermatomyositis.

Case Report

A 62-year-old Japanese woman who had been treated for hyperlipidemia and glaucoma was found to be suffering from erythema at the eyebrows in June 201X. Over the next four months, it spread over her entire face, with general malaise and bilateral thigh pain also reported. In December of the same year, she became aware of pain in both upper arms, shoulders, and back. She was hospitalized for scrutiny because of elevated creatine phosphokinase (CPK) and finger eruption on both hands.

The physical findings revealed erythema from the eyebrows to the forehead and both cheeks, a Gottron-like eruption on the extensor metacarpophalangeal joints of both

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Table. Laboratory Data on Admission.

Complete blood cell count		Blood chemistry		Serological test (normal range)	
White blood cell	8.5×10^9 /L	Total protein	6.5 g/dL	Anti-nuclear antibody	×320
Neutrophil	65.1 %	Albumin	4.2 g/dL	Anti-Jo1-body	<7.0 U/mL
Lymphocyte	25.6 %	Aspartate transaminase	83 U/L	Anti-ARS-body	<5
Monocyte	7.0 %	Alanine aminotransferase	58 U/L	Anti-MDA5-body	<5
Basophil	0.4 %	Lactate dehydrogenase	403 U/L	Anti-Mi2-body	149 (-53)
Eosinophil	1.9 %	Total bilirubin	0.7 mg/dL	Anti-Tif1γ-body	41 (-32)
Hemoglobin	13.0 g/dL	Blood urea nitrogen	17 mg/dL	Soluble Interleukin-2 receptor	1,030 U/mL
Platelet	322.0×10^9 /L	Creatinine	0.7 mg/dL	IgG/IgA/IgM	544/60/183 mg/dL
		C-reactive protein	0.08 mg/dL	Serum immunofixation	IgM-kappa M-protein
Coagulation test		Creatine phosphokinase	1,191 U/L	Free light chain kappa/lambda	698.0/9.3 mg/L
PT-INR	0.97	Aldolase	27.1 U/L	kappa/lambda ratio	75.22
APTT	25.8 s	Myoglobin	643.7 ng/mL		
Fibrinogen	369 mg/dL			Urine test	
D-dimer	0.9 μg/dL			SG 1.033 pH 6.0 Protein 1+	Glucose - Occult blood 1+
				Urine immunoelectrophoresis	BJP-kappa M-protein

PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Ig: immunoglobulin, BJP: Bence-Jones proteins, SG: specific gravity

hands, and weakness in the deltoid and iliopsoas muscles. However, no lymphadenopathy was observed.

The laboratory findings are shown in the Table. The blood cell count was in the normal range, and the number of lymphocytes was 2.2×10^9/L. There were no morphological abnormalities in the blood cells. There was a slight increase in lactate dehydrogenase, a marked increase in CPK, and positivity for some autoantibodies specific for dermatomyositis. Hypogammaglobulinemia was observed, and immunoglobulin (Ig) M-kappa and Bence-Jones proteins-kappa type M-protein were detected by serum immunofixation and urine immunoelectrophoresis, respectively. The free light chain (FLC) ratio was 75.22. The Soluble Interleukin-2 receptor level was 1,030 U/mL.

An electromyogram showed a low amplitude and polyphasic motor unit potential. Contrast-enhanced computed tomography revealed uterine fibroids and a low-density area in the right lobe of the thyroid gland. There was no lymphadenopathy or splenomegaly. In addition, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography was not performed. This thyroid mass was diagnosed as thyroid adenoma by echography and cytology. Upper and lower gastrointestinal endoscopy showed no findings suggestive of malignant tumors. A muscle biopsy showed the infiltration of lymphocytes around the interstitial blood vessels. Muscle fibers surrounded by small round cells and moth-eaten-like fibers were observed. Muscle fibers centered on large nuclei with distinct nucleoli were also scattered (Fig. 1). There were no findings suggestive of neoplastic growth in the infiltrating lymphocytes.

Dermatomyositis was diagnosed based on the type of eruption, the presence of muscle weakness with elevated CPK, positivity for several disease-specific autoantibodies, and findings of the muscle biopsy, and the administration of PSL 50 mg was started. While the dermatomyositis rapidly improved with PSL therapy, lymphocytosis was observed after the start of treatment (Fig. 2). At a bone marrow examination for a detailed examination of the M-proteinemia, the white blood cell count had risen to 22.7×10^9/L, and the lymphocyte count had risen to 7.9×10^9/L. The bone marrow examination revealed 52.4% small to medium-sized lymphocytes with high nucleo-cytoplasmic ratio and little atypia (Fig. 3a). The flow cytometry analysis revealed these cells to be positive for CD19, CD20, and cytoplasmic kappa and negative for CD56 and cytoplasmic lambda (Fig. 3b). A bone marrow biopsy showed a marked infiltration of small lymphocytes positive for CD20 and CD79a and negative for CD138 (Fig. 3c). *In situ* hybridization revealed that these cells were negative for Epstein Barr virus (EBV)-encoded small RNA. By previously reported method (8), MYD88L 265P mutation was negative.

Subsequently, the lymphocytosis worsened, and when flow cytometry was performed on the peripheral blood, the leukocyte count and lymphocyte count were found to have increased to 23.6×10^9/L and 14.3×10^9/L, respectively. Many of the lymphocytes in the peripheral blood showed no abnormal findings, but a flow cytometry analysis revealed these cells to be positive for CD19, CD20, and surface membrane kappa and negative for CD5, CD10, CD23, and surface membrane lambda (Fig. 3d), which was considered to be the same as the lymphocyte population in the bone marrow.

This lymphocytosis gradually improved by decreasing the dose of PSL. When the dose was reduced to 8 mg, however, facial erythema, myalgia, and increased CPK were observed again. Due to the recurrence of dermatomyositis, the dose of PSL was increased to 20 mg and then to 30 mg with intravenous immunoglobulin 400 mg/kg for 5 days. After increasing the PSL dose and adding immunoglobulin therapy, the symptoms disappeared rapidly, but the number of lymphocytes increased again to 12.2×10^9/L. The lymphocytosis gradually improved again after decreasing the dose of PSL

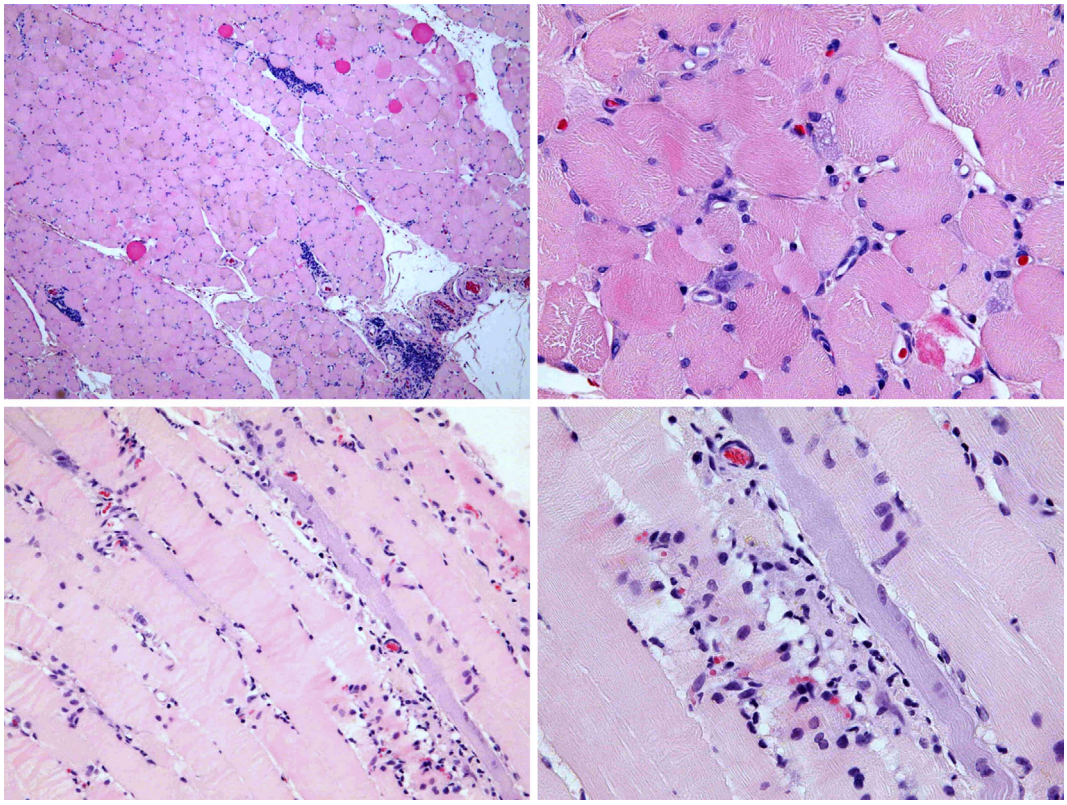

Figure 1. **Muscle biopsy specimen. A muscle biopsy showed the infiltration of lymphocytes around the interstitial blood vessels. Muscle fibers surrounded by small round cells and moth-eaten-like fibers were observed. Muscle fibers centered on large nuclei with distinct nucleoli were also scattered.**

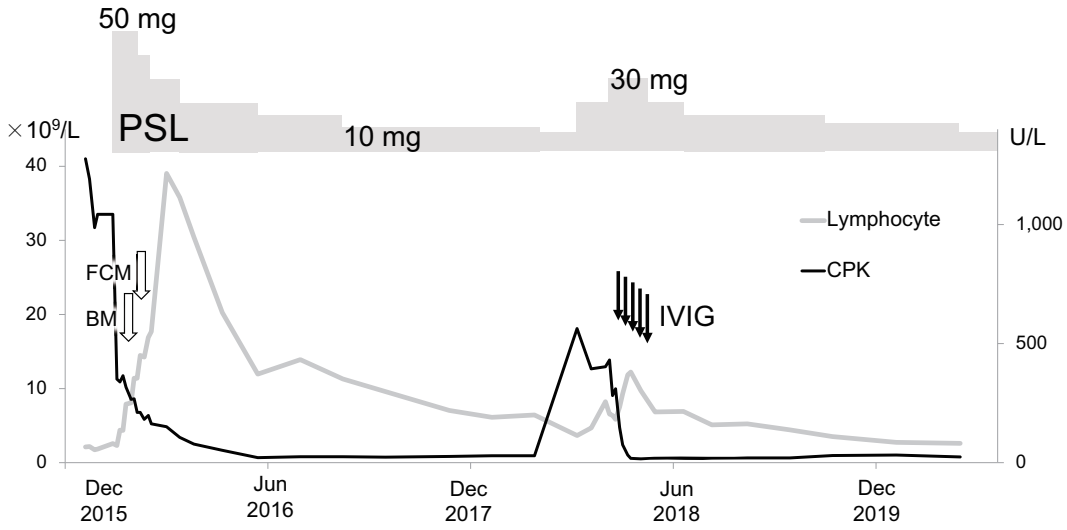

Figure 2. **Clinical course. PSL: prednisolone, BM: bone marrow examination, FCM: flow cytometry analysis of peripheral blood, IVIG: intravenous immunoglobulin, CPK: creatine phosphokinase**

once more. The IgM level consistently remained in the normal range, and the urinary protein level remained almost negative. The FLC ratio also remained in the range of 45 to 93.

At 3 years since obtaining an improvement of dermatomyositis, there has been no recurrence with a PSL dose of 8 mg, and although the exact number of MBL cells is unknown because a flow cytometry analysis has not been performed, the number of lymphocytes is 2.0-3.0×10^9/L.

Discussion

In our case, marked lymphocytosis was observed after PSL therapy for dermatomyositis. Bone marrow and peripheral blood examinations revealed B-cell lymphoproliferative disease. After reducing the dose of PSL, the number of lym-

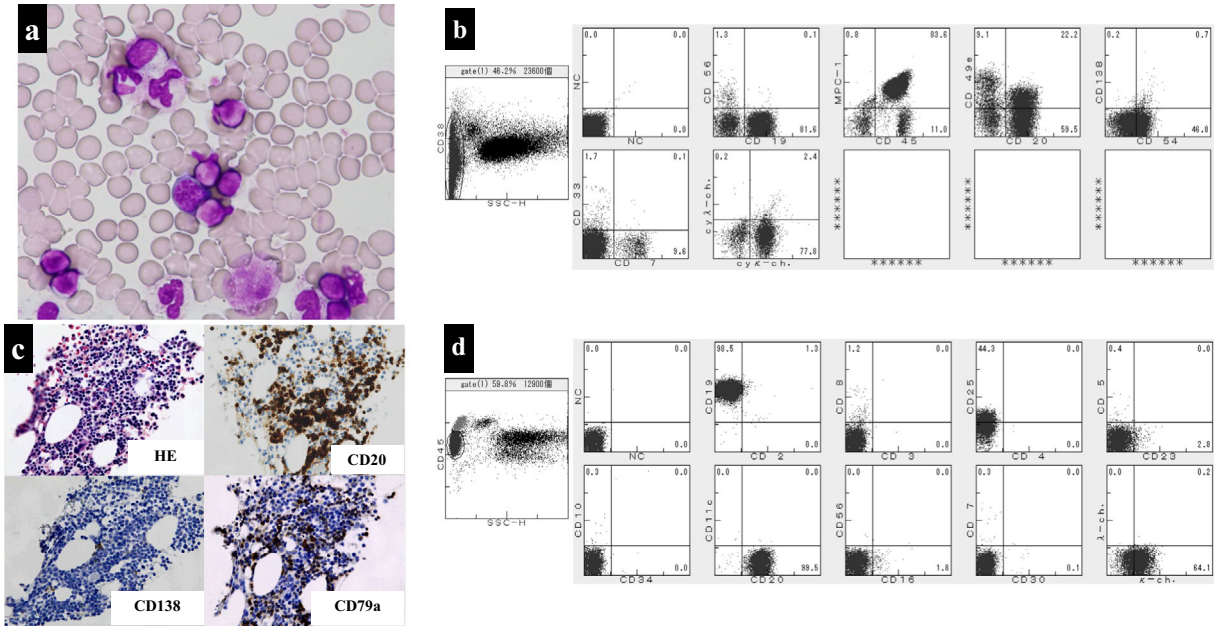

Figure 3. **Results of a bone marrow examination and a flow cytometry analysis of the peripheral blood after the initiation of prednisolone therapy. (a) The bone marrow examination revealed 52.4% small to medium-sized lymphocytes with a high nucleo-cytoplasmic ratio and little atypia. (b) A flow cytometry analysis revealed these cells to be positive for CD19, CD20, and cytoplasmic kappa and negative for CD56 and cytoplasmic lambda. (c) A bone marrow biopsy showed marked infiltration of small lymphocytes positive for CD20 and CD79a and negative for CD138 (×200 magnification. Hematoxylin and Eosin staining). (d) A flow cytometry analysis of the peripheral blood revealed that many lymphocytes with no abnormal finding were positive for CD19, CD20, and kappa and negative for CD5, CD10, CD23, and lambda.**

phocytes decreased to <2.0×10^9/L, and it was confirmed that there were no other lymph node or organ lesions. This was considered to be a case of non-CLL type MBL that was temporarily exacerbated by PSL. Since the MBL cells are indistinguishable from normal lymphocytes, the diagnosis would likely not have been possible without the appearance of marked lymphocytosis after PSL therapy. These findings suggest that there are likely other similar cases that have not yet been diagnosed.

Several indolent B-cell lymphomas needed to be differentiated in the present case. In patients with indolent B-cell lymphoma associated with IgM-monoclonal gammopathy, lymphoplasmacytic lymphoma (LPL) is the most common entity, accounting for over half of cases, followed by CLL/small lymphocytic lymphoma, nodal and extranodal marginal zone lymphoma, and follicular lymphoma (9) LPL is a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells. In our case, LPL was not diagnosed because no differentiation to plasma cells was observed, and no MYD88L265P mutation was found (otherwise seen in 91% of patients with LPL) (10). Although follicular lymphoma and mantle cell lymphoma may exhibit leukemic forms like our case, these lymphomas can be excluded from the diagnosis because of the different surface markers revealed by a flow cytometry analysis. Splenic marginal zone lymphoma and hairy cell lymphoma can also be excluded from the diagnosis because no splenomegaly was found, and the morphology of lymphocytes in the peripheral blood differed from the expected finding.

The concomitant MBL and IgM-monoclonal gammopathy may be one notable point in our case. An epidemiological study of 1909 non-hematooncological patients reported that although there were six cases with concomitant MBL and IgM-monoclonal gammopathy with undetermined significance (MGUS), there was no significant association between MBL and MGUS. In at least two of these coincident cases, MBL and MGUS were of different clonal origins, since both clones had divergent light chain restriction (11). There have been two case reports of concomitant MBL and MGUS (12, 13), including one wherein both clones had divergent light chain restriction (12). In our case, although both MBL and IgM-monoclonal gammopathy had kappa chain restriction, they may not have been the same clone.

The most notable point in our case is that MBL was exacerbated by PSL administration. The course of progression with increasing doses of immunosuppressive drugs and improvement with decreasing doses is a feature of immunodeficiency-associated lymphoproliferative disorders (IA-LPD), which typically is extra-nodal B-cell lymphoma associated with EBV, although its involvement and the histological findings vary (14). Methotrexate is the most common immunosuppressive drug to cause IA-LPD, and IA-LPD caused by PSL has not yet been reported to our knowledge.

Lymphoproliferative diseases have been associated with

various autoimmune diseases (15, 16). There are three possible hypotheses that explain the mechanism underlying complications with lymphoproliferative disease and autoimmune disease. The first is that lymphoproliferative diseases are the cause of autoimmune diseases. In particular, in cases with monoclonal gammopathy, the M-protein itself may be an autoantibody. Such patients do not show any improvement in the autoimmune disease unless the tumor burden of the lymphoproliferative disease is reduced using cytotoxic therapy (17). In the present case, MBL worsened after obtaining an improvement of dermatomyositis, and the dermatomyositis improved without treatment for MBL. It is also deniable that the dermatomyositis was caused by the infiltration of MBL cells into muscle tissue, as a muscle biopsy showed pathological findings typical of dermatomyositis with no findings suggestive of neoplastic growth in the infiltrating lymphocytes. The first hypothesis is not considered to apply to our case. The second hypothesis, however, is that autoimmune diseases are the cause of lymphoproliferative diseases. It is speculated that MBL other than the CLL-type may be a reactive monoclonal expansion triggered by immune stimulation (18). In our case, it is unlikely that dermatomyositis itself was the cause of MBL because PSL therapy improved the dermatomyositis while exacerbating the MBL. However, the transient exacerbation of MBL by PSL therapy appears to indicate that MBL responded to some stimulus. The third hypothesis is that there are some individuals with potentially weakened immune mechanisms that eliminate abnormal B-cells compared to healthy individuals, and in these afflicted individuals, both autoreactive B-cells that cause autoimmune disease and B-cells with neoplastic growth that causes lymphoproliferative disease may develop simultaneously (19). Both dermatomyositis and MBL are known to be associated with malignant disease (5, 7), thus suggesting a potential decline in tumor immunity. The above-mentioned case report of concomitant MBL and MGUS was a human immunodeficiency virus-positive case with cold agglutinin disease (13). One possible hypothesis explaining the exacerbation of MBL by PSL therapy is that if our patient had such a weakened immune mechanism, and PSL therapy for dermatomyositis failed to demonstrate a sufficient antitumor effect against MBL, MBL might have become exacerbated, as the reduced tumor immunity was further reduced by PSL therapy.

In conclusion, we experienced a case of non-CLL type MBL that developed marked lymphocytosis after receiving PSL therapy for dermatomyositis. This case of MBL was exacerbated by increasing the dose of PSL and improved after the dose was decreased. As MBL is difficult to diagnose, cases like ours may therefore not be rare. These findings will thus facilitate our understanding of the mechanism underlying lymphoproliferative diseases and autoimmune diseases.

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

References

1. Campo E, Ghia P, Montserrat E, Harris NL, Muller-Hermelink HK, Stein H, Swerdlow SH. Monoclonal B-cell lymphocytosis. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Swerdlow SH Campo E, Harris NL, Jaffe ES, Pileri SA, Eds. IARC, Lyon, 2017: 220-221.
2. Shanafelt TD, Ghia P, Lanasa MC, Landgren O, Rawstron AC. Monoclonal B-cell lymphocytosis (MBL): biology, natural history and clinical management. Leukemia **24**: 512-520, 2010.
3. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. Blood **126**: 454-462, 2015.
4. Moreira J, Rabe KG, Cerhan JR, et al. Infectious complications among individuals with clinical monoclonal B-cell lymphocytosis (MBL): a cohort study of newly diagnosed cases compared to controls. Leukemia **27**: 136-141, 2013.
5. Solomon BM, Chaffee KG, Moreira J, et al. Risk of non-hematologic cancer in individuals with high-count monoclonal B-cell lymphocytosis. Leukemia **30**: 331-336, 2016.
6. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet **357**: 96-100, 2001.
7. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. Arthritis Rheum **64**: 513-522, 2012.
8. Xu L, Hunter ZR, Yang G, et al. MYD88L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood **121**: 2051-2058, 2013.
9. Lin P, Hao S, Handy BC, Bueso-Ramos CE, Medeiros LJ. Lymphoid neoplasms associated with IgM paraprotein: a study of 382 patients. Am J Clin Pathol **123**: 200-205, 2005.
10. Treon SP, Xu L, Yang G, et al. MYD88L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med **367**: 826-833, 2012.
11. Voigtlaender M, Vogler B, Trepel M, et al. Hospital population screening reveals overrepresentation of CD5(-) monoclonal B-cell lymphocytosis and monoclonal gammopathy of undetermined significance of IgM type. Ann Hematol **94**: 1559-1565, 2015.
12. Matos DM, de Oliveira AC, Tome Mde N, Scrideli CA. Monoclonal B-cell lymphocytosis (MBL), $CD4^{+}/CD8^{weak}$ T-cell large granular lymphocytic leukemia (T-LGL leukemia) and monoclonal gammopathy of unknown significance (MGUS): molecular and flow cytometry characterization of three concomitant hematological disorders. Med Oncol **29**: 3557-3560, 2012.
13. Chen M, Abedi M. Atypical lymphocytosis, cold agglutinin hemolytic anemia, and monoclonal gammopathy in an HIV patient with marrow involvement by diffuse large B-cell lymphoma. Blood **122**: 3711, 2013.
14. Gronbaek K, D'Amore F, Schmidt K. Autoimmune phenomena in non-Hodgkin's lymphoma. Leuk Lymphoma **18**: 311-316, 1995.
15. Hagler KT, Lynch JW Jr. Paraneoplastic manifestations of lymphoma. Clin Lymphoma **5**: 29-36, 2004.
16. Bockorny B, Atienza JA, Dasanu CA. Autoimmune manifestations in patients with Waldenstrom macroglobulinemia. Clin Lymphoma Myeloma Leuk **14**: 456-459, 2014.
17. Karube K, Scarfo L, Campo E, Ghia P. Monoclonal B cell lymphocytosis and "in situ" lymphoma. Semin Cancer Biol **24**: 3-14, 2014.
18. Sands J, Tuscano JM. Geoepidemiology and autoimmune manifestations of lymphoproliferative disorders. Autoimmun Rev **9**: A335-A341, 2010.
19. Knowles DM. Immunodeficiency-associated lymphoproliferative disorders. Mod Pathol **12**: 200-217, 1999.