Case Report

Waldenstrom's Macroglobulinemia: A case report

Nejima Kolikkat[1], Shamsudeen Moideen[2], Aysha Khader[1], T. P. Mohammed[2], N. A. Uvais[3]

Departments of [1]Pathology, [2]Internal Medicine and [3]Psychiatry, Iqraa International Hospital and Research Centre, Calicut, Kerala, India

Abstract

Waldenstrom's macroglobulinemia (WM) is a rare and slowly progressive disorder, a variant of lymphoplasmacytic lymphoma, which needs therapy only when patient becomes symptomatic. WM presents usually with constitutional symptoms, organomegaly, cytopenias, and hyperviscosity syndrome. This neoplasm is composed of small lymphocytes, plasmacytoid lymphocytes, and plasma cells that typically involve the bone marrow, and it is associated with an immunoglobulin M (IgM) gammopathy. Here we report the case a 60-year-old male with WM who initially presented with anemia and fatigue. 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 plasmapheresis and chemotherapy. This case is unusual because the patient lacked the common clinical features of WM. A thorough clinical and hematological work up including serum electrophoresis, bone marrow study, and immunohistochemistry helps in distinguishing WM from other lymphomas and plasma cell dyscrasias.

Keywords: Immunoglobulin M monoclonal gammopathy, lymphoplasmacytic, Waldenstrom macroglobulinemia

Introduction

Waldenstrom's macroglobulinemia (WM) is a rare and slowly progressive disorder, a variant of lymphoplasmacytic lymphoma (LPL), characterized by high levels of monoclonal immunoglobulin M (IgM) protein in the blood.[1] Clinical features include anemia, thrombocytopenia, hepatospleenomegaly, lymphadenopathy, and rarely hyperviscosity syndrome. Presence of IgM monoclonal protein associated with more than 10% clonal lymphoplasmacytic in bone marrow confirms the diagnosis.[2] The L265P mutation in MYD88 is detectable in more than 90% of cases.[3] The symptoms and signs are mainly due to infiltration of marrow leading to cytopenias, especially anemia, which commonly manifests as fatigue and constitutional symptoms such as fever, night sweats, or weight loss. Infiltration of peripheral tissues, leading to lymphadenopathy and hepatosplenomegaly, occurs in 20–30% of patients. The consequences of IgM in the circulation manifest as symptoms of hyperviscosity, mainly neurological, which includes blurring of vision, headache, and rarely stroke and coma.[4] Here we report a case of WM in a patient who presented with nonspecific symptoms highlighting the importance of a proper hematological examination in making an early diagnosis and preventing major complications.

Address for correspondence: Dr. Shamsudeen Moideen, Department of Internal Medicine, Iqraa International Hospital and Research Centre, Calicut - 673 009, Kerala, India.
E-mail: mr.shamsu1234@rediffmail.com

Received: 04-11-2019 **Revised:** 20-12-2019
Accepted: 11-02-2020 **Published:** 26-03-2020

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_972_19

Case Presentation

A 60-year-old male presented with complaints of and tiredness of few weeks duration. General examination showed severe pallor. There was no evidence of icterus, generalized lymphadenopathy, or organomegaly. He was hypertensive for past 10 years and was taking antihypertensive medications. He had history of meningitis 3 years back and he also gives a history of vascular head ache. The hemogram showed hemoglobin 4.6 gm/dl, MCV 85.6fl, MCH

How to cite this article: Kolikkat N, Moideen S, Khader A, Mohammed TP, Uvais NA. Waldenstrom's Macroglobulinemia: A case report. J Family Med Prim Care 2020;9:1768-71.

70.8 pg, MCHC 82.7 gm/dl, platelet count 83,000/mm^3, total white cell count of 5,400/mm^3. The ESR was 130 mm/1st h. Blood grouping and Rh typing could not determined and it was followed by Direct Coombs test which showed 4 plus positivity. Indirect Coombs test was negative. The biochemical profile revealed total bilirubin-2.55 mg/dl, direct bilirubin- 0.99 mg/dl, AST 44U/L, ALT12U/L, Alkaline phoshotase 111IU/L, serum Total protein 7.7g/dL with Albumin 3.7g/dL, Globulin 4 g/dL, LDH 647U/L. ANA and Anti-HCV were nonreactive. RA factor was negative.

USG abdomen showed only Grade 1 fatty liver, mild splenomegaly, and Grade 1 Prostatomegaly. The skeletal survey did not reveal any osteolyticlesions.

Peripheral smear examination on EDTA blood showed RBC agglutination. Direct prick sample showed immune hemolytic anemia and thrombocytopenia. It was followed by cryoglobulin estimation which was negative.

Serum protein electrophoresis revealed M band in the beta1 region. Qualitative immunofixation showed monoclonal gammopathy in IgM and Kappa region. On quantification total IgM was 1,400 mg/dl, Free Kappa light chain 326 mg/dl and Beta 2 microglobulin was 3858 ng/ml. Free Kappa/Lambda Ratio was 6.81.

The bone marrow aspiration smears revealed moderately cellular smears showing marked predominance of erythroid series, small lymphoid cells constituting 10% of all nucleated cells, and plasma cells around 10%. Lymphoid cells were having dense chromatin, inconspicuous nucleoli, and scant amount of cytoplasm. Myeloid series cells were decreased, however showed normal maturation. Megakaryocytes were adequate. Bone marrow biopsy was markedly cellular for the age with erythroid hyperplasia, plasmacytosis around 15% and scattered mononuclear lymphoid cells around 7% [Figure 1]. On immunohistochemistry, the cells were positive for CD20 and CD138 [Figures 2 and 3].

The presence of lymphoid cells, plasma cells in the inter-trabecular region of bone marrow along with elevated serum IgM and kappa levels pointed towards the diagnosis of WM. Ideally, immunophenotyping for antigenic expression patterns such as CD5 (-), CD10(-), CD103(-), CD23 (-), CD25 (+), CD27 (+), FMC7 (+), CD138 (-) should be performed to exclude other lymphomas with lymphoplasmacytoid morphology. Criteria to diagnose WM were fulfilled by the demonstration of an IgM monoclonal protein, along with histological evidence of infiltration of the bone marrow by clonal lymphoplasmacytic cells the diagnosis of WM/lymphoplasmacytic lymphoma (LPL) was made in our patient. During the hospital stay patient developed features of hypervicosity and IgM quantification was repeated which showed a value of 24 gm/dl. The patient was counselled regarding the nature of his illness, and he was treated with plasmapheresis.

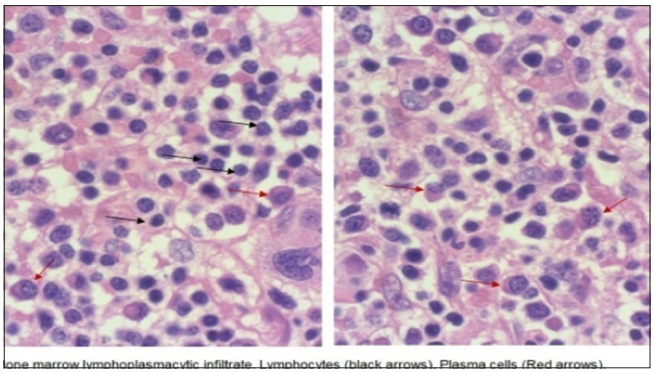

Figure 1: Bone marrow biopsy showing erythroid hyperplasia, plasmacytosis and scattered mononuclear lymphoid cells

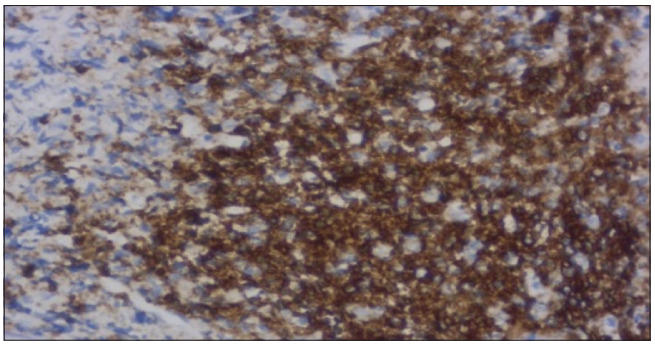

Figure 2: Showing immunohistochemistry showing cells positive for CD20

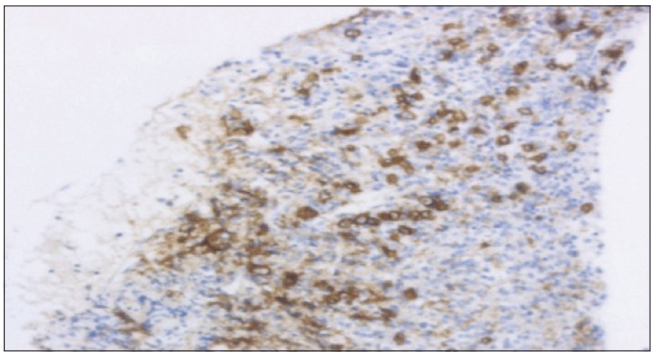

Figure 3: Showing immunohistochemistry showing cells positive for CD138

Discussion

WM was named after the Swedish oncologist Jan G. Waldenström in 1944 who reported two patients with epistaxis, hypofibrinogenemia, lymphadenopathy, neoplastic plasma cells in bone marrow, and macroglobulinemia.[5]

Lymphoplasmacytic lymphoma (LPL) is defined in the *WHOClassification of Tumours of Haematopoetic and Lymphoid Tissues,* fourth edition as a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and spleen, which does not fulfil the criteria for any of the other small B-cell lymphoid neoplasms that can also have plasmacytic differentiation. WM is defined as

LPL involving bone marrow associated with an IgM monoclonal paraprotein of any concentration, and is found in the majority of patients with LPL.[6] The great majority (>90%) of LPLs have MYDBB L265P mutation, which can make the diagnosis either more or less likely; however, this abnormality is neither specific nor required.[6] As per WHO 2016 criteria, WM has been kept under the heading of mature B-cell neoplasm with subcategory of LPL. Plasma cell neoplasms also include WM partly.

The overall incidence of WM is approximately five cases per one million persons per year. The incidence has remained steady over time as suggested by Wang *et al.*, who reported an incidence of 0.38 per100,000 persons per year.[7] It accounts for about 1–2% of hematologic malignancies. The incidence is highest among white people and is rare in other population groups.[7] LPL occurs in adults, with a median age in the seventh decade of life, and shows a slight male predominance.[8] It is diagnosed by infiltration of lymphoplasmacytoid cells in BM in the presence of IgM protein in the blood.[9]

WM is rarely reported in Indian clinical settings. Our patient was a 60-year-old male who presented with fatigue and anemia. The etiology is unclear, and no specific environmental or occupational exposure linked to this entity in our case. Like our case, in most of the reported cases, it appears to be sporadic. Possible associations between the hepatitis C virus (HCV) and human herpes virus-8 and WM have been suggested.[10] However, this association was refuted in some studies.[11] Our case did not present with organomegaly or lymphadenopathy but had fatigue and anemia. His peripheral smear examination showed marked rouleaux formation, immune hemolytic anemia, and thrombocytopenia. Bone marrow aspiration and biopsy revealed marked erythroid hyperplasia along with plasmacytosis and increased lymphoid cell infiltrate. On immunohistochemistry the cells were positive for CD20 and CD138. Serum protein electrophoresis showed M spike and immunofixation electrophoresis (IFE) identified M spike as Ig M, Kappa. Correlating with clinical features, increased serum IgM levels, bone marrow findings, and immunohisochemistry, a diagnosis of WM was made.

It is often difficult to diagnose WM morphologically because the lymphoplasmacytoid cells in the bone marrow can resemble mature lymphocytes or plasma cells. These cells lack expression of specific antigens commonly assessed in the workup of B-cell malignancies, like CD5, CD10, CD23, and CD103. Immunophenotypically, LPL cells generally express CD19, CD20, and kappa light chain. In addition, CD38 and/or CD138 can be used to identify plasma cells. Recent studies have shown that there are several genomic abnormalities that are characteristic for WM: The most common are the L265P mutation in MYD88 (found in 95-97% of patients with WM) and a somatic mutation in CXCR4 (found in 30–40% of patients with WM).[3] Infiltration of the bone marrow and extramedullary sites, such as lymph nodes, spleen, and liver, by malignant B cells and elevated IgM levels contribute to symptoms associated with pancytopenia, organomegaly, and hyperviscosity.

WM is a diagnosis of exclusion and other entities should also be considered. Clonal B lymphoplasmacytic infiltration in bone marrow with increased IgM levels can be observed in other conditions like splenic marginal zone lymphoma (SMZL). SMZL always has splenomegaly and circulating villous lymphocytes both of these findings were absent in our case. In addition, the k/l ratio is 1.2:1 for SMZL and 4.5:1 for WM, which could also be a differentiating point.[8,12] In our patient, the k/l ratio was 6.8 going in favor of WM. 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 had bone marrow plasma cells around 15%. FISH is highly useful in differentiating WM from IgM-MGUS as (6q-) is not observed in IgM MGUS and is observed in WM.[13] Due to financial constraints, our patient could not undergo a FISH.

B-cell CLL may mimic WM, but our case had no lymphadenopathy or peripheral blood persistent lypmphocytosis. Bone marrow morphology and immunophenotyping can help to differentiate the two. WM show CD 20, bcl 2, and CD 5 positivity and CD23 negativity in contrast to B-CLL, which would have both CD 5 and 23 positivity.[6] Due to financial constraints, our patient could not undergo CD 5 and 23 IHC, but he fulfilled the criteria to diagnose WM by the demonstration of an IgM monoclonal protein, along with histological evidence of infiltration of the bone marrow by clonal lymphoplasmacytic cells.

Current consensus criteria for initiation of therapy and treatment recommendations are based on a series of International Workshops on WM (IWWM) that has convened over the last decade. These guidelines were last updated in 2012 based on results of several phase 2 studies.[14] Rituximab-based therapy may be the preferred initial treatment for most patients with WM. When rapid disease control is needed, the use of cyclophosphamide-based therapy such as R-CHOP or DRC could be an appropriate choice. Early reports for the combination of bortizomib, dexamethasone, and rituximab may represent an ideal choice for patients with hyperviscosity in whom rapid reduction of paraprotein is needed.[14]

Conclusion

This case is unusual because the patient lacked the common clinical features of WM except for anemia. Such cases often initially presents in primary care settings. Primary care and family physician should be aware that a thorough clinical and hematological workup including serum electrophoresis, bone marrow study and immunohistochemistry helps in distinguishing WM from other lymphomas and plasma cell dyscrasias. Since the initial symptoms of WM vary significantly and hyperviscosity related dysfunction can arise, it is essential to promptly measure serum IgM levels and to institute appropriate therapy immediately when WM is confirmed in a patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Costa PZ, Chorão P, Póvoa A, Vieira P, Cabrera H, Mendes O, *et al.* Waldenström macroglobulinemia and cerebral venous thrombosis: From diagnosis to complication. Case Rep Med 2019;2019:3. Article ID 9581605. doi: 10.1155/2019/9581605.
2. Arjunan A, Rai H. Central nervous system involvement by Waldenstrom macroglobulinemia: A case report of the Bing-Neel syndrome. Case Rep Hematol 2019;2019: 3. Article ID 4075960. doi: 10.1155/2019/4075960.
3. Gertz MA. Waldenstrom macroglobulinemia: 2017 update on diagnosis, risk stratification, and management. Am J Hematol 2017;92:209-17.
4. Sethi B, Butola KS, Kumar Y. A diagnostic dilemma: Waldenström's macroglobulinemia/plasma cell leukemia. Case Rep Pathol 2012;2012:271407.
5. Waldenstrom J. Incipient myelomatosis or "essential" hyperglobulinemia with fibrinognenopenia—A new syndrome? Acta Med Scand 1944;117:216-47. doi: 10.1111/j. 0954-6820.1944.tb03955.x.
6. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al.* WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.
7. Wang H, Chen Y, Li F, Delasalle K, Wang J, Alexanian R, *et al.* Temporal and geographic variations of Waldenstrom macroglobulinemia incidence: A large population based study. Cancer 2012;118:3793-800.
8. Dimopoulos MA, Kyle RA, Anagnostopoulos A, Treon SP. Diagnosis and management of Waldenstrom's macroglobulinemia. J Clin Oncol 2005;23:1564-77.
9. Ghobrial IM, Witzig TE. Waldenström macroglobulinemia. Curr Treat Options Oncol 2004;5:239-47.
10. Nipp R, Mitchell A, Pishko A, Metjian A. Waldenström macroglobulinemia in hepatitis C: Case report and review of the current literature. Case Rep Oncol Med 2014;2014:165670. doi: 10.1155/2014/165670.
11. Leleu X, O'Connor K, Ho AW, Santos DD, Manning R, Xu L, *et al.* Hepatitis C viral infection is not associated with Waldenström's macroglobulinemia Am J Hematol 2007;82:83-4.
12. Owen RG, Treon SP, Al-Katib A, Fonseca R, Greipp PR, McMaster ML, *et al.* Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus panel recommendations from the second international workshop on Waldenstrom's macroglobulinemia. Semin Oncol 2003;30:110-5.
13. Schop RF, Van Wier SA, Xu R, Ghobrial I, Ahmann GJ, Greipp PR, *et al.* 6q deletion discriminates Waldenstrom macroglobulinemia from IgM monoclonal gammopathy of undetermined significance. Cancer Genet Cytogenet 2006;169:150-3.
14. Dimopoulos MA, Kastritis E, Owen RG, Kyle RA, Landgren O, Morra E, *et al.* Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7consensus. Blood 2014;124:1404-11.