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Case Report

Internal Medicine Section

Case of Waldenstrom Macroglobulinaemia Mimicking Multiple Myeloma: A Diagnostic Challenge

HARSHITHA REDDY[1], TUSHAR SONTAKKE[2], LALIT RAUT[3], NEHA RAHUL[4], JASWANTH VARMA ALLURI[5]

ABSTRACT

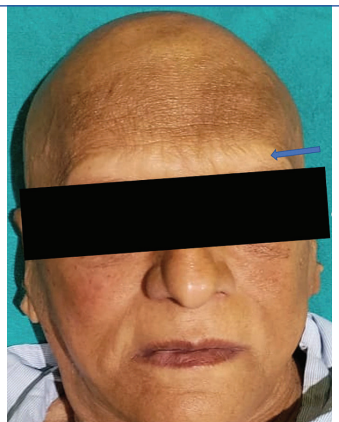
A rare form of lymphoplasmacytic lymphoma, Waldenstrom's Macroglobulinaemia (WM) progresses slowly and requires treatment only when the patient exhibits symptoms. Organomegaly, cytopenia, hyperviscosity syndrome, and constitutional symptoms are the most common presentations of WM. The main affliction of the tumour is with the bone marrow, which is made up of plasma cells, tiny lymphocytes, and plasmacytoid lymphocytes. An Immunoglobulin M (IgM) gammopathy is also present in the circulating blood. Here, we describe a 77-year-old man who complained of epistaxis, hair loss, elevated serum creatinine, hypercalcaemia, and a reversal of the albumin-to-globulin ratio. Additionally, the patient showed M band positive, which led to the diagnosis of WM rather than multiple myeloma, as was first believed. Our case report highlights the importance of considering WM in the differential diagnosis of patients presenting with symptoms such as epistaxis, fatigue, weakness, and Raynaud's phenomenon, particularly in elevated serum IgM levels. Prompt recognition and diagnosis of WM are essential for appropriate management and prognosis. In summary, our case underscores the importance of vigilance in recognising the clinical manifestations of WM and the necessity of a comprehensive approach to diagnosis, treatment, and follow-up care. Further research is warranted to elucidate the underlying pathogenesis of WM and to develop more effective and targeted therapeutic strategies for this rare haematological malignancy.

Keywords: Cancer, IgM, Lymphoma, Monoclonal immunoglobulin, Raynaud's phenomenon, Waldenström macroglobulinaemia

CASE REPORT

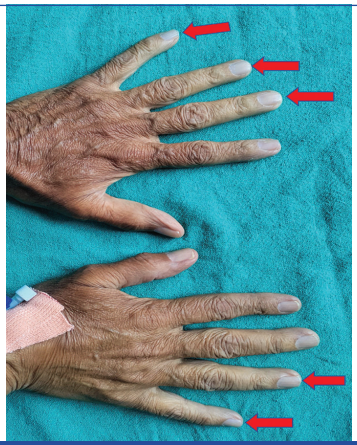
A 77-year-old man presented to the otolaryngology clinic with a one-year history of recurrent epistaxis. He reported frequent nosebleeds, occurring spontaneously and resolving spontaneously. There was no bleeding from any other sites. The patient had a gradual loss of hair from the eyebrows and scalp. The patient lost appetite, had easy fatiguability, and significant weight loss. The patient denied any history of fever, trauma, nasal obstruction, or coagulation disorders. The patient had no co-existing medical conditions and denied ever using anticoagulant, antihypertensive, or antiplatelet medication.

On general examination, his pulse rate was 88 beats per minute, Blood Pressure (BP) was 100/70 mmHg, respiratory rate was 22 cycles per minute, and saturation on ambient air was 95%. On further examination, he had pallor and generalised lymphadenopathy. There was loss of eyebrows and hair from the scalp [Table/Fig-1].



[Table/Fig-1]: Loss of eyebrows (red arrow) and hair from the scalp.

There was also history of episodic bluish discolouration of the hands in the lateral two-and-a-half fingers features similar to Raynaud's phenomenon. Also, whitish discolouration was observed in the fingers [Table/Fig-2].



[Table/Fig-2]: Whitish discolouration of the lateral two-and-a-half fingers (red arrows).

Respiratory examination auscultation findings were absent air entry on the right-side in the inframammary, mammary, infra-axillary, and scapular region; while the left-side was normal. Abdominal examination revealed hepatosplenomegaly. Other system examinations were within normal limits.

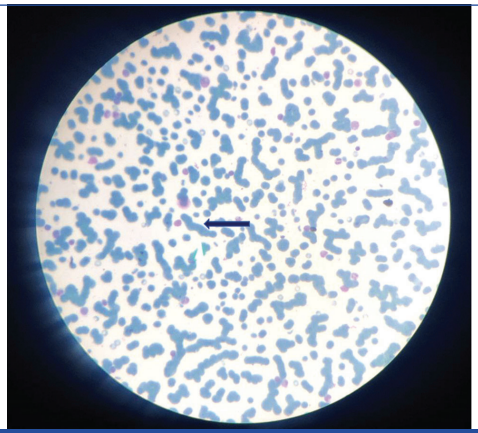
Patient basic investigations were done and shown in the table [Table/Fig-3].

Laboratory investigations	Value of the patient	Normal values
Haemoglobin	7.2	13.2-15.5 g/dL
Leucocyte number	8220	4200-10300/ cumm
Platelets	3.37	1.5-4.5 Lacs/cumm
RBC number	3.32	4.1-5.3 millions/cumm
Mean Corpuscular Haemoglobin Concentration (MCHC)	28.9	30-36 gm/dL
Mean Corpuscular Volume (MCV)	76.3	75-105 fL

Mean corpuscular Haemoglobin (MCH)	22.9	28-34 pg
Haematocrit (Hct)	26.3	34-54%
Polymorphonuclear leukocytes	64	42-74%
Lymphocytes	22	18-48%
Eosinophils	5.4	1-4%
Monocytes	8.4	2-12%
Basophil	0.1	<1%
Urea	72.5	12-18 mg/dL
Creatinine	1.9	0.4-1.1 mg/dL
Sodium	148	132-146 mmol/L
Potassium	4.1	3.4-5 mmol/L
Calcium	12	8.1-10.2 mg/dL
Alkaline phosphatase	89	40-120 unit/L
Serum glutamic-pyruvic transaminase	24	<46 U/L
Serum glutamic-oxaloacetic transaminase	18	14-56 U/L
Total protein	9.64	6-8 gm/dL
Albumin	2.1	3.3-5.1 gm/dL
Total bilirubin	0.40	0.2-1.0 mg/dL
Globulin	7.8	2.2-3.3 gm/dL
Erythrocyte sedimentation rate	72	<14 mm/hr
International Normalised Ratio (INR)	1.10	0.8-1.2
Activated partial thromboplastin clotting time	29.4	29.3 Control
Prothrombin time	12.9	11.9 Control
Thyroid stimulating hormone	4.38	0.5-8.9
Antinuclear antibody	0.34	<1
C reactive protein	78	0-6 mg/L
Vit B12	295.9	200-911

[Table/Fig-3]: Laboratory investigations are shown in the table.

Peripheral smear examination of blood revealed rouleaux formation [Table/Fig-4]. Differentials for rouleaux formation are Multiple Myeloma (MM), Waldenstrom's Macroglobulinaemia (WM), autoimmune diseases, and lymphoma.

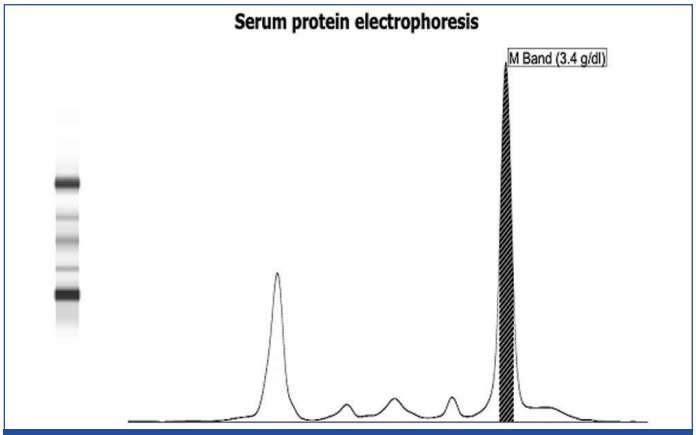


[Table/Fig-4]: Peripheral smear examination of blood revealed rouleaux formation (black arrow).

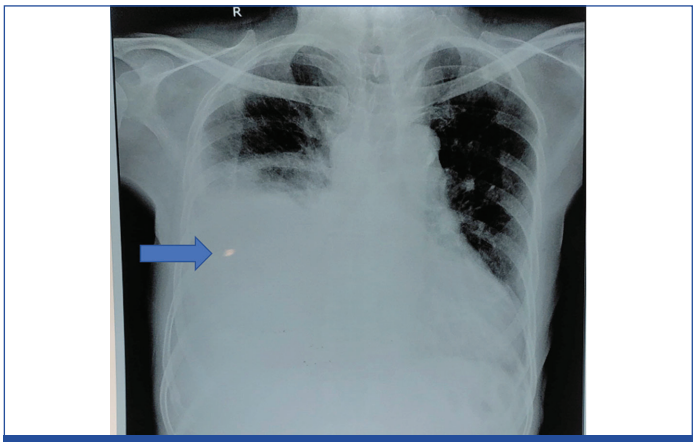
Serum cryoglobulins (qualitative) were negative. Serum protein electrophoresis was done, and an M band was present in the Beta 2 region- 3.4 gm/dL [Table/Fig-5].

Urine for routine was negative for protein and Bence Jones protein. A nasal endoscopy was done, which was normal.

Chest X-ray shows obliteration of costophrenic angle on the right-side, suggesting pleural effusion [Table/Fig-6].



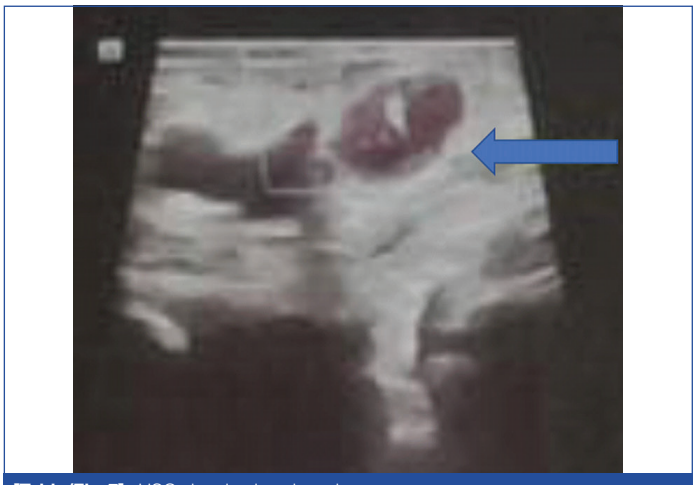
[Table/Fig-5]: Serum protein electrophoresis showing M band.



[Table/Fig-6]: Chest X-ray shows right-side pleural effusion (blue arrow).

Pleural fluid cytology revealed transudate effusion. Pleural fluid for Adenosine Deaminase (ADA) was negative, ruling out tuberculosis.

The Ultrasonography (USG) abdomen and pelvis revealed enlarged lymph nodes in the upper paraaortic, aortocaval, bilateral external iliac, and bilateral inguinal lymph nodes, probably of neoplastic aetiology. USG neck and bilateral axilla revealed bilateral neck and right axilla with lymph nodal mass in the left infraclavicular region of neck or upper apical region of thorax, probably of neoplastic [Table/Fig-7].

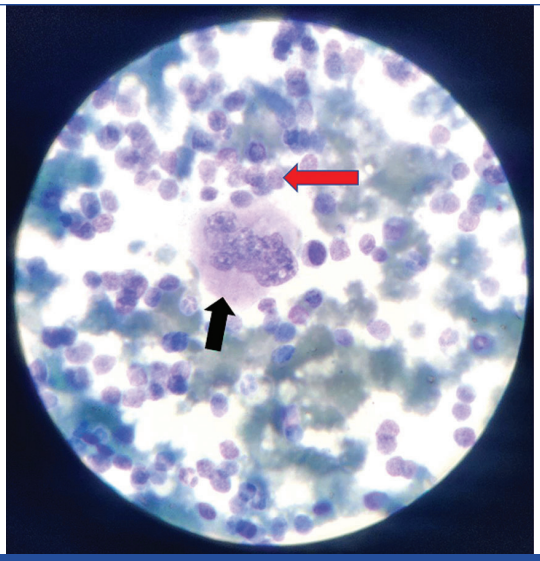


[Table/Fig-7]: USG showing lymph node.

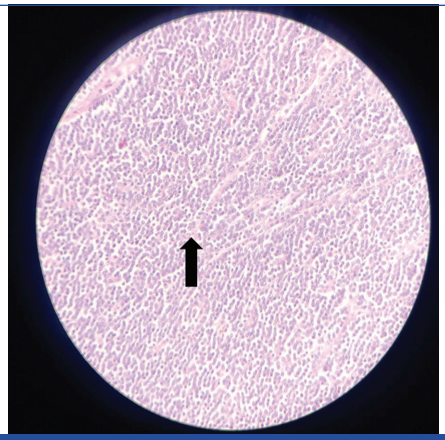
Bone marrow aspiration and biopsy showed the presence of atypical small lymphocytes [Table/Fig-8].

The myeloid and erythroid series are normal in maturation and morphology, and the myeloid erythroid ratio is 2:1. Megakaryocytes were seen, and the lymphoid series are 31%, all mature forms and plasma cells were 1%.

Lymph node biopsy showed atypical small to medium lymphoproliferation favouring lymphoma [Table/Fig-9].

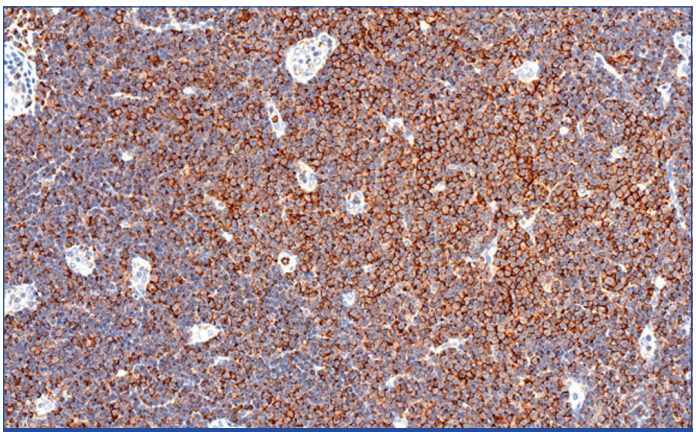


[Table/Fig-8]: Bone marrow showing the presence of atypical small lymphocytes Wright-Giemsa stain (1000x).



[Table/Fig-9]: Lymph node biopsy shows atypical small to medium lymphocytes Haematoxylin-eosin (H&E) stain (40x).

Immunohistochemistry: Atypical lymphoid cells are immunoreactive for CD-20 [Table/Fig-10].



[Table/Fig-10]: Immunohistochemistry showing lymphocytes are immunoreactive for CD-20. It was also positive for PAX-5, Bcl-2, CD-23, CD-43, Lambda and Ki-67 index is 10% Chromogranin A (CgA) (20x).

The flow cytometry report showed that 62% of B lymphocytes expressed bright CD45 and CD19, CD20, CD22, CD23, CD 49d, and CD200 positivity.

Because of rouleaux formation on the peripheral smear, serum immunofixation was performed, which showed the presence of IgM monoclonal gammopathy. Positron emission tomography revealed low-grade to non-18F-Fluorodexyglucose acid multiple supradiaphragmatic bilateral cervical, mediastinal, and axillary nodes noted. Multiple infra diaphragmatic abdominopelvic nodes were noted. MYD88 and CXCR4 were not done

The overall picture confirmed the presence of WM. The differential diagnosis of WM includes MM, marginal zone lymphoma, chronic lymphocytic leukaemia, and cryoglobulinaemia, all of which may present with monoclonal IgM and lymphoplasmacytic or B-cell proliferation.

After detailed counselling, rituximab and bendamustine therapy of six cycles duration was planned for administration.

DISCUSSION

WM/lymphoplasmacytic lymphoma is a slow-growing blood cancer due to the expansion of lymphoplasmacytic cells within the bone marrow, along with the generation of a monoclonal immunoglobulin M (IgM) protein [1]. Five instances of WM are estimated to occur in every million people annually and are rarely seen in Indian patients. The Swedish physician Jan G. Waldenström, who described two patients with nose bleeding, lymph node enlargement, bone marrow filled with plasma cells, and macroglobulianemia in 1944, is credited with naming WM [2]. Anaemia, thrombocytopenia, hepatosplenomegaly, generalised lymphadenopathy, and hyperviscosity syndrome are among the clinical symptoms. The effects of IgM in the bloodstream appear as hyperviscosity symptoms, primarily neurological. These symptoms include headaches, blurred vision, and, infrequently, stroke and coma [2]. A rare extramedullary symptom of WM is Bing Neel syndrome, where the lymphoplasmocytic lymphocyte infiltrates the central nervous system [3].

Due to the presence of IgM monoclonal protein, an M band could be present, representing a discrete monoclonal protein peak on electrophoretic analysis, which can provide valuable diagnostic and prognostic information in the evaluation of WM. Detecting a monoclonal protein, often called the M protein, in the serum or urine is a critical diagnostic feature of WM.

IgM is a pentameric immunoglobulin circulating in the blood. In WM, IgM production is increased; hence, it is called macroglobulinaemia [4].

It is well acknowledged that the clonal cells originate from B-lymphocytes with somatically altered VH genes in the post-germinal centre, with a preference for VH3/JH4 gene families, VH3-23 single segment, and intraclonal homogeneity, without isotype switching [4]. Additionally, the lack of intraclonal changes and somatic hypermutation of VH indicates that the majority are CD27-, and some of them are CD27+ cells, suggesting that they originated from memory B-cells and which tell us there might be divergent pathways for the origin of WM [5]. There have been suggestions of potential connections between WM and the Human Herpes Virus-8 (HHV-8) and the Hepatitis C Virus (HCV) [6].

The WHO classifies clonal WM cells with flow cytometry-determined immunophenotypic profiles as negative for CD5, CD10, and CD23 and positive for light chains (mostly kappa), IgM, CD19, and CD20. Variability can occur, though, and it has been shown that some antigens- such as CD11c, CD22, CD25, CD38, CD52, CD79b, FMC7, and B-cell Lymphoma-2 (BCL-2) are positive. A minority of individuals with unambiguous WM have also been shown to have variable expression of CD5, CD10, and CD23 [7].

Although they frequently complain of weakness, exhaustion, fever, and weight loss, the majority of patients are asymptomatic when they first come.

Cytopenia and normochromic normocytic anaemia are caused by features associated with increased clonal cell growth due to widespread lymphoplasmacytic infiltration in the bone marrow; however, this sign may also be related to the short life span of erythrocytes, increased blood viscosity which leads to reduced production of erythropoietin, and autoimmune haemolysis. Usually less than 50,000/mm^3, the platelet count can occasionally be caused by immune thrombocytopenic purpura [8].

Diagnosing WM based on morphology can be challenging as the lymphoplasmacytic cells in the bone marrow may mimic the appearance of mature lymphocytes or plasma cells. Certain antigens, including CD5, CD10, CD23, and CD103, frequently evaluated in the workup of B-cell malignancies, are not expressed by these cells. Lymphoplasmacytic Lymphoma (LPL) cells commonly display CD19, CD20, and kappa light chains regarding immunophenotyping.

Furthermore, plasma cells can be identified by CD38 and CD138 [8]. According to recent research, WM is associated with several genetic disorders including the most prevalent ones are a somatic mutation in CXCR4 and the L265P mutation in MYD88, which is present in almost 95% of individuals with WM [1].

WM is typically diagnosed through a process of exclusion, and other possible conditions should also be taken into consideration. Other diseases, such as IgM-Monoclonal Gammopathy of Unknown Significance (MGUS) and Splenic Marginal Zone Lymphoma (SMZL) should also be considered among the potential differentials [9]. It is uncommon for WM to develop into other blood disorders. Few reports exist that WM can develop into mantle cell lymphoma or diffuse large B-cell lymphoma. Immunophenotyping and bone marrow morphology can be utilised to differentiate between B-cell Chronic Lymphocytic Leukaemia (B-CLL) and WM, as the two may seem similar. Compared to B-CLL, WM exhibits CD 20, BCL-2, CD 5, and CD 23 negative [10].

For most WM patients, rituximab-based therapy may be the recommended course of action. Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone (R-CHOP) and Dexamethasone, Rituximab, Cyclophosphamide (DRC) are two examples of cyclophosphamide-based therapies that may be used when quick disease control is required [10]. The combination of bortezomib, dexamethasone, and rituximab has been suggested in early reports as a suitable option for patients with hyperviscosity who require a quick decrease of paraprotein. The current therapy for WM with hyperviscosity is plasma separation. Ibrutinib is effective in patients refractory to rituximab. Rituximab and ibrutinib may be considered if swelling of the lymph nodes and organs occurs [11].

CONCLUSION(S)

This case emphasises how crucial it is to rule out haematologic malignancies when making a differential diagnosis for individuals with symptoms similar to those of WM, particularly when there are increased serum IgM levels and M-band positive on serum protein electrophoresis. In summary, monoclonal IgM gammopathy and lymphoplasmacytic cells in the bone marrow are the hallmarks of WM, an uncommon and indolent B-cell lymphoproliferative illness. Despite its rarity, WM poses significant diagnostic and management challenges due to its heterogeneous clinical presentation and potential complications.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Associate Professor, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Professor, Department of Haematology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
4. Assistant Professor, Department of Radiation Oncology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
5. Postgraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Harshitha Reddy,
Postgraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research,
Wardha-442001, Maharashtra, India.
E-mail: harshureddy95@gmail.com

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