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Waldenstrom's Macroglobulinemia: A Case Report

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Abstract **Case Report**

Waldenström's macroglobulinemia (WM) is a rare, slow-growing hematologic malignancy marked by elevated levels of monoclonal immunoglobulin M (IgM) and bone marrow infiltration by lymphoplasmacytic cells. This case details a 72-year-old man who, during a pre-anesthetic consultation for lumbar spinal stenosis surgery, presented with neurological symptoms, fatigue, and headaches. Examination revealed pallor, and laboratory tests indicated anemia and an elevated erythrocyte sedimentation rate. Serum protein electrophoresis identified a monoclonal IgM spike, and bone marrow aspiration showed significant infiltration by small lymphoid cells, lymphoplasmacytoid cells, and plasma cells. WM was confirmed, and the patient was treated with dexamethasone, rituximab, and cyclophosphamide, with positive follow-up progress. This case underscores the importance of considering WM in the differential diagnosis for patients with unexplained anemia and elevated IgM levels, highlighting the need for timely diagnosis and treatment to manage potential complications.

Keywords: Waldenstrom Macroglobulinemia, Immunoglobulin M Monoclonal Gammopathy, Hematologic Malignancy, Bone Marrow Infiltration, Anemia.

INTRODUCTION

Waldenstrom's macroglobulinemia (WM) is a rare, slowly progressing condition, classified as a variant of lymphoplasmacytic lymphoma (LPL), characterized by elevated levels of monoclonal immunoglobulin M (IgM) protein in the bloodstream [1]. Clinical manifestations encompass anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and infrequently, hyperviscosity syndrome. Confirmation of diagnosis involves the presence of IgM monoclonal protein with more than 10% clonal lymphoplasmacytic cells in the bone marrow [2]. Symptoms primarily result from marrow infiltration causing cytopenias, notably anemia, typically presenting with fatigue and constitutional symptoms like fever, weight loss and night sweats. In 20-30% of patients, there is infiltration of peripheral tissues, resulting in lymphadenopathy and hepatosplenomegaly. IgM's circulation consequences manifest as hyperviscosity symptoms, primarily neurological, including headache, blurred vision and in rare cases, strokes and coma [3]. We present a case of Waldenstrom's macroglobulinemia in a patient scheduled for surgery for lumbar spinal stenosis, who presented during the pre-anesthesia consultation with neurological symptoms related to the spinal canal narrowing, along with other nonspecific yet significant symptoms. This case underscores the importance of appropriate hematological examination for early diagnosis and prevention of major complications.

CASE PRESENTATION

A 72-year-old man presented during a pre-anesthetic consultation with complaints related to his lumbar spinal stenosis, including lower back pain and lower limb paresthesias. Additionally, he reported nonspecific symptoms such as fatigue and headaches dating back a few weeks. General examination revealed pallor of the skin and mucous membranes. There were no signs of jaundice, lymphadenopathy, or splenomegaly. He had been hypertensive for the past 5 years and was on antihypertensive medications. He had a history of benign prostatic hyperplasia for which he underwent transurethral resection. Concerning the laboratory results, the hemogram revealed hemoglobin 9.7 g/dl, MCV 90 fl, MCHC 32.9 g/dl, platelet count 237,000/mm3, total white cell count of 6,050/mm3. The biochemical investigations showed total bilirubin 4 umol/l, ASAT 18 U/L, ALAT 10 U/L, alkaline phosphatase 68 U/L, serum total protein 100 g/L with

Albumin 36 g/L, LDH 166 U/L. The ESR was 82 mm/1st h. Direct Commbs test and anti-HCV were negative.

There were no signs of hyperviscosity on ophthalmological examination.

The thoraco-abdomino-pelvic CT scan did not reveal any abnormalities apart from prostatic hypertrophy.

The peripheral blood smear examination showed red blood cells aligned in rouleaux formation, presenting a stacked appearance akin to coins (Figure 1).

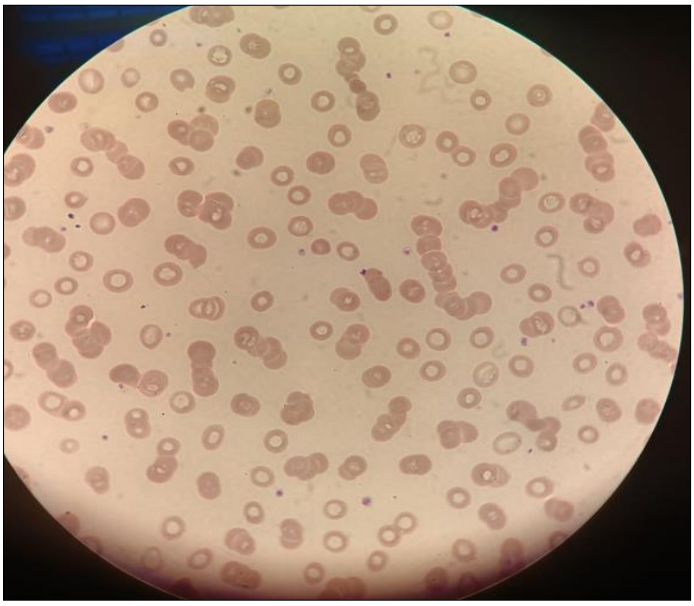
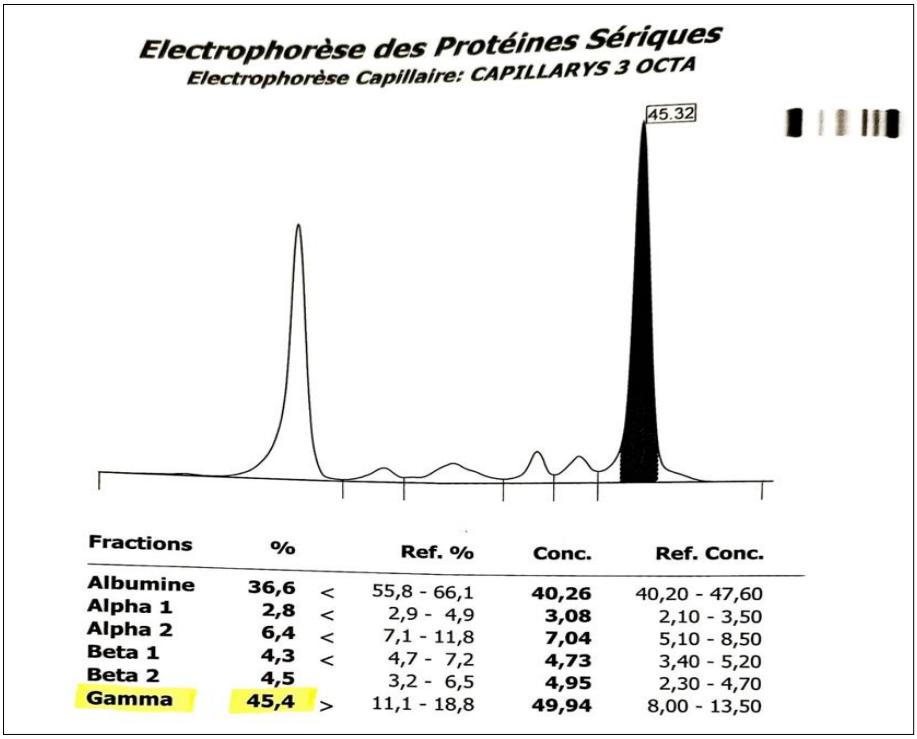


Figure 1: Peripheral blood smear showing the rouleaux formation of red blood cells

Serum protein electrophoresis revealed a monoclonal spike in the gamma globulin region estimated at 45.32 g/L (Figure 2). *Regarding immunotyping, immunosubtraction on capillary electrophoresis identified the monoclonal immunoglobulin as IgM, Lambda (Figure 3).*



Fractions	%		Ref. %	Conc.	Ref. Conc.
Albumine	36,6	<	55,8 - 66,1	40,26	40,20 - 47,60
Alpha 1	2,8	<	2,9 - 4,9	3,08	2,10 - 3,50
Alpha 2	6,4	<	7,1 - 11,8	7,04	5,10 - 8,50
Beta 1	4,3	<	4,7 - 7,2	4,73	3,40 - 5,20
Beta 2	4,5		3,2 - 6,5	4,95	2,30 - 4,70
Gamma	45,4	>	11,1 - 18,8	49,94	8,00 - 13,50

Figure 2: Serum protein electrophoresis revealed a monoclonal spike in the gamma globulin region

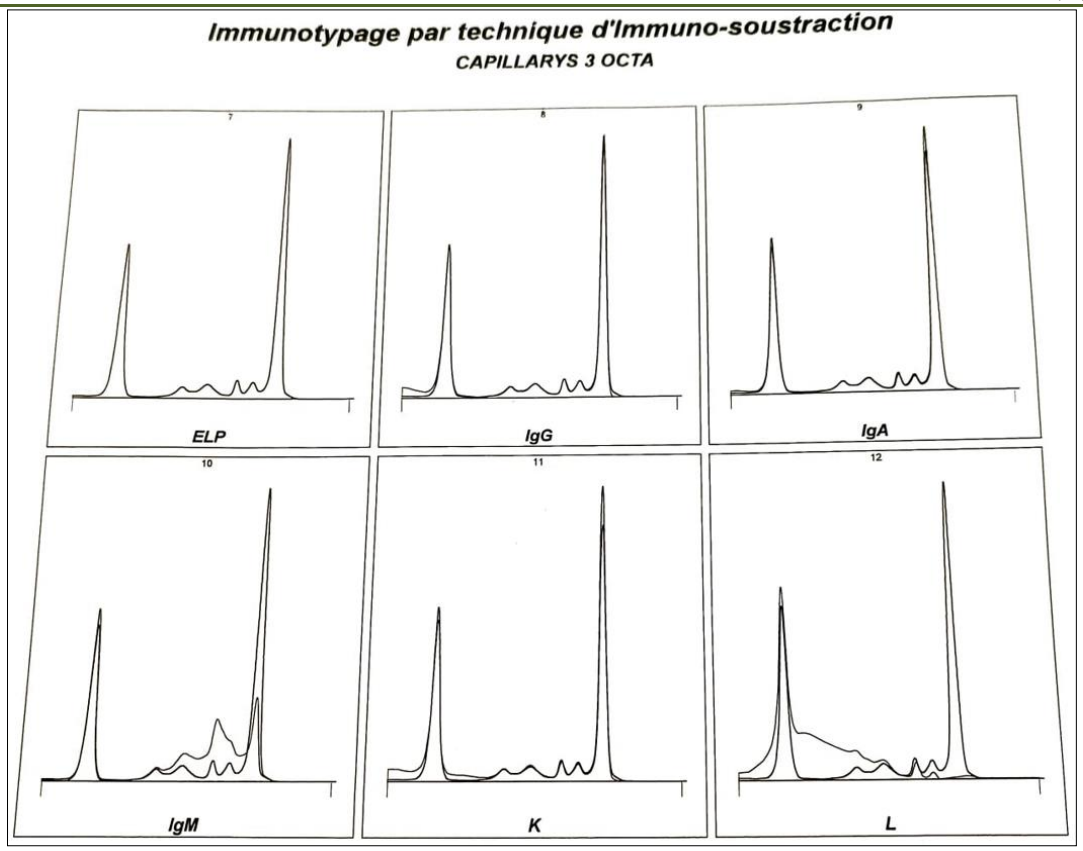


Figure 3: I*mmunosubtraction on capillary electrophoresis identifying the monoclonal immunoglobulin as IgM, Lambda*

The bone marrow aspiration smears revealed moderately cellular smears showing rare megacaryocytes and marked predominance of small lymphoid cells constituting 43 % of all nucleated cells. The lymphoid cells exhibited dense chromatin and scant cytoplasm. Lymphoplasmacytoid cells accounted for approximately 21 % and plasma cells for about 18 % of all nucleated cells. The granulocytic and erythroid series cells were quantitatively decreased without signs of dysplasia.

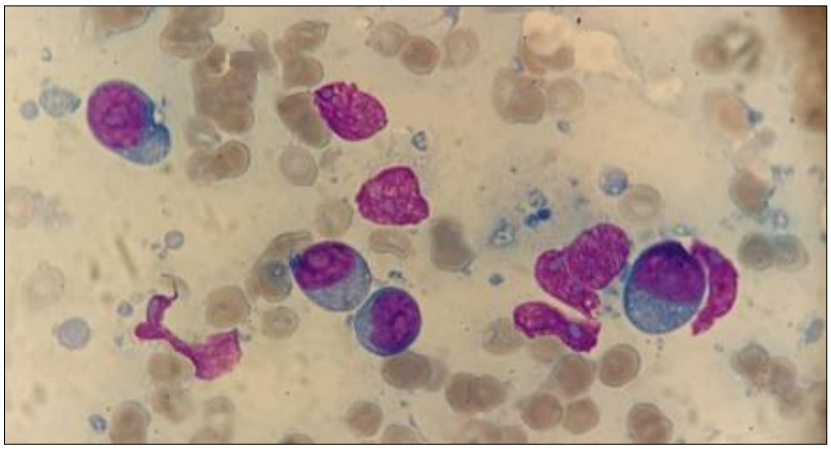


Figure 4: Bone marrow aspiration smear showing diffuse lymphoplasmacytoid cell infiltration

The diagnosis of Waldenström's macroglobulinemia is established based on bone marrow infiltration by small lymphocytes, lymphoplasmacytes, and plasma cells, along with the presence of IgM monoclonal gammopathy. The patient was initiated on the treatment protocol DRC: Dexamethasone, Rituximab and Cyclophosphamide. The patient was progressing well at the last follow-up.

DISCUSSION

WM was initially described by Jan G. Waldenström in 1944 [4, 5]. It represents a rare neoplasm of B cells, constituting 1-2% of hematological

malignancies [5, 6]. According to the World Health Organization (WHO) 2008 classification, WM is characterized as a lymphoplasmacytic lymphoma involving bone marrow with IgM monoclonal gammopathy of any level. The exact cause of WM remains unclear, although various studies suggest associations with autoimmune diseases and exposure to environmental factors. Clinical manifestations include hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%), with fatigue related to normocytic normochromic anemia being the most commonly reported symptom at presentation [5-9]. The clinical manifestations arise from the deposition of IgM in the liver, spleen, and/or lymph nodes. This results in symptoms such as anemia, hyperviscosity, lymphadenopathy, hepatomegaly, splenomegaly, and neurological symptoms.

The hallmark feature of WM is hyperviscosity, observed in only 15% of cases, clinically manifesting as oro-nasal hemorrhage, visual impairments, and various neurological abnormalities [7-10]. The primary diagnostic criteria include a distinctive peak on serum protein electrophoresis and the presence of malignant cells in bone marrow biopsy samples [8-10]. Our patient did not show organomegaly or lymphadenopathy but had a history of fatigue and headaches.

WM is diagnosed after ruling out other conditions, and it's important to consider alternative diagnoses. Conditions like splenic marginal zone lymphoma (SMZL) can also exhibit clonal B lymphoplasmacytic infiltration in the bone marrow with elevated IgM levels [9-11]. However, SMZL typically presents with splenomegaly and circulating villous lymphocytes, both of which were absent in our case.

For asymptomatic patients with elevated monoclonal IgM and less than 10% bone marrow plasma cells, IgM monoclonal gammopathy of undetermined significance (MGUS) should be considered in the differential diagnosis. However, in our case, the patient presented with symptoms.

Patients with WM may be asymptomatic, and treatment is indicated only for those who experience symptoms. Treatment is considered for WM patients showing signs of aggressive disease progression or presenting with clinical and laboratory manifestations associated with the condition [12, 13].

Alkylating agents, the anti-CD20 monoclonal antibody rituximab, and dexamethasone are considered suitable options for initial treatment of symptomatic patients with WM, achieving at least a partial response in 30% to 50% of patients [14].

The median survival of patients with WM is 5 years, which seems relatively short despite the disease's generally indolent nature, likely due to diagnosis occurring at an advanced age. A deeper understanding of WM pathophysiology, including the recent discovery of the recurrent MYD88 L265P mutation in WM patients, may pave the way for novel therapeutic strategies. This mutation enhances the growth and survival of WM cells and has implications for both diagnosis and treatment [15, 16].

CONCLUSION

This case is atypical due to the absence of frequent clinical features of WM, except for asthenia. Such presentations are common in primary care settings. Primary care physicians should be vigilant and conduct a clinical and hematological evaluation, including serum electrophoresis and bone marrow examination, to differentiate WM from other lymphomas and plasma cell disorders. Given the variability in initial symptoms of WM and the potential for hyperviscosity related complications, timely measurement of serum IgM levels and initiation of appropriate therapy upon confirmation of WM diagnosis are crucial.

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