

# Waldenstrom Macroglobulinemia Complicated with Hyperviscosity Syndrome

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**Objectives:** Waldenstrom Macroglobulinemia (WM) is a malignant disease of the B lymphocytes. We report on a patient in Mongolia having WM complicated with hyperviscosity syndrome. **Methods:** A 28 year-old Mongolian woman had symptoms due to hyperviscosity syndrome such as vision loss, headache, dizziness and, epistaxis. Upon examination, her morphology, biochemistry, histology, flow cytometry and serum protein electrophoresis indicated WM complicated with hyperviscosity syndrome. **Results:** The patient was successfully treated with a combination chemotherapy and plasmapheresis. **Conclusion:** Hyperviscosity syndrome manifestations should be treated with plasmapheresis.

**Keywords:** Immunoglobulin M, Plasma Cells, Plasmapheresis

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## Introduction

Waldenstrom Macroglobulinemia (WM) is a malignant disease of the B lymphocytes. It is characterized by the presence of a lymphoplasmocytic infiltrate in the bone marrow and the presence of a high level of a monoclonal immune globulin (IgM) in serum. WM is relatively rare disease (1-2% of hematologic malignancies) and approximately 3 cases occur in 1 million people [1, 2]. It has a low chance of being treated by chemotherapy. Monoclonal antibody therapy and hematopoietic stem cell transplantation

can increase the overall survival of the patient [3].

Proliferation of lymphoplasmocytes is caused by a MYD88 gene mutation in the post-germinal zone of lymphopoiesis. MYD88 gene mutation occurs in most patients, but it is not a useful diagnostic tool of WM [4-6]. About 25% of patients are asymptomatic at clinical presentation and are diagnosed incidentally from routine blood work. In physical examination, hepatomegaly, splenomegaly, lymphadenopathy, bleeding, anemia and hyperviscosity syndrome (HVS) may occur alone or simultaneously. The clinical presentation of HVS consists

principally of the triad of mucosal bleeding, visual changes, and neurologic symptoms [7-9].

No definitive etiology exists for WM, but infection of hepatitis C virus, autoimmune diseases and usage of some pesticides have been associated with an increased risk of developing the disease [10, 11]. The laboratory diagnosis of WM is contingent upon demonstrating a significant monoclonal IgM protein, infiltration of small lymphocytes, and lymphoplasmacytoid cells or plasma cells in the bone marrow. The pattern of infiltration is diffuse, nodular or interstitial. The surface expression of B-cell differentiation markers are immunophenotypes such as CD19+, CD20+, sImM+, CD5-, CD10-, and CD23- [3, 10, 12]. Treatment consists of a combination of chemotherapy with or without monoclonal antibody and hematopoietic stem cell transplantation. The treatment of choice for symptoms related to hyperviscosity is urgent plasmapheresis [3].

There is no statistical data of WM available in Mongolia. The aim of this case report is to introduce a patient with WM complicated with HVS from our clinical practice in Ulaanbaatar, Mongolia.

## Case Report

The patient was a 28 year-old female with a seven-month history of fatigue and fever with unknown etiology. She was misdiagnosed with liver cirrhosis caused by hepatitis C virus due to a low level of albumin in serum and was treated in the Department of Internal Medicine. However, she did not respond treatment and her situation worsened with loss of vision, epistaxis, dizziness, headache and severe anemia in CBC. The patient was scheduled to receive a blood transfusion, but the blood transfusion was cancelled due to mismatches in compatibility testing. Subsequently a hematologist was sought. After admission to the Hematology Department, it was difficult to the evaluate patient's laboratory tests because the hematological analyzers could not detect patient's blood cells due to hyperviscosity. Therefore, we diluted the patient's blood for testing.

Her biochemistry showed a total protein of 117.55 g/L, with a hypoalbuminemia of 22 g/L and her IgM was elevated at 54.32 mmol/L. Normo-chromic-normo-cytic anemia was suggested on CBC, with her RBC and HGB being low at  $3 \times 10^6/\mu\text{L}$  and 86 g/L, respectively. Her bone marrow smear revealed

rouleaux formation, increased lymphocytes at 46.9% and plasmacytes at 7%. The flow cytometry of her bone marrow sample demonstrated that lymphoid cells were CD138, CD20, CD3, CD38, and CD19 positive.



**Figure 1.** Funduscopy examination revealing several hemorrhages in retina of the eyes.

Hepatomegaly, splenomegaly and enlargement of kidneys were detected in abdominal ultrasound. Several hemorrhages were detected in the retina and vitreous body on funduscopy examination (Figure 1).

Based on these findings, the patient was diagnosed with WM and treated with plasmapheresis due to the hyperviscosity of ocular disturbance. The plasmapheresis was done 3 times. Then patient started combination chemotherapy of BRD (bortezomib, rituximab, dexamethasone) and monoclonal antibody (rituximab) therapy. After 3 cycles of combination chemotherapy, the patient's situation improved. Her serum protein decreased to within the normal range (Table 1), her lymphocytes became 5.6% in the bone marrow, her spleen size was decreased, and her vision was improved, but not completely.

**Table 1.** Patient’s main laboratory tests and ultrasound imaging at diagnosis, during therapy and after therapy

Parameter	Before treatment	During treatment	After treatment
Total protein (g/L)	117.5	97.4	78.0
Albumin (g/L)	22	27	28
IgM (mmol/L)	54.3	-	-
Creatinine (mg/dL)	0.35	0.26	0.35
Calcium (mmol/L)	1.78	2.06	2.04
RBC (10 <sup>6</sup> /μL)	3.0	3.9	3.7
HGB (g/L)	86	95	98
PLT (10 <sup>3</sup> /μL)	285	142	288
Spleen (cm)	23.5	19.0	16.0
Lymphocytes in bone marrow (%)	36.4	46.9	5.6

Between the 2nd and 3rd cycle of chemotherapy, it was possible to perform serum protein electrophoresis (SPEP) in our laboratory, so we evaluated the patient’s serum proteins (Table 2, Figure 2).

In SPEP, the alpha-1, alpha-2 and beta-1 fractions increased, a monoclonal peak was present in the gamma fraction, and a beta-gamma bridge was present. Total protein was increased to 92.2 g/L (60-83 g/L) and albumin to globulin ratio was decreased to 0.5 (1.2-2.0).

**Table 2.** SPEP results for the patient compared to reference ranges

Fractions	Percent (%)	Reference percent (%)	Concentration	Reference concentration
Albumin	33.2	55.8-66.1	30.6	40.2-47.6
Alpha-1	6.4	2.9-4.9	5.9	2.1-3.5
Alpha-2	11.3	7.1-11.8	10.4	5.1-8.5
Beta-1	8.3	4.7-7.2	7.6	3.4-5.2
Beta-2	6.7	3.2-6.4	6.2	2.3-4.7
Gamma	34.1	11.1-18.8	31.4	8.0-13.5

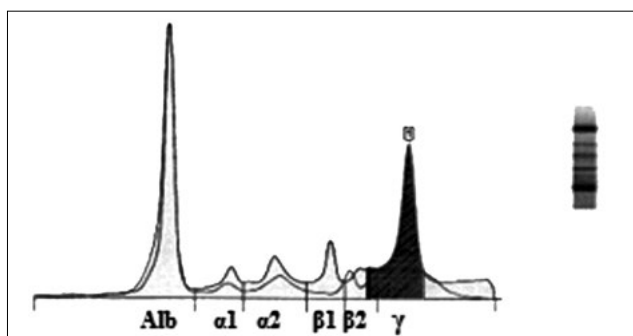


Figure 2. SPEP demonstrating a monoclonal component with beta-to-gamma mobility (Clinical Laboratory, First Central Hospital of Mongolia).

## Discussion

As mentioned previously, no definitive etiology exists for WM. Environmental, familial, genetic, and viral factors have been

reported. Hepatitis C and human herpes virus 8 have been implicated. However, there is no strong data supporting a causative link between these viruses and WM.

The tendency to bleed is the most common manifestation

of HVS. Mucosal bleeding may occur due to prolonged bleeding time caused by monoclonal proteins interfering with platelet function. Visual changes range from blurred vision to vision loss. Neurologic manifestations are headaches, vertigo, hearing loss and parasthesias [13]. Confusion and mental-status changes result from the increased viscosity of the blood and decreased cerebral blood flow. This sludging leads to segmental dilation of retinal veins and retinal hemorrhages.

The diagnosis of HVS is confirmed by measurement of elevated serum viscosity and other laboratory tests such as biochemistry and electrophoresis. HVS manifestations should be treated promptly, and emergent care is paramount [12]. The principle behind management is that 80% of all IgM is confined to the intravascular space. Most often, half of the volume or more should be removed to significantly lower the serum viscosity.

In our clinical practice, we successfully diagnosed and treated WM for the first time. The WM is caused by IgM paraprotein and malignant lymphoplasmocytic cell infiltration of the bone marrow. HVS occurs due to high level of monoclonal protein-IgM in the blood. Plasmapheresis is the treatment of choice for initial management and stabilization of HVS. A limitation of this case report was that measurement of serum protein fractions was made after combination chemotherapy and plasmapheresis. Future direction of our study is to diagnose paraproteinemia with SPEP.

## Conflict of Interest

The authors state no conflict of interest.

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