Biclonal lymphoplasmacytic lymphoma/Waldenström macroglobulinemia associated with POEMS syndrome: A case report and literature review

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Abstract. Due to its unique clinical, immunological and molecular genetic characteristics, biclonal lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes (POEMS) syndrome is extremely rare in clinical practice, and there is no standard treatment for patients afflicted with this condition. In the present case report, a rare case of double LPL/WM with POEMS syndrome is described. The patient, a 65-year-old male, exhibited significant renal impairment and polylymphadenopathy. The patient was treated with rituximab and his symptoms were resolved following two courses of treatment. A review of the literature was performed, comparing the present case with previous cases. It is hoped that this case report will enable clinicians to gain a better understanding of this disease.

Introduction

Lymphoplasmacytic lymphoma (LPL) is a rare inert mature B-cell lymphoma, which is known as Waldenström macroglobulinemia (WM) when it secretes monoclonal IgM. WM constitutes the majority of LPL cases, with only a small proportion of LPLs secreting monoclonal IgA, IgG or no monoclonal immunoglobulin (1,2). Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes (POEMS) syndrome, also known as Takatsuki syndrome or osteosclerotic myeloma, is a rare paraneoplastic syndrome caused by an underlying plasma cell disease (3). The clinical presentation of POEMS usually involves multisystem damage characterized by multiple neuropathies, visceral enlargement, endocrine disorders and changes in skin and M-protein levels (4). To raise awareness of this disease, the present study reports a case of biclonal lymphoblastic lymphoma associated with POEMS syndrome and reviews the relevant literature.

Case report

A 65-year-old male with a 1-month history of polydipsia and polyuria with aggravated symptoms for 1 week in addition to severe peripheral neuropathy was referred to the Department of Endocrinology, Gansu Provincial Hospital (Lanzhou, China) on March 8, 2019. One month prior to hospitalization, the patient presented with symptoms of polydipsia and polyuria without obvious cause; the patient drank ~3,000 ml liquid daily and the urine volume was similar to this. The symptoms became significantly aggravated 1 week prior to admission, when the urine volume increased to ~5,000 ml per day. The patient had no noteworthy personal or family health history.

Physical examination revealed a mildly anemic appearance and decreased muscle strength of the lower limbs with obvious edema. A routine blood biochemical examination showed the following, with the normal range presented in parentheses: White blood cell count, $7.8x10^9$/l ($3.5\text{-}9.5x10^9$/l); red blood cell count, $3.62x10^{12}$/l ($4.0\text{-}5.5x10^{12}$/l); hemoglobin (Hb), 113 g/l (120-160 g/l); platelet count $204x10^9$/l ($100\text{-}300x10^9$/l); total protein, 54.1 g/l (65-85 g/l); albumin (ALB), 29.2 g/l (40-55 g/l); globulin, 24.9 g/l (20-40 g/l); creatinine, 121.7 μmol/l (53-106 μmol/l); uric acid, 451 μmol/l (210-440 μmol/l); potassium, 3.3 mmol/l (3.5-5.3 mmol/l); calcium, 1.84 mmol/l (2.11-2.52 mmol/l); fasting blood glucose (FBG), 7.0 mmol/l (3.9-6.1 mmol/l); 2-h postprandial plasma glucose (2 h-PG), 12.0 mmol/l (3.9-7.8 mmol/l); and glycated Hb, 5.9% (4.0-6.0%). Serum immunofixation electrophoresis was also performed (Fig. 1), which provided the following results: IgG (+), IgA (-), IgM (+), IgG-κ (+) and IgM-λ (+). In addition, serum protein electrophoresis yielded an M band (+).

The case was considered a plasma cell disease and transferred to the Hematology Department on March 12, 2019. Further laboratory examination was performed, the results of which were as follows: Ferritin, 350.62 ng/ml (21.84-274.66 ng/ml); β_2-microglobulin, 4.3 mg/l (0.8-1.8 mg/l); erythrocyte sedimentation rate, 23 mm/h (0-15 mm/h); cardiac troponin T, 28.8 ng/l (<14 ng/l); N-terminal-pro B-type natriuretic peptide, 1,153 pg/ml (<125 pg/ml); urine protein, 0.304 g/24 h (0-0.141 g/24 h); creatinine clearance,

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56.82 ml/min (80-120 ml/min); IgG, 9.22 g/l; IgA, 2.06 g/l; IgM, 1.36 g/l; complement C3, 0.31 g/l (0.79-1.52 g/l); complement C4, 0.10 g/l (0.16-0.38 g/l); κ, 7.78 mg/l; λ, 3.15 mg/l; and vascular endothelial growth factor (VEGF), 449.06 pg/ml (0-142 pg/ml). An ultrasound examination revealed hemangioma in the left lobe of the liver and multiple lymph node echoes in the neck, armpit and groin. The largest lymph node was 27x7 mm, with no evident abnormal lymph node structure. A molecular biology test was positive for rearrangement of the gene immunoglobulin heavy locus (IGH), and testing for the fusion gene myeloid differentiation factor 88 (MyD88)-L265P was also positive. Examination of molecular cytogenetics using fluorescence in situ hybridization showed that the cells were fibroblast growth factor receptor 3/IGH and MAF/IGH negative. Bone marrow chromosome karyotyping revealed 10 normal metaphase karyotypes. Bone marrow biopsies (Fig. 2) showed highly active bone marrow hyperplasia (50-60%) and a low ratio of granulocytes to red blood cells. Cells of all stages of the granulocyte lineage were visible, with the majority of the cells being in the middle and lower stages. Cells at all stages of the red blood cell lineage were observed, which were mainly middle- and late-stage erythrocytes. Plasma cells and lymphocytes were abundant and were either scattered or clustered. The reticular fiber staining result was grade MF-1, indicating early-stage primary myelofibrosis. For flow cytometry, 1.5-2.0 ml EDTA bone marrow sample was taken, single nucleated cells were isolated, and immunofluorescent labelling was applied. (APCH7, APD, PECY7, FITC, CD45 V500 Beckman Coulter Commercial Enterprise Detection by BC NAVIOS flow cytometry (Beckman Coulter); the medullary phenotype was normal (Fig. 3). Most granulocytes were mature, and no abnormal phenotypes were observed for red blood cells, monocytes, T-lymphocytes and natural killer cells. However, there were two groups of abnormal B cells. One group of abnormal B-lymphocytes constituted 3.82% of the nuclear cell population and were CD19 and CD20 positive, and CD5, CD10, CD103, IgD, IgM, CD23 and FMC7 negative, similar to CD5 and CD10 negative monoclonal B-lymphocytes. The other group of abnormal B-lymphocytes, which constituted 1.88% of the nuclear cell population, had restricted λ expression, were CD19 and CD20 positive, IgM positive, IgD dim, and κ, CD5, CD10, CD103, CD23 and FMC7 negative, also similar to CD5 and CD10 negative monoclonal B-lymphocytes. Plasma cells accounted for 0.20% of the nuclear cells. Furthermore, the serum κ level was 4,025.0 mg/l (3.3-19.4 mg/l), serum λ level was 92.0 mg/l (5.71-26.3 mg/l) and serum κ/λ ratio was 43.75 (0.26-1.65), while the urine κ level was 194.0 mg/l (0.39~15.1 mg/l), urine λ level was 16.7 mg/l (0.81-10.10 mg/l) and urine κ/λ ratio was 11.62 (0.461-4.0). Bone density tests indicated reduced bone mass. A vibration perception threshold test (VPT) indicated mild-to-moderate sensory impairment of the foot sensory nerve and severe peripheral neuropathy, which was classified as clinical neuropathy grade 2. These observations in combination with the aforementioned laboratory results led to the patient being diagnosed with LPL/WM associated with POEMS syndrome.

Based on this diagnosis, the patient was treated with rituximab, intravenous immunoglobulin and ALB support treatments to relieve symptoms. After two courses of treatment, the symptoms were in remission and the patient was discharged. The patient accepted routine follow-up appointments, and after 6 months the condition of the patient remained stable.

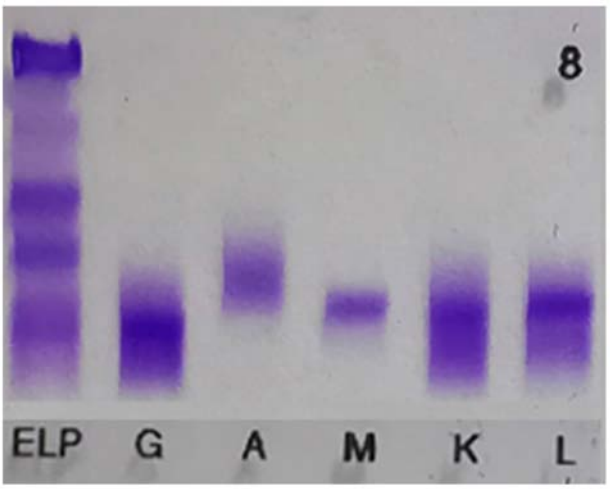

Figure 1. Serum immunofixation electrophoresis. Number 8 marked on the image is the patient number. ELP, electrophoresis; G, IgG; A, IgA; M, IgM; K, IgG-κ; L, IgM-λ.

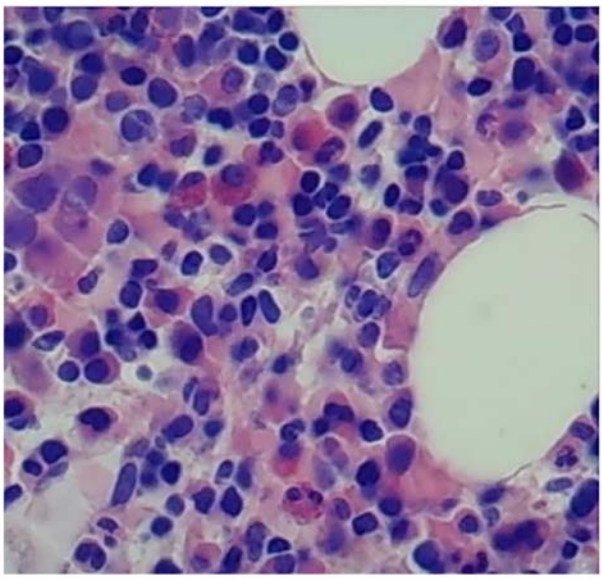

Figure 2. Bone marrow biopsy showed highly active bone marrow hyperplasia (50-60%) and a low ratio of granulocytes to red blood cells. Cells of all stages of the granulocyte lineage were visible, with the majority of the cells being in the middle and lower stages. Cells at all stages of the red blood cell lineage were observed, which were mainly middle- and late-stage erythrocytes. Plasma cells and lymphocytes were abundant and were either scattered or clustered. The reticular fiber staining result was grade MF-1, indicating early-stage primary myelofibrosis. Hematoxylin and eosin staining (magnification, x200).

Discussion

LPL/WM is a proliferative disease of lymphoplasmacytic cells characterized by the secretion of monoclonal IgM in the bone marrow, which is classified by the World Health Organization as a non-Hodgkin's LPL (3). The diagnostic criteria for LPL/WM include three elements: i) The presence

Table I. Clinical data of five cases of biclonal lymphoplasmacytic lymphoma/Waldenström macroglobulinemia.

First author, year	Age, years	Sex	Symptoms	Type	IgM (g/l)	IgG (g/l)	(Refs.)
He, 2019	73	F	Lymphadenopathy, weakness, lymphadenopathy	IgG-λ, IgM-κ	8.3	9.6	(9)
	54	M	Weakness, loss of weight	IgG-κ, IgM-κ	7.2	1.2	
	64	F	Anemia, weakness	IgG-κ, IgM-κ	23.5	9.7	
	66	M	Anemia, fever	IgG-κ, IgM-κ	36.6	14.5	
Present study	65	M	Anemia, polydipsia, polyuria	IgG-κ, IgM-λ	1.35	9.22	-

F, female; M, male.

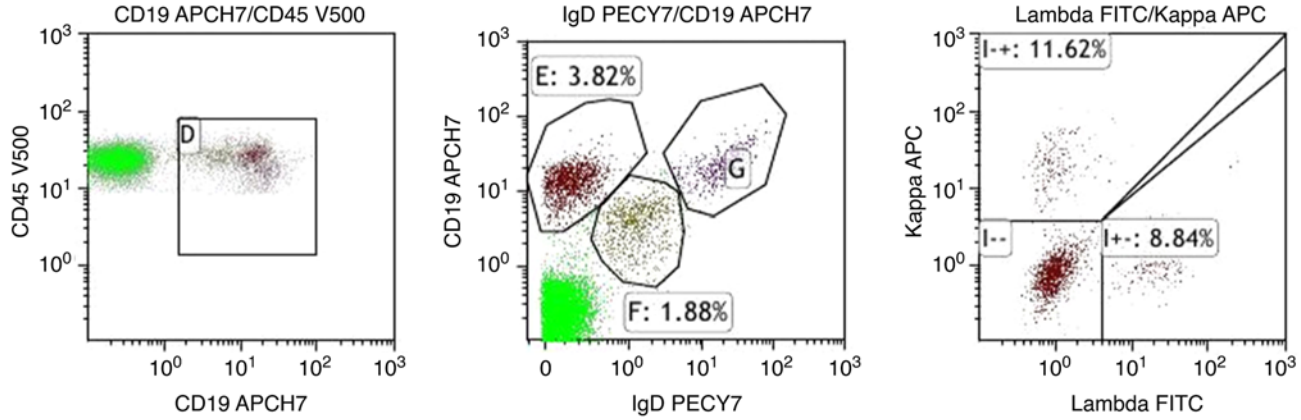

Figure 3. Immunophenotyping of the medullary phenotype by flow cytometry. APCH7, APC-H7 dye conjugate; APC, allophycocyanin; V500, organic chromophore; PECY7, phycoerythrin-cyanine7 fluorophore conjugate; FITC, fluorescein isothiocyanate.

of monoclonal IgM immunoglobulin in the serum of patients with WM; ii) the presence of typical lymphoplasmacytic cells in the bone marrow space; and iii) the presence of associated clinical symptoms, including fever, weight loss and enlargement of the liver, spleen and superficial lymph nodes. Lin and Medeiros (4) suggested that when IgM protein levels are higher than 30-40 g/l, the increase in concentration of IgM may lead to systemic amyloidosis and cryoglobulinemia. Furthermore, Baehring *et al* (5) identified peripheral neuropathy in 20% of patients with LPL/WM. The most common clinical presentation of LPL/WM is symmetrical slow bilateral numbness of the lower extremities with demyelination, and anti-myelin-associated glycoprotein antibodies are often detected in the serum of these patients. The neuropathological features of POEMS syndrome are typically demyelination, with polyneuropathy and monoclonal plasma cell proliferative disorder being the two mandatory criteria for POEMS syndrome. In addition, for the diagnosis of POEMS syndrome, at least one other major and one minor criterion are required (6,7); polyneuropathy with monoclonal protein is the primary diagnosis and organomegaly, endocrinopathy with skin changes is the secondary diagnosis.

Physical examination findings of the patient in the present study included a mildly anemic appearance, mild lid edema, palpable superficial lymph nodes and severe edema of both lower extremities. Serum immunofixation electrophoresis results were positive for IgG-κ and IgM-λ, along with globulin M. Other molecular biology tests were positive for IGH gene rearrangement and the fusion gene MyD88-L265P. Flow cytometry revealed that plasma cells accounted for 0.20% of the nuclear cells. Two sets of abnormal B lymphocytes (CD5 and CD10 negative, CD19 and CD20 positive) were detected, indicating the presence of a plasma cell phenotype. Based on these findings, the patient was diagnosed with LPL/WM (7,8). VPT of the foot showed mild to moderate profound sensory deficits with severe peripheral nerve disease, and the FBG and 2h-PG levels were above the normal range. VEGF levels were also markedly elevated, and the patient presented with multiple lymphadenitis, edema and abnormal plasma cell proliferation. Therefore, he was considered to have LPL/WM with POEMS syndrome based on a retrospective analysis.

The clinical features of previously reported patients were analyzed and compared with the present case. The four patients (9,10) reported in the previous literature comprises three males and one female with an age of onset between 54 and 73 years, with a mean age of 64.3 years. Three patients had higher IgM levels than IgG levels and the other patient had lower IgM levels than IgG levels. The patient in the present case was a 65-year-old male, who was identified as having both IgG-κ and Ig M-λ according to immunofixation electrophoresis analysis, with IgM levels lower than those of IgG, as shown in Table I. Cases of LPL with coexisting IgM and IgG are very rare, and their presence in combination with POEMS syndrome have not previously been reported, to the

best of our knowledge. Therefore, it is not possible to explain the differences or similarities between the present case and the previously reported cases, nor the etiology of IgM and IgG coexistence.

MyD88 and CXC motif chemokine receptor 4 (CXCR4) mutational activations are the most common molecular genetic alterations that occur in LPL/WM. MyD88 is an adaptor that binds to Toll-like receptor 4, as well as to interleukin-1 and interleukin-2 receptors. When MyD88 binds to these receptors, they can be activated directly or indirectly through interactions with TIR domain-containing adaptor protein and Bruton's tyrosine kinase, thereby activating the NF-κB signaling pathway (11). Hunter *et al* (12) found that methylation of the PR domain-containing protein 5 and WNK lysine deficient protein kinase 2 genes led to inhibition of the NF-κB signaling pathway, which suggests that hypomethylating drugs may be effective in the treatment of LPL/WM. The L265P mutation in MyD88 occurs in 90% of patients with WM, making this mutation useful for differentiating LPL/WM from marginal zone lymphoma (13). CXCR4 is a G-protein-coupled receptor that plays an important role in cytokine release and chemotaxis. Kristinsson and Landgren (14) found that LPL/WM cells express the chemokine receptor SDF-1a. Knockout of the CXCR4 gene or the use of CXCR4 inhibitors and G protein inhibitors to target SDF-1a inhibits the migration and adhesion of WM cells. LPL/WM cells also express another chemokine receptor, a4b1 integrin very late antigen-4 (VLA-4), which interacts directly with CXCR4, thereby activating the AKT and MAPK signaling pathways, which promotes LPL/WM cell survival and resistance to apoptosis (15,16). Varettoni *et al* (17) suggested that mutation of CXCR4 may be an independent risk factor for a shorter treatment-free survival as patients progressed from asymptomatic to symptomatic LPL/WM. The CXCR4/SDF-1 axis interacts with VLA-4 and regulates the migration and adhesion of WM cells to the basement membrane, while CXCR4 regulates migration, in particular transcortical migration, as well as adhesion to stromal and endothelial cells (18). We hypothesize that CXCR4 mutations are a risk factor for promoting the transition from asymptomatic WM to symptomatic WM.

As an inert and incurable disease, it must be emphasized that the clinical treatment LPL/WM should be initiated only after patients have been identified as having the relevant indications. Current treatment is primarily aimed at relieving symptoms, rather than achieving complete hematological remission. Since patients also express high levels of CD20, the application of rituximab is a promising treatment option. Rituximab inhibits lymphocyte proliferation and induces apoptosis through antibody-dependent cytotoxicity. Ghobrial *et al* (19) suggested that IgM expression increases in response to treatment during the early phase of rituximab therapy, which is referred to as an IgM burst. Current treatment regimens are mainly based on rituximab combinations, including rituximab combined with alkylating agents, such as chlorambucil or cyclophosphamide, or rituximab combined with nucleoside analogs, for example, fludarabine. Simon *et al* (20) noted that, although fludarabine is used as a first-line treatment, fludarabine-containing regimens are more appropriate for use as a treatment option for patients with relapsed or refractory WM due to the high risk of secondary malignancies. Rituximab can also be used in combination with bortezomib and dexamethasone, and a study on relapsed or refractory WM (21) suggested that bortezomib should be used in the treatment regimen when herpes zoster prophylaxis is a priority. Rituximab has also been used in combination with immunomodulatory agents, including lenalidomide or thalidomide, and a study showed that R-FC combination chemotherapy containing rituximab resulted in improved overall objective disease response rates and faster optimal response times in patients with LPL/WM (22). Brown *et al* (23) reported no significant differences in clinical characteristics, treatment response or prognosis between patients with biclonal immunoglobulinemia and those with traditional LPL/WM. Due to the limited number of cases described, however, the issue of treatment response and patient prognosis requires further study to determine the best treatment option(s). Souchet *et al* (24) described the use of rituximab to treat WM with POEMS syndrome. Studies have also shown that rituximab or low doses of chlorambucil are safe and effective treatment options for elderly patients (25-27). In the present case, the patient was a 65-year-old male, and rituximab was selected as a monotherapy. The patient was discharged with remission of symptoms following two courses of treatment. After 6 months of follow-up, the condition of the patient was stable, and the treatment was subsequently abandoned due to financial issues.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QW wrote the manuscript and made a significant contribution to the conception and design of the study. WG and HL collected data. HL interpreted data. QL revised the manuscript critically for important intellectual content WG analyzed data. QL and QW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics and Research Committee of Gansu Provincial People's Hospital.

Patient consent for publication

Informed written consent was obtained from the patient for publication of this report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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