

Waldenstrom's Macroglobulinemia Presenting in A Hypertensive Patient: Diagnostic Approach with Brief Review of Literature

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ABSTRACT

Waldenstrom's macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma. It is characterized by a wide range of clinical presentations related to direct tumor infiltration and the production of IgM. Usually it presents with constitutional symptoms, organomegaly, cytopenias and hyperviscosity syndrome. We report a case of WM in a 75-year-old male who initially presented with only epistaxis and unconsciousness. The patient had no lymphadenopathy or any organomegaly. The diagnosis of WM was made after morphological and immunohistochemical examination of bone marrow of the patient along with an elevated serum IgM level. The patient responded well to chemotherapy. This case is unusual because the patient lacked the common clinical features of WM. This case report discusses wide variety of clinical presentations of WM along with various other lymphoid lesions as differential diagnosis.

Keywords: Bone Marrow, Hyperviscosity, Lymphoplasmacytoid Cells, M Band, Waldenstrom's Macroglobulinemia

Introduction

Waldenstrom's macroglobulinemia (WM) is a B-cell neoplasm characterized by infiltration of the bone marrow by a lymphoplasmacytic infiltrate and an IgM monoclonal gammopathy. [1-2] It is a rare disorder and the overall incidence is very low. [1-3] The median age of diagnosis is 65 years with male preponderance. Varied clinical presentation can be attributed to either tissue infiltration by neoplastic B cell or because of elevated serum IgM levels. WM is an incurable disease and treatment option includes combination of chemotherapeutic agents. [4-16] Here we report a case of WM in a hypertensive patient highlighting the importance of a proper clinico-hematological examination in making an early diagnosis & preventing major complications.

Case Report

A 75-year-old male presented with epistaxis and 2 episodes of loss of consciousness. General examination showed pallor. He was a known hypertensive and was taking antihypertensive medications. There was no evidence of hepatomegaly, splenomegaly or lymphadenopathy. The peripheral blood film examination revealed hemoglobin concentration of 6.2 g/dL, total white cell count of 5400/cmm, and platelet count of approximately 3.5 lakh/cmm. Red blood cells were normocytic normochromic with few macrocytes, rouleaux formation and a few nucleated RBCs were also noted. The smears revealed mild shift to left with presence of myelocytes (1%), metamyelocyte (2%) along with neutrophils (55%), mature lymphocytes

(36%), occasional eosinophil (1%), monocyte (1%) and a population of plasmacytoid lymphocyte (4%).

The bone marrow aspiration smears revealed moderately cellular smears showing marked predominance of small lymphoid cells constituting 52% of all nucleated cells. Lymphoid cells were having dense chromatin, inconspicuous nucleoli and scant amount of cytoplasm. Lymphoplasmacytoid cells and plasma cells also constituted around 7% and 4% of all nucleated cells respectively. Myeloid series cells were decreased however showed normal maturation. Megakaryocytes were adequate and showed features of mild dysmegakaryopoiesis.

The biochemical profile revealed serum calcium ion levels of 13.8 mg/dL (reference range of 8.50–10.5 mg/dL), serum creatinine 4.2mg/dL (0.60–1.2 mg/dL), serum urea 89mg/dL (15–45 mg/dL), serum protein 10.3g/dL (6.0–8.0 g/dL) with albumin 2.9g/dL (3.5–5.0 g/dL), globulin 7.4g/dL (1.5– 3.5 g/dL), A:G ratio came out to be 0.3 (0.9–2.0). p ANCA and c ANCA were negative. The skeletal survey did not reveal any osteolytic lesions.

Bone marrow biopsy was markedly cellular showing diffuse infiltration by abnormal lymphoid cells, interspersed lymphoplasmacytoid cells and scattered plasma cells were also seen. On immunohistochemistry the cells were positive for CD20, IgM, Kappa light chain and negative for CD5, CD10, Lambda light chain. Serum protein electrophoresis had M spike in gamma region of 4.55g/dl. Immunofixation electrophoresis (IFE) identified M spike as Ig M, Kappa. Bence Jones proteins was negative. ESR was 52 mm in first hour.

The presence of atypical lymphocytes, plasma cells and plasmacytoid cells in the inter-trabecular region of bone marrow along with elevated serum IgM levels pointed

towards the diagnosis of Waldenstroms macroglobulinemia. The patient was started on chemotherapy and was doing well till the last follow up.

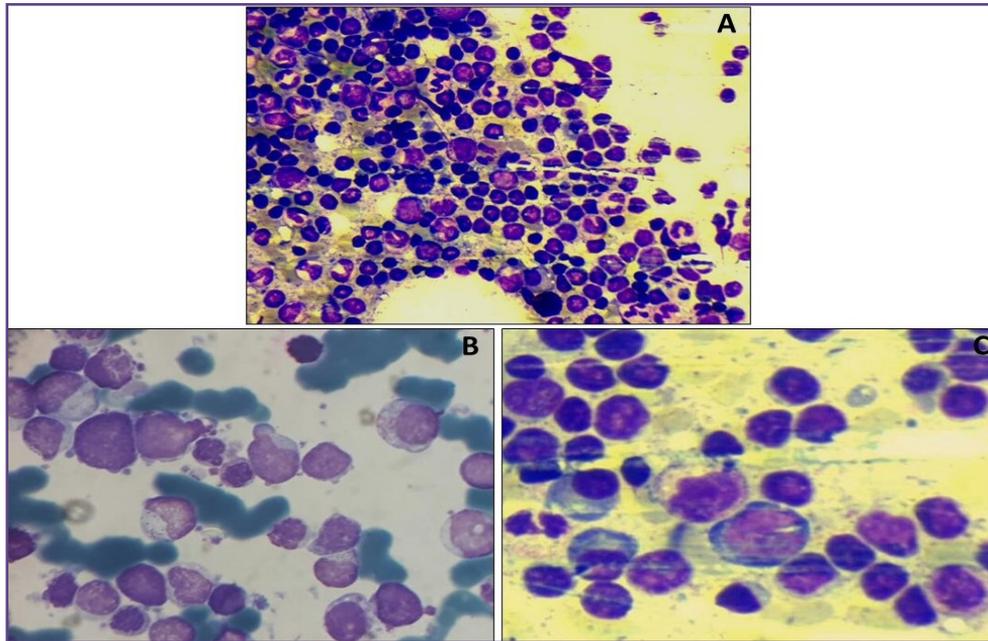


Fig. 1: A- BMA smears showing marked predominance of small lymphoid cells constituting 52% of all nucleated cells (Leishman, 20X). B- Lymphoid cell having dense chromatin, inconspicuous nucleoli and scant amount of cytoplasm (Leishman, 40X). C-Lymphoplasmacytoid cells & plasma cells also constituted around 7% and 4% of all nucleated cells respectively (Leishman, 40X).

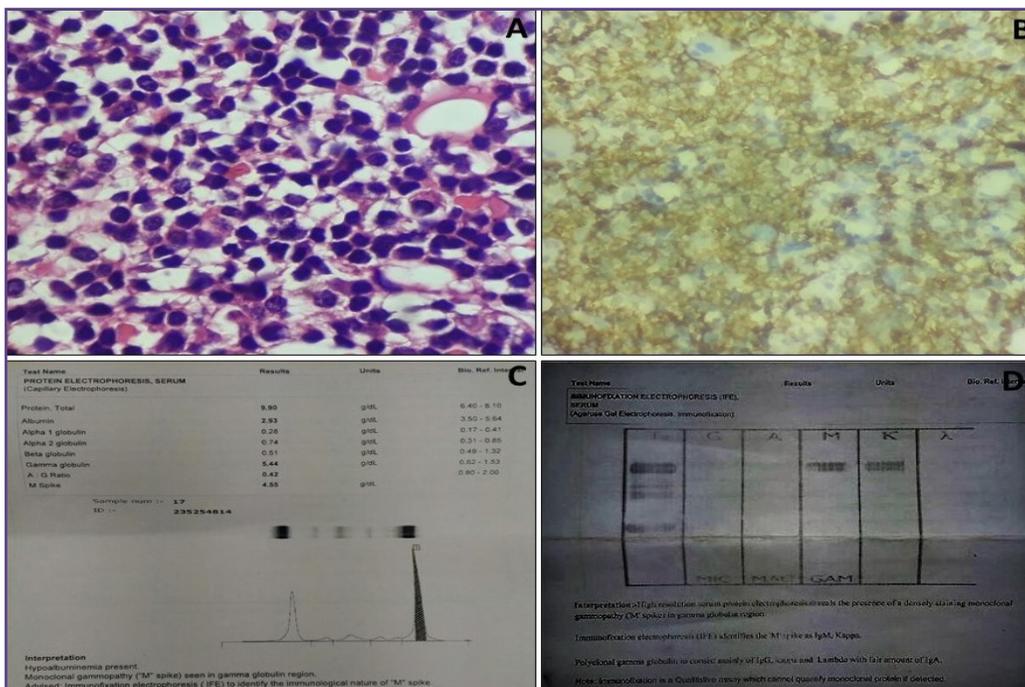


Fig. 2: A- BMB showing diffuse infiltration by abnormal lymphoid cells, interspersed lymphoplasmacytoid cells & scattered plasma cells. B- Cells with positivity for CD20. C & D- Serum protein electrophoresis revealing M spike in gamma region of 4.55g/dl.

Discussion

WM was first described by Jan G Waldenstrom in 1944.^[1,2] It is a rare B cell neoplasm, accounts for 1-2% of haematological malignancies.^[2,3] World Health Organization (WHO) 2008 defines WM as a lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration. The etiology of WM is still unknown and various studies suggest relationship with autoimmune diseases, exposure to environmental factors. The clinical manifestations of this disorder are hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%) but the most common presenting symptom is fatigue related to normocytic normochromic anemia.^[2-6] Clinical manifestations are due to deposition of IgM in the liver, spleen, and/or lymph nodes, so it presents with anemia, hyperviscosity, lymphadenopathy, hepatomegaly, splenomegaly and neurologic symptoms.

The most characteristic feature of WM is hyperviscosity which is seen in only 15% of the cases and is clinically characterized by oro-nasal hemorrhage, visual defects, and multiple neurological abnormalities.^[4-7] The main diagnostic criteria are a typical peak on serum protein electrophoresis and malignant cells in bone marrow biopsy samples.^[5-7]

Our case did not present with organomegaly or lymphadenopathy but had 2 episodes of loss of consciousness and bleeding from nose. When the patient was worked up for multiple myeloma; he had hypercalcemia, renal function derangement and anaemia, however he did not have any lytic bony lesions. Though monoclonal IgM was elevated but clonal plasma cells in bone marrow were < 10%. A diagnosis of WM was made based on IHC (the cells being positive for CD20, IgM, Kappa light chain) and SPE with M spike in gamma region of 4.55g/dl (IgM, Kappa on IFE).

WM is a diagnosis of exclusion and other entities should also be considered in the differential diagnosis. Clonal B lymphoplasmacytic infiltration in bone marrow with increased IgM levels can be observed in other conditions like splenic marginal zone lymphoma (SMZL).^[6-8] SMZL always has splenomegaly and circulating villous lymphocytes both of these findings were absent in our case.

Nodal marginal zone lymphoma (NMZL) could also be a differential diagnosis for WM. Both NMZL and WM present with lymphadenopathy; however, bone marrow involvement is observed in only one-third of patients with NMZL, while it is more common in WM.^[7-10] CD5 and CD23 are usually negative, being reported in less than 10% of patients with NMZL. In our patient there was no lymphadenopathy so NMZL was unlikely.

In patients without symptoms, monoclonal IgM elevation and with bone marrow plasma cells less than 10%, IgM-monoclonal gammopathy of unknown significance (MGUS) should also be kept in the list of differential diagnosis. However, in our case, the patient was symptomatic.

B-cell CLL may mimic WM, however, bone marrow morphology and immunophenotyping can help to differentiate the two. Our patient had CD5 and CD23 negativity in contrast to B-CLL, which would have both CD5 and CD23 positivity.^[9-11]

The patients may be asymptomatic, and treatment is required only in the symptomatic patients. Patients with WM are candidates for treatment if they have clinical evidence of aggressive disease progression or if they have had clinical and laboratory manifestations associated with WM.^[11-12]

Alexander P et al reported a case of WM where patient presented with bilateral simultaneous central retinal vein occlusion.^[3] Similarly, Nayak et al published a case of WM presenting as pancreatic mass.^[14] Hence, unusual presentation of WM should also be kept in mind while evaluating a lesion.

Besides effective plasmapheresis in the management of hyperviscosity, chemotherapy with a combination of rituximab & 2-chloro-2'-deoxyadenosine (2-CDA), or of rituximab & bendamustine, has been proven effective for WM.^[13-14] Most symptomatic patients are treated with Rituximab as monotherapy or combined with chemotherapy.^[14-15]

The median survival for patients with WM is 5 years; the survival appears short for a disease felt to have an indolent nature because patients present at an advanced age. New therapeutic approach could emerge from a better understanding in WM pathophysiology, as for the recent discovery of the recurrent mutation of MYD88 L265P in WM patients. This mutation promotes the growth and survival of WM cells and could also be used for diagnosis and treatment.^[12-15]

Conclusion

This case is unusual, since the patient lacked the common clinical features of WM with exception of anemia and short history of epistaxis and unconsciousness. A proper clinico-hematological approach along with immunohistochemistry helps in distinguishing WM from the other common differential diagnosis. Since the initial symptoms of WM are ambiguous and vary significantly and hyperviscosity-related dysfunction can arise, it is essential to promptly measure serum IgM levels and to institute appropriate care immediately when WM is confirmed in a patient.

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Financial or other Competing Interests: None.