OPEN ACCESS

Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) | ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Case Report

Waldenström's Macroglobulinemia with Biclonal Gammopathy: A Case Report

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DOI: https://doi.org/10.36348/sjm.2025.v10i04.009 | **Received:** 11.03.2025 | **Accepted:** 17.04.2025 | **Published:** 24.04.2025

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Abstract

Waldenström macroglobulinemia (WM) is a rare, indolent lymphoproliferative disorder characterized by the accumulation of abnormal lymphoplasmacytic cells in the bone marrow. These cells produce excessive amounts of monoclonal immunoglobulin M (IgM) protein, leading to symptoms such as fatigue, bleeding problems, and increased susceptibility to infections. In recent years, biclonal gammopathy, defined as the presence of two distinct monoclonal proteins in a patient's blood or urine, has been increasingly recognized in some WM patients. For instance, Nakazaki *et al*., (2010) reported cases of WM with coexisting non-IgM gammopathy, specifically IgG.

Keywords: Waldenström macroglobulinemia, Lymphoplasmacytic lymphoma (LPL), IgM monoclonal gammopathy, IgM paraprotein, Hyperviscosity syndrome.

INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare lymphoma, accounting for approximately 1% to 2% of hematological malignancies. It is characterized by the accumulation of lymphoplasmacytic cells that produce monoclonal immunoglobulin M (IgM) [1].

The diagnosis of WM relies on identifying lymphoplasmacytic lymphoma cells infiltrating the bone marrow, detecting the MYD88 L265P mutation to confirm the diagnosis, and identifying a serum IgM monoclonal paraprotein [2]. This monoclonal paraprotein results from the clonal proliferation of plasma cells or their B-lymphoid progenitors, leading to the production of abnormal immunoglobulins, known as M proteins or paraproteins. Typically, M proteins appear as a single (monoclonal) component; however, in some cases, two distinct paraproteins are present, a condition known as biclonal gammopathy. Biclonal gammopathies account for approximately 5% of all identified gammopathies [3]. The objective of this case report is to highlight the biochemical and clinical characteristics of biclonal gammopathy in WM and to emphasize the importance of accurate laboratory diagnosis to ensure appropriate patient management.

OBSERVATION

An 88-year-old female patient presented with profound fatigue persisting for one year, leading her to consult a private physician. Initial investigations revealed anemia, prompting a blood transfusion at a private clinic and treatment for thyroid dysfunction (details unavailable), before referral to our facility for suspected gammopathy. On admission, clinical examination indicated the patient was conscious and afebrile, with mucocutaneous pallor but no bone pain or tumor syndrome. Biological testing revealed normocytic normochromic anemia (hemoglobin: 8.4 g/dL, mean corpuscular volume: 93.7 fL, mean corpuscular hemoglobin: 29.4 pg), hyperleukocytosis (leukocytes: 25,000/µL), neutropenia (neutrophils: 1.9 x 10^3/µL), lymphocytosis (lymphocytes: 20,500/µL), monocytosis (3,500/µL), and thrombocytopenia (platelets: 80,000/µL). Hemostasis parameters were normal, with

serum calcium at 104 mg/L, blood urea at 0.34 g/L, and serum creatinine at 6 mg/L.

Electrophoretic protein fractionation (EPP) showed hypoglobulinemia with biclonal hypergammaglobulinemia. Serum immunofixation identified two monoclonal bands: IgM kappa and IgG lambda. Bence Jones proteinuria confirmed free kappa light chains. Quantitative immunoglobulin levels were IgA: 1 g/L, IgG: 5.64 g/L, and IgM: 16.75 g/L.

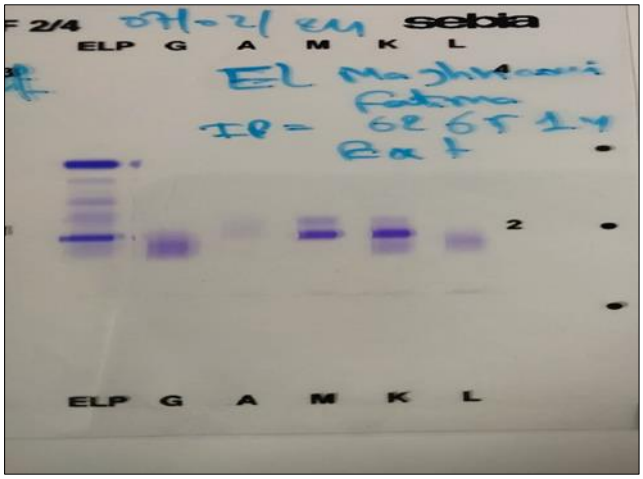

Figure 1: Serum immunofixation showing a monoclonal IgM kappa band and a slight IgG lambda band

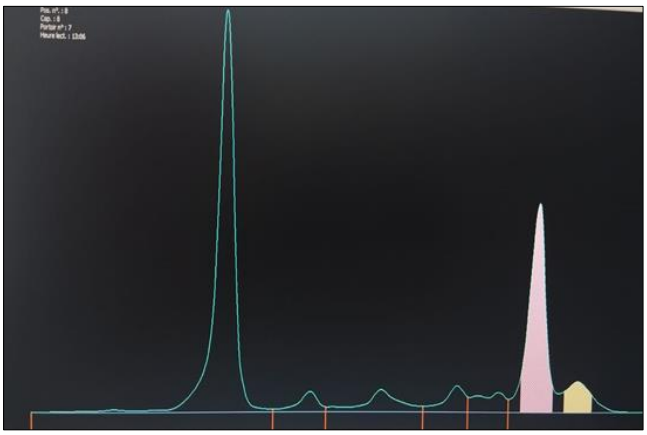

Figure 2: Serum protein electrophoresis diagram showing a biclonal peak in the gamma globulin fraction

Sternal bone marrow aspiration revealed hypercellular marrow infiltrated by lymphoplasmacytic cells, plasma cells, and plasmablasts (approximately 72% of total cellularity), consistent with Waldenström macroglobulinemia (WM). Due to financial constraints, MYD88 mutation testing was not performed. Staging via computed tomography (CT) showed no suspicious bone lesions but identified multiple sub- and supra-diaphragmatic lymphadenopathies, splenomegaly, and a nodular lesion in the upper outer quadrant of the right breast. Cervical ultrasound revealed a normal-sized, nodular thyroid classified as EU-TIRADS III. The patient was diagnosed with WM and started on chlorambucil therapy.

After 12 courses of chlorambucil treatment, the patient exhibited both biological and radiological improvements. Computed tomography with arterial phase (CTAP) imaging demonstrated a significant reduction in the size of supra-diaphragmatic (axillary and right sub-pectoral) and sub-diaphragmatic (latero-aortic, inter-aortic-caval, primitive iliac, internal, and external) lymphadenopathies compared to prior imaging, as well as the nodular lesion in the upper outer quadrant of the right breast, with overall stability in other findings.

Table 1: Evolution of Immunoglobulin Levels (IgA, IgM, IgG) Before and After Treatment

	Before treatment	1/2/2024	28/10/2024
Ig A	1 g/L	1.21 g/L	0.69 g/L
IgM	16.76g/L	16.25 g/L	15.8 g/L
Ig G	5.64 g/L	8.62 g/L	6.65 g/L

EPP: 18/05/2024

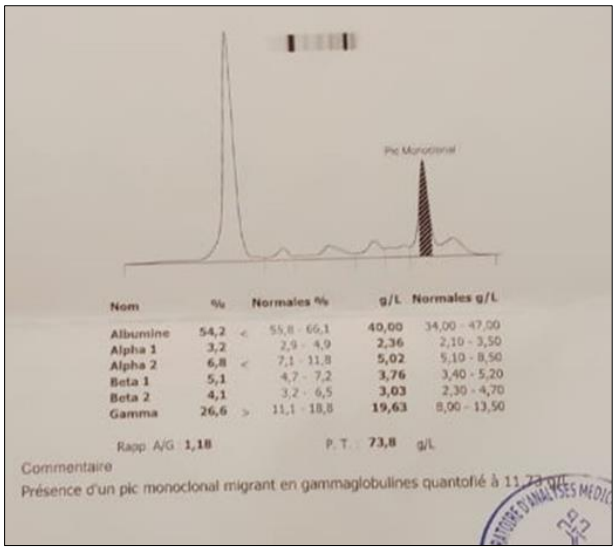

Figure 3: The schematic of serum protein electrophoresis showing a biclonal peak in the gamma globulin fraction

EPP: 28/10/2024

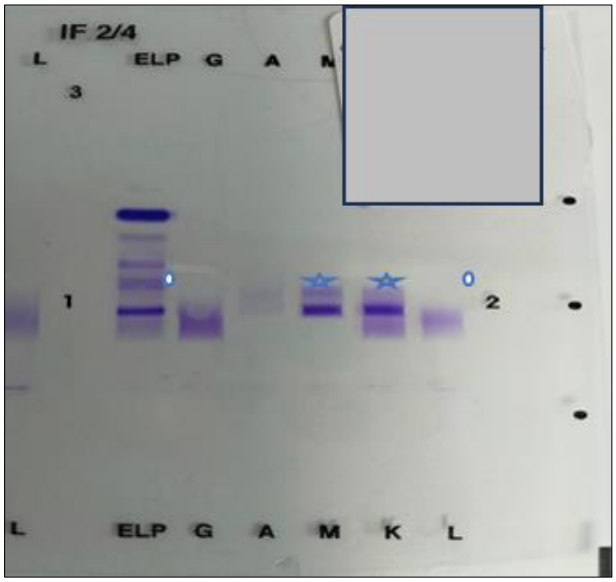

Figure 4: Serum immunofixation showing a monoclonal IgM kappa band

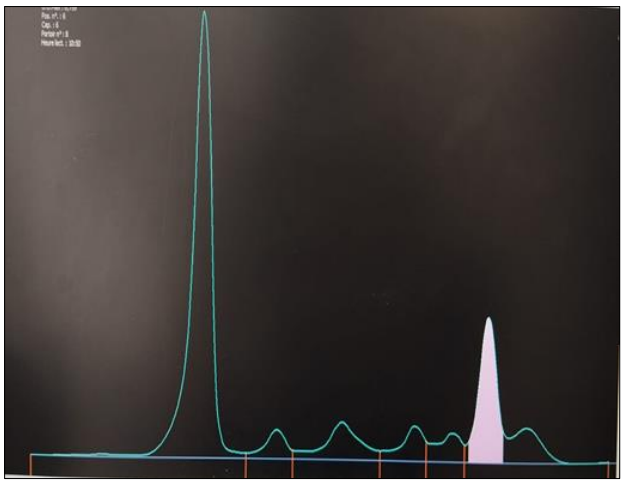

Figure 5: Serum protein electrophoresis diagram showing a monoclonal peak in the gamma globulin fraction

Table 2: Changes in Blood Parameters Before and After Treatment: A Longitudinal Study

Blood test	Before treatment	After treatment (03 cures)	After treatment (09 cures)	After treatment (12 cures)
Hemoglobin	8.4 g/dL	12 g/dL	12.1 g/dL	11.2 g/dL
Polynuclear neutrophils	1900 /uL	1400/uL	1160/uL	5830/uL
Lymphocyte	20000/uL	1020/uL	670/uL	420/uL
Monocyte	3500/uL	340/uL	210/uL	340/uL
Platelet	8000/uL	112000/uL	93000/uL	105000/uL
Calcium	104 mg/L	101 mg/L	95 mg/L	88 mg/L
Urea	0.34 mg/L	0.22 mg/L	0.35 mg/L	0.27 mg/L
Créatinine	6 mg/L	5 mg/L	5 mg/L	8 mg/L

DISCUSSION

Monoclonal macroglobulinemia, the hallmark of Waldenström macroglobulinemia (WM), arises from the proliferation of a plasma cell clone producing monoclonal immunoglobulin [1]. However, in a small proportion of patients, multiple monoclonal proteins may be observed, resulting in biclonal or, rarely, triclonal gammopathies [4, 5]. These may manifest as a single malignant gammopathy, such as WM or multiple myeloma [6], as seen in our patient, or reflect two distinct immune disorders in the same individual [3-7]. As noted earlier, biclonal gammopathies constitute ~5% of gammopathies [3], a rarity that complicates diagnosis in cases like ours.

They may arise from two separate plasma cell clones, each secreting a distinct immunoglobulin, or from a single clone producing two immunoglobulin forms with differing polymerization states [8-10]. For example, Mefire *et al*., described a case of indolent IgA lambda multiple myeloma with two monoclonal peaks (beta-2-globulin and gamma-globulin zones), confirmed as polymerized IgA forms via immunotyping [9]. In our case, financial constraints prevented molecular analysis to confirm clonality, but the distinct light chains (kappa and lambda) strongly suggest a biclonal origin [8, 9].

The clinical features of biclonal gammopathies depend on immunoglobulin heavy chain classes. The IgG/IgM combination is typically linked to WM [7], while IgG/IgG or IgG/IgA combinations are associated with multiple myeloma [7]. Narayanan *et al.*, noted that symptoms often correlate with the predominant immunoglobulin class [11], consistent with our patient, where elevated IgM (16.75 g/L) drove the clinical presentation, while low IgG (5.64 g/L) produced no specific symptoms. This highlights IgM's pathogenic role and the variability of clinical manifestations in biclonal gammopathies.

The coexistence of two proliferative immunocyte disorders is rare [11]. Eddou *et al*., reported a case of biclonal gammopathy (IgG kappa and IgM kappa) revealing multiple myeloma in a patient with chronic lymphocytic leukemia (CLL), confirmed by marrow infiltration with B lymphocytes (CD20+, CD23+) and plasma cells (CD138+, kappa+) [12]. Grosbois *et al*., described a patient with triclonal gammopathy, initially presenting with IgM kappa WM, followed by multiple myeloma 20 years later, with three distinct peaks on electrophoresis [10]. McCracken *et al*., documented five cases of WM with plasma cell neoplasms (PCN), showing biclonal M peaks with distinct heavy chains but concordant light chains, confirmed by immunohistochemistry in most cases [13]. Similarly, Nakazaki *et al*., reported a WM patient with IgM-J and IgG gammopathy, developing immune thrombocytopenia linked to platelet-associated IgG, with bone marrow showing plasmacytoid cells expressing IgM-J and IgG [14], aligning with our findings of IgM kappa and IgG lambda in WM.

Accurate diagnosis requires advanced techniques (e.g., intracellular immunofluorescence, DNA analysis) to distinguish single-clone class switching from multiple clones [10]. DNA analysis of immunoglobulin gene rearrangements is critical for establishing clonality and understanding pathogenesis [8-10]. In our patient, chlorambucil treatment led to significant clinical and biological improvements, consistent with Dimopoulos and Kastritis, who highlight its efficacy in targeting malignant plasma cells [1]. Hematological parameters improved (Table 2), tumor lesions regressed on imaging, and EPP showed disappearance of the IgG lambda band with reduced IgM kappa intensity, reflecting a partial yet significant response.

CONCLUSION

Waldenström macroglobulinemia (WM) is a rare bone marrow disorder characterized by the proliferation of abnormal B lymphocytes producing monoclonal immunoglobulin M (IgM). In some instances, as in our patient, IgM and IgG coexist, posing diagnostic challenges that necessitate careful laboratory evaluation. This case also demonstrates chlorambucil's effectiveness in achieving significant clinical and biological improvements.

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