

Case report

Glucocorticoid-induced redistribution lymphocytosis in mantle cell lymphoma with hyaline vascular Castleman disease-like features

Kazuto Togitani,¹⁾ Mitsuko Iguchi,²⁾ Tadashi Asagiri,³⁾ Fumiya Ogasawara,¹⁾ Ichiro Murakami,²⁾ Kensuke Kojima¹⁾

We report a case of mantle cell lymphoma mimicking Castleman disease. A 76-year-old man presented with generalized lymphadenopathy, splenomegaly, anemia, polyclonal gammopathy, and pulmonary infiltrations. Lymph node biopsy revealed histological features of hyaline vascular Castleman disease. Treatment with prednisolone induced lymphocytosis with immunophenotypic and genetic features of mantle cell lymphoma. A detailed immunohistochemical study of the lymph node demonstrated a mantle cell lymphoma-mantle zone growth pattern. Glucocorticoid-induced redistribution lymphocytosis has not been reported in mantle cell lymphoma. Careful observation of circulating lymphocytes during steroid treatment may enable diagnosis of the underlying occult lymphoma in a subset of patients exhibiting clinical manifestations of Castleman disease.

Keywords: mantle cell lymphoma, hyaline vascular Castleman disease, redistribution lymphocytosis, glucocorticoid

INTRODUCTION

Mantle cell lymphoma (MCL) is a distinct type of B-cell lymphoma genetically characterized by balanced t(11;14) (q13; q32) translocation involving the CCND1 gene at 11q13 and immunoglobulin heavy chain (IGH) gene at 14q32.¹ MCL is histologically subclassified into diffuse, nodular, and mantle zone growth patterns.² The diffuse pattern is the most frequent (~ 80%), followed by the nodular growth pattern (~ 18%), and much less frequently, the mantle zone growth pattern (MZGP) (< 2%).³ In MCL-MZGP, lymph node architecture is preserved, as seen in *in situ* mantle cell neoplasia (ISMCN), a condition formerly known as *in situ* MCL.⁴ Patients with ISMCN do not require treatment in the absence of coexisting overt MCL, and as the clinical impact of the diagnosis is unclear, close follow-up is recommended. As routine staining for cyclin D1 is not usually applied to reactive-appearing lymph nodes, MCL-MZGP and ISMCN represent a diagnostic challenge.⁵ Castleman disease (CD), also known as angiofollicular lymph node hyperplasia, is a heterogeneous group of lymphoproliferative disorders.⁶ Multicentric CD is characterized by generalized lymphadenopathy, hepatosplenomegaly, cytopenia, and organ

dysfunction in association with increased levels of interleukin (IL)-6 and other pro-inflammatory cytokines.⁷ Onion skin pattern mantle zone hyperplasia is a histological feature of hyaline vascular CD, which is reminiscent of MCL-MZGP.⁵ Redistribution lymphocytosis, a condition in which rapid lymph node shrinkage occurs with an increased number of peripheral blood lymphocytes, is now widely recognized as an on-target effect of the Bruton tyrosine kinase inhibitor ibrutinib in MCL and chronic lymphocytic leukemia. Before its recognition, redistribution lymphocytosis was sporadically reported in patients with CLL receiving glucocorticoids as a single agent.⁸


We report a case of MCL-MZGP in which glucocorticoid-induced redistribution lymphocytosis helped establish a diagnosis of MCL in a patient presenting with hyaline vascular CD-like features. Glucocorticoid-induced redistribution of lymphocytosis has not been previously reported in MCL. Our case suggests that careful observation of circulating lymphocytes during steroid treatment enables the diagnosis of the underlying occult lymphoma in a subset of patients exhibiting clinical manifestations of CD.

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¹⁾Department of Hematology, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan, ²⁾Department of Pathology, Kochi Medical School, Kochi University, Nankoku, Kochi, Japan, ³⁾Department of Laboratory Medicine, Kochi Medical School Hospital, Nankoku, Kochi, Japan

Corresponding author: Kazuto Togitani, M.D., Department of Hematology, Kochi Medical School, Kochi University, Nankoku, Kochi 783-8505, Japan. E-mail: togitani@kochi-u.ac.jp

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CASE REPORT

A 76-year-old man with diabetes mellitus was referred to our hospital because of generalized lymphadenopathy and abnormal findings on chest imaging. He reported mild non-productive cough, but was otherwise asymptomatic. Chest radiography revealed bilateral infiltrative opacities (Fig. 1a). Computed tomography (CT) demonstrated airspace consolidation with air bronchogram in the right upper lung lobe, systemic lymphadenopathy, and splenomegaly (Fig. 1b-d). His hemoglobin level was 11.5 g/dL, white blood cell count was $3200/\mu\text{L}$ with 10% segmented neutrophils, 4% eosinophils, 1% basophils, 26% monocytes, and 59% lymphocytes, and platelet count was $18.7 \times 10^4/\mu\text{L}$. The serum lactate dehydrogenase level was within the normal range (112 U/L, normal: 124–222 IU/L). Increased serum levels of creatinine (3.45 mg/dL, normal: 0.65–1.07 mg/dL), C-reactive protein (6.08 mg/dL, normal: <0.14 mg/dL), and IL-6 (49.1 pg/mL, normal: ≤ 4.0 pg/mL), and polyclonal hypergammaglobulinemia (IgG, 4623 mg/dL, normal: 861–1747 mg/dL; IgA, 787 mg/dL, normal: 93–393 mg/dL; IgM, 214 mg/dL, normal: 33–183 mg/dL) were observed. Immunofixation electrophoresis did not detect monoclonal proteins in serum or urine. The serum levels of lung cancer markers, including pro-gastrin-releasing peptide, cytokeratin 19 fragment, and carcinoembryonic antigen, were all within the normal range. The serum level of soluble IL-2 receptor increased to 5398 U/mL (normal: 157–475 U/mL). Both human immunodeficiency virus antibody and anti-nuclear antibody tests were negative. ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) revealed a modest uptake in the neck,

mediastinal, paraaortic, pelvic, and inguinal lymph nodes and spleen, with high maximum standardized uptake (SUVmax) values of 3–5 and higher uptake in lung consolidations of 7.3–7.6 (Fig. 1e). The patient declined bronchoscopy with transbronchial biopsy. Biopsy of the right inguinal lymph node revealed an increased number of follicles with inconspicuous germinal centers and slightly expanded mantle zones (Fig. 2a). Hyalinized blood vessels penetrating into germinal centers were observed (Fig. 2b). Immunohistochemistry did not detect latent nuclear antigen-1 of human herpesvirus 8 or immunoglobulin light chain restriction.

He was tentatively diagnosed with hyaline vascular CD and received daily oral prednisolone at 1 mg/kg. One week later, an abrupt increase in circulating lymphocytes, reaching $7100/\mu\text{L}$, was observed (Fig. 2c, Fig. 3). Rapid shrinkage of the lung lesions (92% reduction in sum of the product of the perpendicular diameters (SPD)), enlarged lymph nodes (38% reduction in SPD), and spleen (55% reduction in splenic volume) was observed on CT (Fig. 1f-h). Flow cytometric (FCM) analysis revealed that the lymphocytes were positive for CD5, CD19, CD20, CD22, CD79a, and cytoplasmic kappa light chain, and negative for CD23 and CD200. Interphase fluorescence *in situ* hybridization analysis revealed a CCND1-IGH gene fusion signal characteristic of t(11;14) in 66% of peripheral blood mononuclear cells. A detailed immunohistochemical study of the lymph node specimen revealed that mantle zone cells exclusively expressed cyclin D1 (Fig. 2d) and SOX11 (Fig. 2e). Identical monoclonal IGH gene rearrangements in peripheral blood and lymph node cells were found in polymerase chain reaction (PCR)-amplified fragments using IGH gene consensus primer

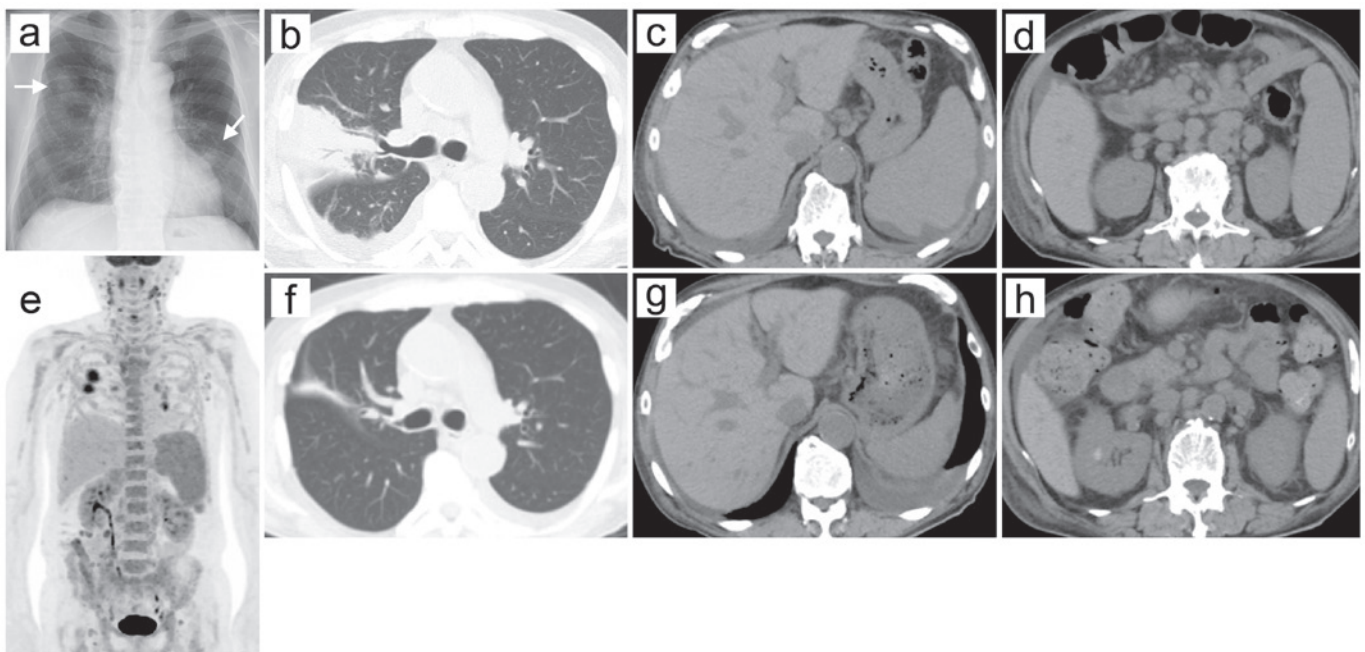


Fig. 1. (a) Chest X-ray showing bilateral air space consolidation opacities (arrows). (b-d) Initial computed tomography showing right lung consolidations, systemic lymphadenopathy, and splenomegaly. (e) ^{18}F -fluorodeoxyglucose positron emission tomogram showing a modest uptake in neck, mediastinal, paraaortic, pelvic, and inguinal lymph nodes and spleen, with high maximum standardized uptake values of 3–5 and higher uptake in lung consolidations of 7.3–7.6. (f-h) Computed tomography one month after the introduction of prednisolone and during lymphocytosis showing shrinkage of the lung lesions and enlarged lymph nodes and spleen.

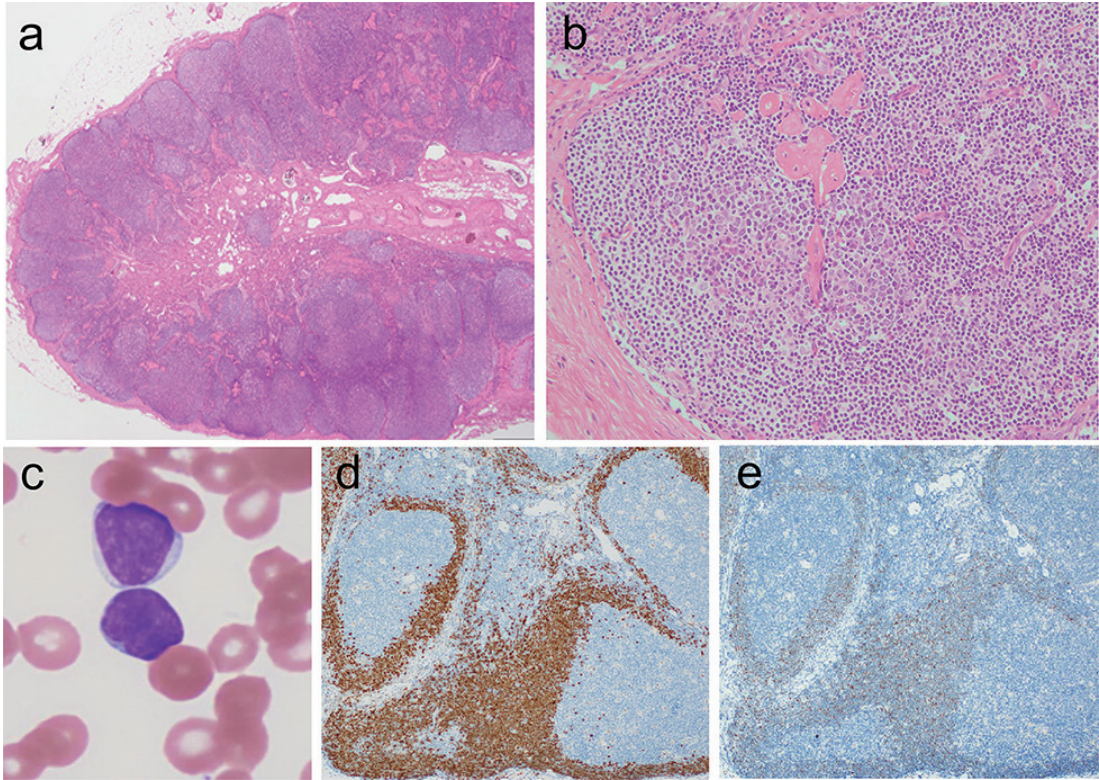
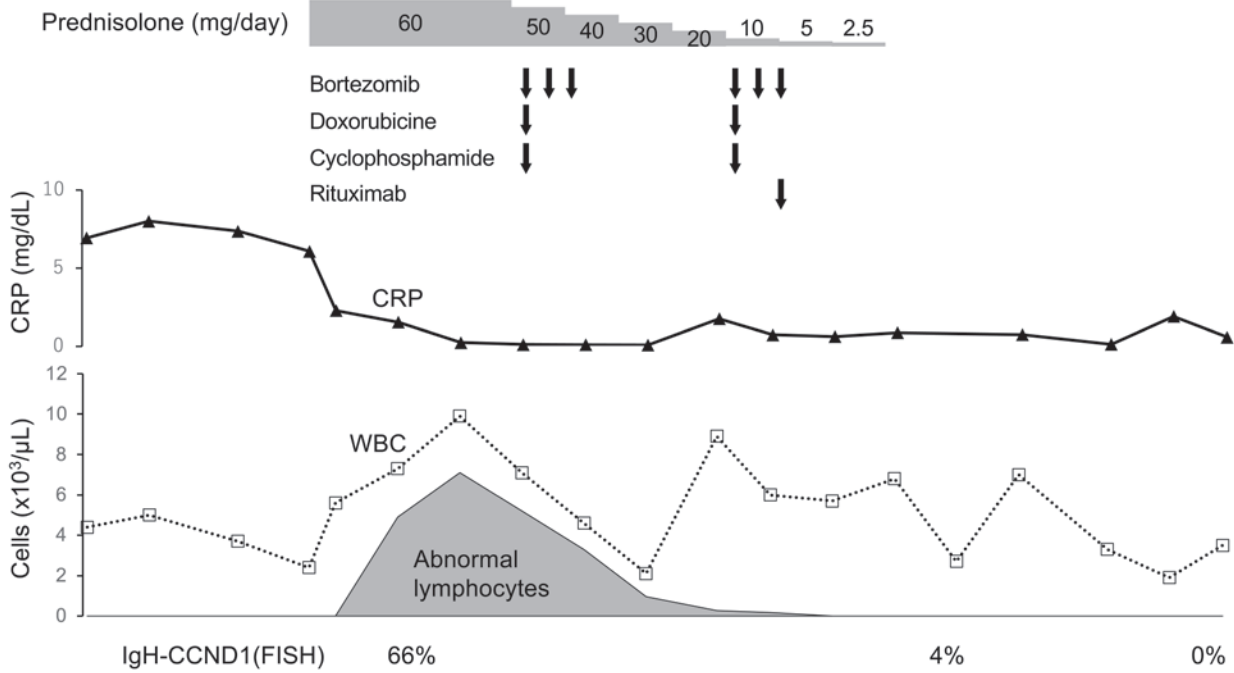


Fig. 2. (a-b) Biopsy of the right inguinal lymph node showing an increased number of follicles with inconspicuous germinal centers and slightly expanded mantle zones (a), and hyalinized blood vessels penetrating into germinal centers (b). (c) Peripheral blood smear during prednisolone treatment showing medium-sized lymphoid cells with clumped chromatin and nuclear clefts (May-Giemsa staining, $\times 1000$). (d-e) Immunohistochemical study showing cyclin D1- (d) and SOX11-expressing (e) mantle zone cells.



sets (FR1, FR2, and FR3-JH) (Fig. 4).⁹ A diagnosis of MCL-MZGP with glucocorticoid-induced redistribution lymphocytosis was made. The patient received VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone) chemoimmunotherapy,¹⁰ which resulted in complete remission.

DISCUSSION

We reported a case of mantle cell lymphoma initially diagnosed as CD. CD is characterized by systemic inflammatory symptoms, polyclonal lymphoproliferation, hypergammaglobulinemia, cytopenia, and multiple organ system dysfunction. Although a high IL-6 level is indicative of CD, it is not CD-specific and has been described in a wide range of inflammatory and malignant disorders. As CD is an exclusion diagnosis, histopathology of affected lymph nodes is essential to establish the diagnosis.⁷ In a recent histopathological validation study of CD diagnosed at a single institute over a period of 20 years, 2 of 273 (0.7%) lymph node

specimens from CD patients exhibited histological features of non-Hodgkin's lymphoma (NHL).¹¹ In that study, SUVmax values of affected lymph nodes in FDG-PET helped differentiate lymphoma lesions from those of CD. The median SUVmax value was as low as 4.5 and higher SUVmax values were associated with lymphoma. SUVmax values ranged from 3 to 5 in our case, emphasizing the difficulty in determining the underlying lymphoma.

There have been seven reported cases of MCL presenting with CD-like features, including ours (Table 1).¹²⁻¹⁵ Histological subtypes were available in six cases: MZGP (n=5) or ISMCN (n=1). There were no cases of diffuse or nodular MCL subtypes. As normal lymph node architecture is preserved in MZGP and ISMCN, immunohistochemical staining of cyclin D1 and immunoglobulin light chains may improve the diagnostic accuracy for MCL with CD-like features. Considering the localized proliferation of lymphoma cells exclusively in the mantle zone in MZGP and ISMCN, flow cytometric analysis of whole lymph node cells may have limited efficacy. In our case, the kappa/lambda light chain ratio in cells from

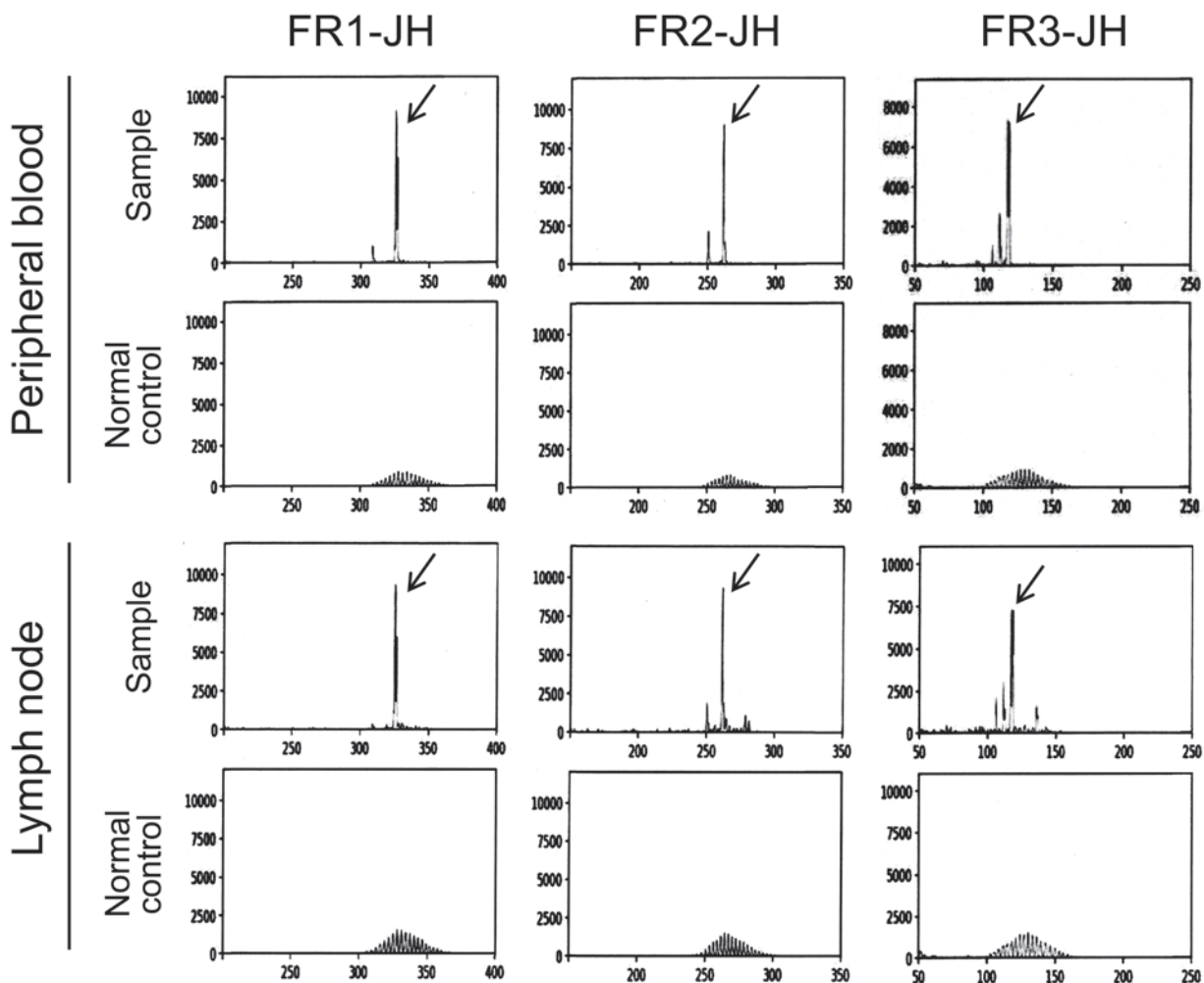


Fig. 4. Detection of monoclonal immunoglobulin heavy chain gene rearrangement in peripheral blood cells during lymphocytosis, and the affected lymph node specimen using the FR1-JH, FR2-JH, and FR3-JH consensus primer sets (arrows). The expected polymerase chain reaction product sizes for FR1-JH, FR2-JH, and FR3-JH in normal control are 310-360 base pairs (bp), 250-295 bp, and 100-170 bp, respectively.

Table 1. Summary of mantle cell lymphoma with Castleman disease-like features.

Case no.	Age/Sex	CD histology	MCL histology	SOX11	Immunoglobulin light chains	Treatment	Follow-up (months)	Reference
1	51/M	PC	MZGP	+	κ chain: 14.2%, λ chain: 19.4%	H-CVAD/MA	NA	Igawa T, 2017 ¹²
2	81/M	PC	MZGP	+	κ chain: 75.7%, λ chain: 3.5%	R-THP-COP+BR	Alive (8)	Igawa T, 2017 ¹²
3	74/M	PC	MZGP	+	κ chain: 81.5%, λ chain: 13.1%	NA	NA	Igawa T, 2017 ¹²
4	81/M	NA	NA	NA	NA	RX	DOD (21)	Yatabe Y, 2001 ¹³
5	31/F	HV	ISMCN	NA	NA	None	Alive (8)	Dobrea C, 2011 ¹⁴
6	70/M	HV	MZGP	NA	κ light chain+	None	NA	Siddiqi IN, 2011 ¹⁵
7	76/M	HV	MZGP	+	κ chain: 68.8%, λ chain: 16.5%	PSL, VR-CAP	Alive (8)	Present Case

Abbreviations: BR, bendamustine plus rituximab; CD, Castleman's disease; DOD, died of disease; F, female; H-CVAD/HD-MTX+AraC, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone combined with high-dose methotrexate and cytarabine; HV, hyaline vascular; ISMCN, in situ mantle cell neoplasia; M, male; MZGP, mantle zone growth pattern; NA, not available; ND, not determined; PC, plasma cells; R-THPCOP, rituximab, pirarubicin (tetrahydropyryl adriamycin [THP]), cyclophosphamide, vincristine, and prednisolone; RX, radiation.

the affected lymph node was 4.2, probably due to background normal B-cells (Table 1). The normal kappa/lambda ratio was described in a previously reported case (case 1).

In our case, prednisolone treatment triggered MCL cell release from the node lesions into the circulation. Circulating MCL cells were not morphologically detected before treatment. We hypothesize that glucocorticoid-induced redistribution lymphocytosis occurs through the inactivation of important MCL homing mediators, including adhesion molecules and chemokine receptors,^{8,16-20} thereby interfering with lymphoma-stroma interaction in the tumor microenvironment. In either case, CD-related increases in IL-6 and other pro-inflammatory cytokines may sensitize MCL to glucocorticoid-induced redistribution. Of note, activated NF- κ B signaling, which is observed in MCL cells, has been reported to be actively involved in IL-6 overproduction in CD.²¹

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COMPLIANCE WITH ETHICAL STANDARDS

Written informed consent was received from the patient for publication.

CONFLICT OF INTEREST

Kensuke Kojima received scientific grants from Daiichi-Sankyo, Kyowa-Kirin, Ono Pharmaceutical, and honoraria from Janssen.

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