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. 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 of 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 workup including serum electrophoresis, bone marrow study, and immunohistochemistry helps in distinguishing WM from other lymphomas and plasma cell dyscrasias.

Case Presentation

A 60-year-old male presented with complaints of anemia and fatigue of a 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 headache. The hemogram showed hemoglobin 4.6 gm/dl, MCV 85.6fl, MCH
70.8 pg, MCHC 82.7 gm/dl, platelet count 83,000/mm³, total white cell count of 5,400/mm³. The ESR was 130 mm/1“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 phosphotase 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 osteolytics.

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 hyperviscosity 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.

**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.[8]

Lymphoplasmacytic lymphoma (LPL) is defined in the WHO Classification 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.\(^9\) The great majority (>90%) of LPLs have MYD88 L265P mutation, which can make the diagnosis either more or less likely; however, this abnormality is neither specific nor required.\(^9\) 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 per 100,000 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 immunohistochemistry, 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).\(^13\) 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.\(^10,12\) 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 (6q2) 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 lymphocytosis. 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.\(^10\) 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 lymphoplasmacytoid 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 bortezomib, 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.

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Conflicts of interest
There are no conflicts of interest.

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