Journal of Investigative Medicine High Impact Case Reports
Volume 10: 1–7

DOI: 10.1177/23247096211052187
journals.sagepub.com/home/hic
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Blurry Vision as a Presentation of Waldenström's Macroglobulinemia: A Case Report With Review of Current Management

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Abstract

A patient was diagnosed with Waldenström's macroglobulinemia (WM) after the initial findings of anemia and ophthalmological findings of retinal hemorrhage. Upon further workup, the patient was found to have an IgM predominant monoclonal gammopathy on serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP). This highlights the need for open communication between different specialties, streamlining rapid and accurate diagnosis. Also highlighted are the unique pathophysiological changes involved in the development of WM. A patient's primary complaint was blurry vision. After the patient was noted to have a monoclonal gammopathy on SPEP, bone marrow biopsy was performed. The bone marrow biopsy findings were consistent with lymphoplasmacytic lymphoma (LPL). The patient received plasmapheresis and chemotherapy. The disease course is described. The patient saw rapid improvement in all lab abnormalities after the beginning of the appropriate therapy of plasmapheresis and chemotherapy. Remission is common with WM. Regular follow-up with this patient is important.

Keywords

hematology oncology, ophthalmology, pathology

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Introduction

Waldenström's macroglobulinemia (WM) is non-Hodgkin lymphoma characterized by a clonal population of lymphoid cells that secrete monoclonal IgM antibodies. The elevated IgM protein can lead to increased serum viscosity which increases the resistance of blood to flow. The resulting hyperviscosity syndrome (HVS) can result in end-organ complications such as stroke, retinal hemorrhage, or other neurologic findings such as nystagmus, tinnitus, or ataxia.[1-3] Studies have shown that IgM levels greater than 3000 mg/dL lead to the highest risk of complications.[1-5]

Plasma cells are responsible for the secretion of polyclonal antibodies responsible for humoral immunity. WM and multiple myeloma cause end-organ damage due plasma cell hyperproliferation and secretion of immunoglobulins. Typically, the plasma cells in multiple myeloma produce a monoclonal spike of an immunoglobulin component with IgG or IgA heavy chain subtypes. Unlike multiple myeloma, WM is characterized by the monoclonal secretion of IgM.

Case Report

A 59-year-old man presented to the Veterans Administration ophthalmology clinic with progressive blurry vision for 7 months. On dilated retinal examination, there was extensive bilateral retinal hemorrhage noted (Figure 1). The remainder of the physical examination was without abnormality. The patient's medical history was significant for hypertension, hyperlipidemia, and a seizure disorder related to head trauma approximately 30 years prior to presentation.

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Received June 24, 2021. Revised September 5, 2021. Accepted September 21, 2021.

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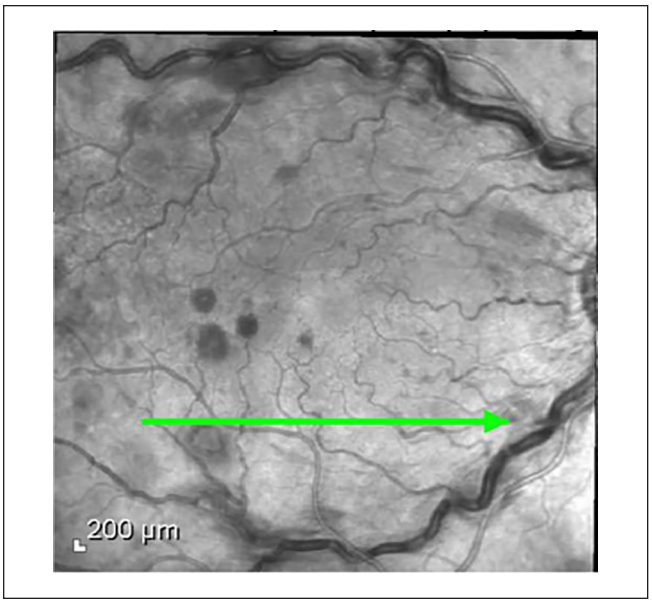

Figure 1. Fundoscopic exam findings of the patient's retina showing retinal hemorrhages.

There was a concern for a hyperviscosity state as the cause for the retinal changes and the patient was referred to hematology. On evaluation in the clinic, he did not have weight loss, fevers, chills, night sweats, abdominal pain, weakness, or paresthesia, but did report some easy bruising. The physical examination was notable for some scattered patches of ecchymosis on the forearms. A complete blood count showed normocytic, normochromic anemia with hemoglobin (Hgb) of 8.1g/dL (normal= 14.0-18.0 g/dL); a Hgb value from 2 years prior was normal. A serum protein electrophoresis (SPEP) revealed a monoclonal protein (M spike) of 2.97 g/dL (normal= 0.0 g/dL) characterized as IgM by immunofixation. The IgM on quantitative immunoglobulin assessment was 6700 mg/dL (41-255mg/dL). Serum viscosity was 5.43 centipoise (cP) (normal=1.1 – 1.4 cP). A bone marrow aspiration was attempted, but a "dry tap" resulted and only core biopsies were obtained.

The patient was admitted in order to expedite a start of 1.5 times plasma exchange with plans to start chemotherapy for the presumptive diagnosis of WM on the basis of elevated serum IgM and viscosity values in the setting of retinal hemorrhage.

Flow cytometry immunophenotyping on the patient's bone marrow core biopsy detected a monotypic, small-sized, CD5-/CD10- B-cell population. The patient's marrow was hypercellular for age with cellularity approaching 80% to 90%. An infiltrate of CD20+/CD5-/CD10-/Cyclin D1- small-sized B lymphocytes replaced 60-70% of the marrow, with the remainder showing decreased trilineage hematopoiesis (Figure 2-5). Polymerase chain reaction testing performed on core biopsy was positive for the MYD88 L265P mutation.

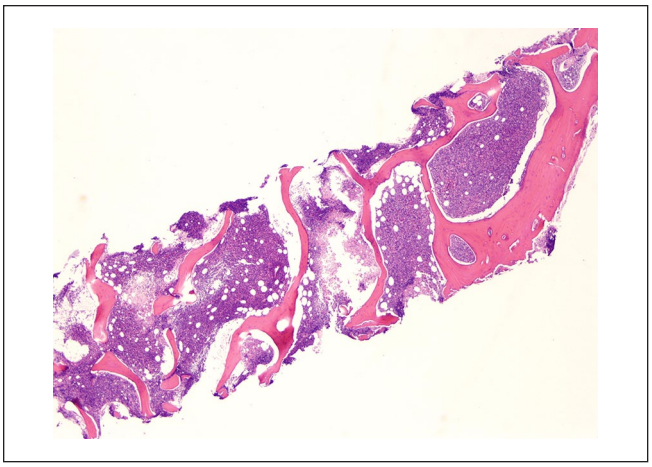

Figure 2. A micrograph (20 x) of bone marrow core biopsy obtained from the patient depicting hypercellular marrow with a diffuse infiltrate of small lymphocytes.

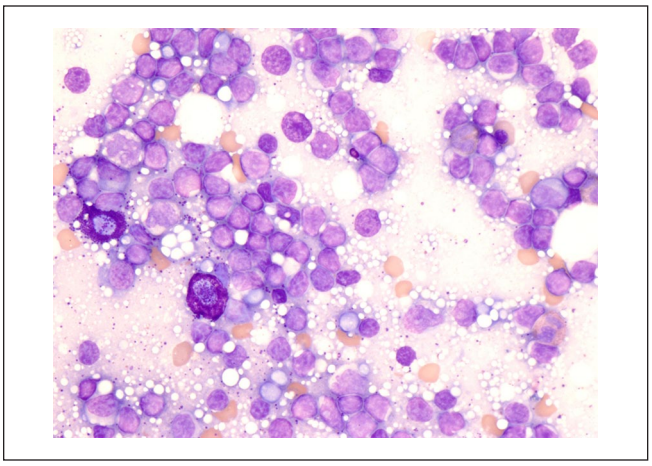

Figure 3. Core biopsy of patient's bone marrow prepared with a touch preparation (Wright stain).

These findings were supportive of a diagnosis of lymphoplasmacytic lymphoma (LPL) with WM.

Following plasma exchange, his IgM and serum viscosity decreased to 4,170 mg/dL and 1.98 cP, respectively. Rituximab and bendamustine (BR) were then initiated. Following 1 cycle of BR, the patient reported no worsening of vision changes and had a continued decrease in quantitative IgM value (3,020 mg/dL) as well as a decrease in M spike (1.37 g/dL). He went on to continue BR every 28 days for 4 cycles in total. He tolerated therapy well without adverse effects. On laboratory evaluation, his quantitative IgM and M spike were near normal reference range and almost undetectable, respectively, before his last cycle of BR. His Hgb improved while on BR and returned to near normal (13.9 g/dL) after completion of BR; the Hgb continues to remain in the normal ranging around 14 to 15 g/dL.

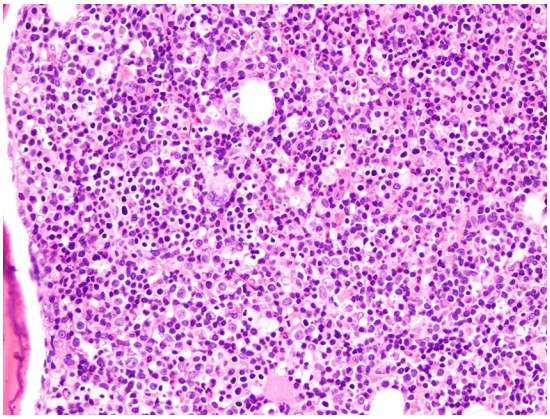

Figure 4. Hematoxylin and Eosin-stained core biopsy of patient's bone marrow showing mostly small-sized lymphocytes and decreased trilineage hematopoiesis.

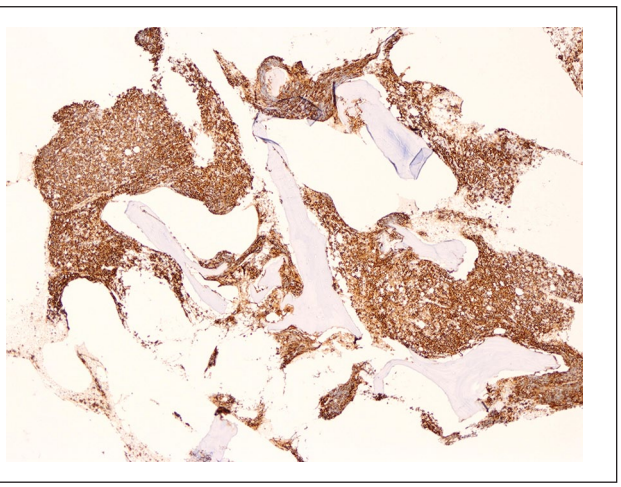

Figure 5. A micrograph of a core biopsy sample of the patient's bone marrow with immunohistochemical stain for CD20+ cells depicting a diffuse infiltrate of CD20+ small B lymphocytes.

One year after completion of BR, the IgM is no longer elevated, and an M spike is not detectable. (Table 1) Clinically, his blurry vision has resolved, and he remains fully active.

Discussion

Bone marrow involvement in LPL can have nodular, diffuse, interstitial, and occasionally paratrabecular pattern of infiltration. Contrast this with marginal zone lymphoma (MZL), which can also produce an IgM paraprotein and can be a challenge to distinguish from LPL/WM. MZL has a nodular, nonparatrabecular infiltration pattern in 75% of patients. Both are characterized as CD20¬+ cell populations that are negative for CD5 and CD10. Working closely with an experienced hematopathologist is important for making this distinction as this can affect therapy choice.

MYD88 and CXCR4 mutations are identified in 90% and 30% to 40% of LPL patients, respectively but are rare in other IgM secreting B cell malignancies.[6] The MYD88 gene encodes for the MyD88 protein, which functions to transfer signals from the extracellular environment to the appropriate intracellular targets.[7] Among these signal transductions, MyD88 is involved in the signaling cascade of toll-like receptors and interleukin-1 (IL-1), 2 important pathways within the innate immune system. MYD88 is also implicated in the nuclear factor-kappa-B signaling cascade, a fundamental pathway in the expression of pro-inflammatory and pro-inflammatory reactions. MYD88 is also notable for its anti-apoptotic properties.[8]

MYD88 L265P mutations are also present in >90% of patients with WM. The MYD88 L265P mutation is a gain-of-function mutation. The increased anti-apoptotic pathway combined with the pro-immunomodulatory capabilities of this protein introduces an "oncogenic spark" and clonal cell proliferation. Fortunately, the presence of the MYD88 mutation is associated with better prognoses when compared to its mutation-negative counterparts.[9,10]

CXCR4 is a surface receptor that functions as a G-protein coupled receptor. Among its functions is to act as a receptor for the homing peptide, stromal cell-derived factor-1 (SDF-1). SDF-1 acts as a signal designating the B-cell migration to the bone marrow. The mutant CXCR4 also aids in the adhesion of B-lymphocytes to the bone marrow stroma resulting in the hypercellular, plasmacytic bone marrow of WM.[9,11-13]

WM has an incidence of approximately 3 cases per one million people per year. About 1400 new cases are diagnosed in the United States per year, comprising of 2% of all cases of non-Hodgkin's lymphoma.[1,3] Compared with other ethnic groups, WM is more common in Caucasians. For example, approximately only 5% of cases are Black. Majority of patients are male, comprising of about 60%. This is a disease of older individuals as less than 10 percent of patients are less than 50 years of age, and the median age at diagnosis is 70 years old.[2,14]

WM is felt to be an incurable disease. However, it is common that an individual patient's life can be significantly prolonged with a median survival of 8.2 years. Fortunately, this median survival rate has been increasing, up from 7 years in 1991 to 2001.[14] When a patient is diagnosed with WM, an international scoring system for WM is used to assess their overall prognosis, and patients are categorized into low, intermediate, and high risk based on age greater than 65, β2-macroglobulin greater than 3 mg/L, anemia (Hgb ≤ 11.5 g/dL), platelet less than 100,000, serum monoclonal protein concentration (IgM > 7 g/dL), granulocyte level (≤1.5 x 109/L), and albumin level (≤3.5 g/dL). Patients are a low risk if they have one of the factors above and is less than 65 years old, intermediate risk with 1 to 2 factors above and age is greater than 65, and high

Table 1. Gross Data for Treatment Response.

Date	Days post Clinical Presentation	IgM	Monoclonal protein	Gamma globulin fraction	Serum protein	Hemoglobin	WBC	Platelets
1/1/2019								
5/30/2019	0					12.9	7.4	127
7/10/2019	41					8.1	6.4	
7/17/2019	48		2.97	4.41	10.5	9.1	6.8	
7/24/2019	55		2.78	4.78	10.7	8.4	5.9	
8/8/2019	70					12.6	6.8	118
9/9/2019	102	3020	1.37	2.05	7.6	10.4	1.8	100
10/7/2019	130	1440	0.58	1.04	6.8	12.1	2.3	123
11/4/2019	158	234	0.14	0.43	6.2	13.9	1.8	98
12/2/2019	145	94.7	0.05	0.32	6.4	14.1	0.9	127
12/16/2019	159	70.5	0.03	0.3	5.9	14.2	2.7	119
8/5/2020	392	15.4	0	0.26	6	15.5	3.9	199

Abbreviations: WBC, white blood cells.

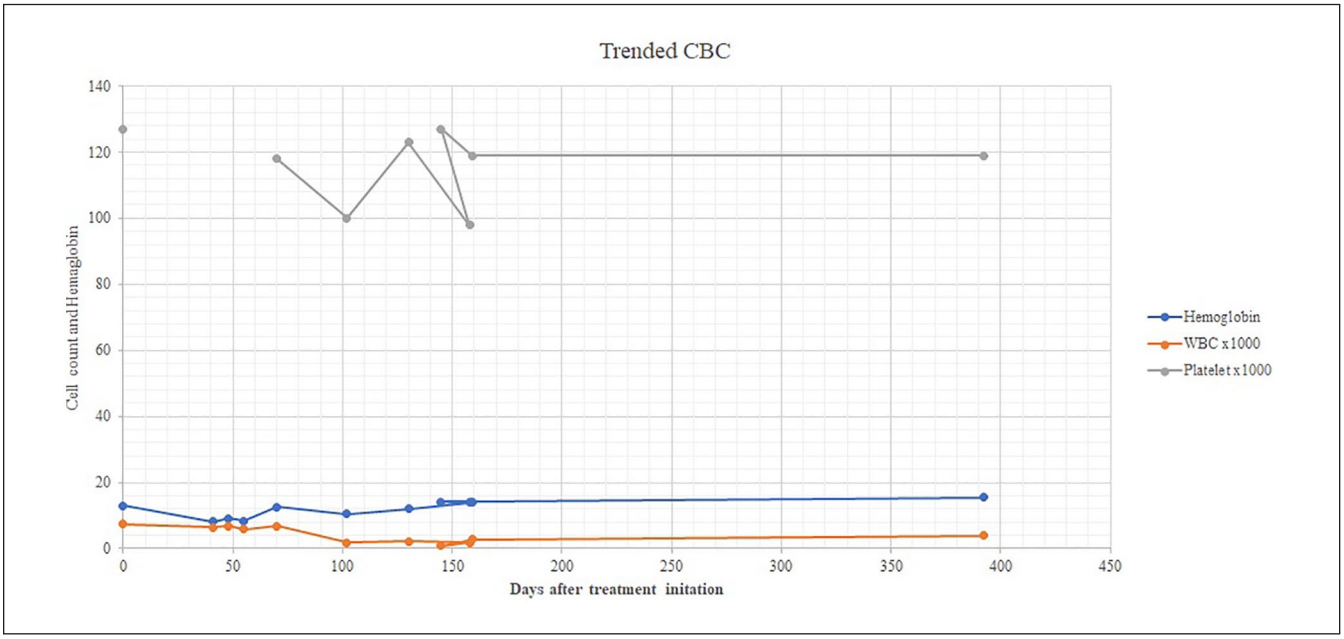

Figure 6. This depicts the patient's baseline anemia showing the hemoglobin, hematocrit, red blood cell count $(x10)^3$, and white blood cell count $(x10)^3$ and the trends that follow treatment initiation at x = 0 days.

risk if they have 3 or more of the above-mentioned factors. The 5-year survival for the aforementioned risk groups is 87%, 68%, and 36%, respectively.[15]

WM has a well-described association with chronic inflammatory states, such as those seen in autoimmunity, infection, and familial histories of similar nature. Persons with a personal history of an autoimmune disease has an increased risk of WM, specifically: Sjogren syndrome, autoimmune hemolytic anemia, giant cell arteritis, polymyalgia rheumatica, systemic sclerosis, or other chronic inflammatory disorders.[16] First-degree family members of patients with WM have an increased frequency of developing WM; although, the absolute risk remains low. In 1 large database, the diagnosis of WM was 15.8-fold higher among first-degree relatives than among the general population.[16]

HVS associated with WM is largely attributed to increased serum IgM concentration. As the quantity of IgM increases, the immunoglobulin forms complexes with water. This increases the plasma oncotic pressure. Also, immunoglobulins are positively charged. This leads to electrostatic interactions with red blood cells. With the effects on oncotic pressure and electrostatic interactions, immunoglobulins cause dysfunctional blood transit, congestion of microvasculature, and downstream tissue ischemia.[17-19]

HVS is described with a "classic triad" of visual disturbances, neurologic symptoms, and bleeding. Neurological

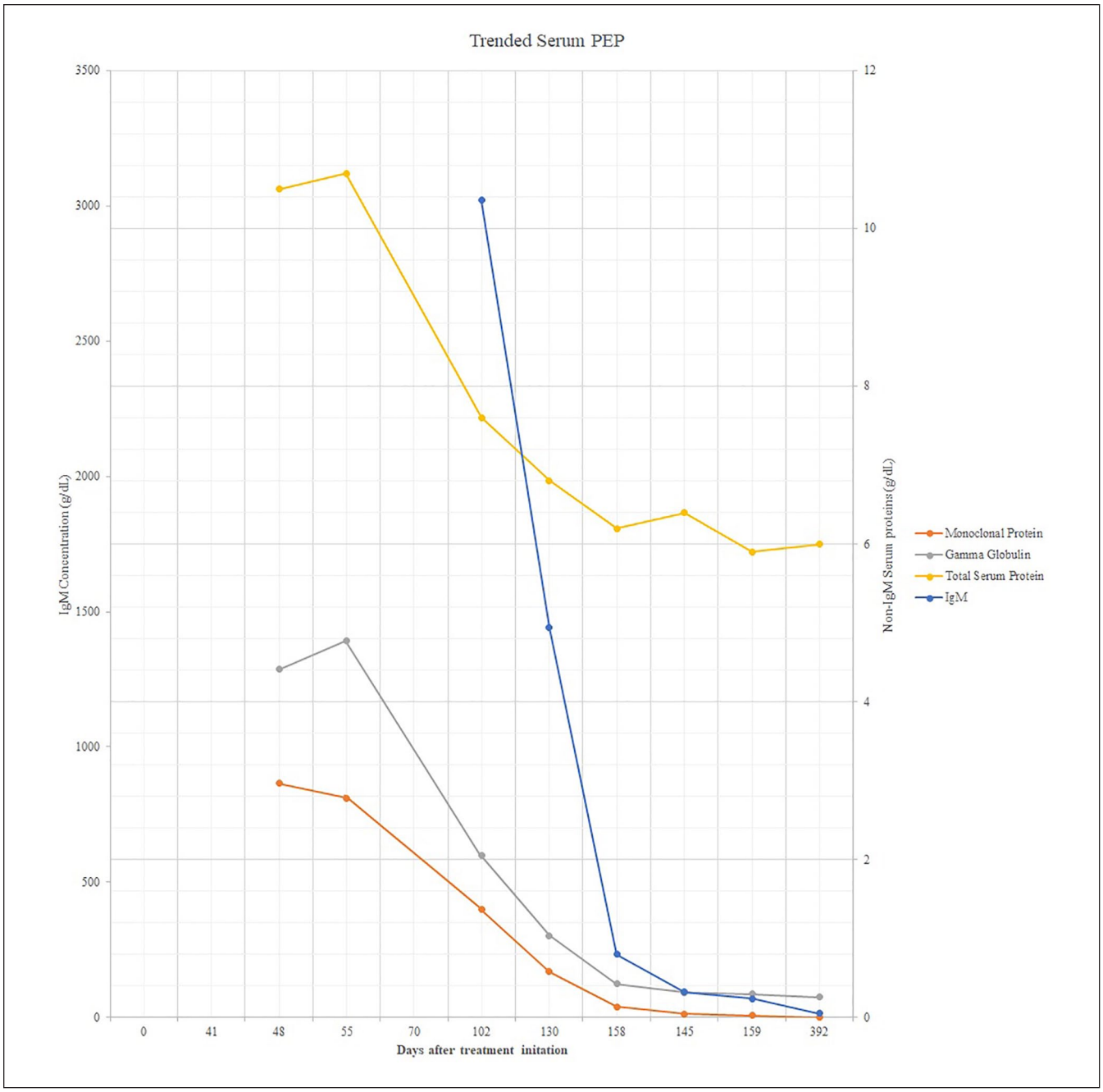

Figure 7. This depicts the serological findings and the trends that follow treatment initiation. IgM, total serum protein, monoclonal protein, and gamma globulin fraction are shown trending toward normal limits.

symptoms can be attributed to decreased microcirculation in the brain. The symptoms include headache, altered mental status, nystagmus, vertigo, seizures, or coma.[17] Visual symptoms include blurry vision caused by dilated retinal veins that can eventually become occluded and hemorrhage.[18] Bleeding is caused by paraproteins coating thrombocytes and inducing platelet dysfunction.[19]

Interestingly, there is no clear relationship between serum viscosity and symptomatology. Symptoms are absent in nearly one-third of patients with serum viscosity of 4 cP or greater.[20,21] Unfortunately, there is limited data on the long-term prognosis of the visual disturbances associated with HVS. However, there are a few case reports that suggest visual disturbances are largely reversible with early detection and treatment of HVS. It is reassuring that these cases represent similar results as the patient presented in this case.[22,23]

Plasmapheresis is indicated in symptomatic patients or in those with end-organ dysfunction caused by HVS. It is especially recommended to precede chemotherapy in

patients who require immediate paraprotein control such as our patient. For example, in patients who received rituximab for WM, a so-called IgM "flare" can occur in which the IgM will temporarily rise before declining: rituximab-induced IgM flare can occur in 40% to 60% WM patients which can worsen or accentuate IgM-related HVS.[6] As such, plasmapheresis is also recommended in patients with a serum IgM $\geq$ 4000 mg/dL to preempt this flare phenomenon. Patients with HVS are considered a medical emergency, thus, they require plasmapheresis to decrease IgM more quickly than can be achieved with chemotherapy alone.[6] It is important to recognize that patients often have decreased red blood cell counts; however, there is a risk of worsening the HVS with red blood cell transfusion. To mitigate the risk of intensifying HVS, transfusion should occur after plasmapheresis. Although, the risk of worsening HVS with transfusion is mostly theoretical.[6,24]

Rituximab is a monoclonal antibody targeting CD-20+ cells and depletes the B-cell population, via direct signaling, complement-dependent cellular cytotoxicity, and antibody-dependent cellular cytotoxicity.[23] In essence, rituximab is highly efficacious in the clearance of malignant B-cell populations and nonpathological B-cells. Rituximab can be used as a single agent treatment in patients not requiring immediate disease control. Single-agent rituximab therapy confers a median progression-free survival (PFS) of 16 to 29+ months.[1]

However, since our patient required rapid disease control, an alkylator-based regimen with bendamustine was utilized in combination with rituximab (BR). The combination has shown longer PFS (69 vs 29 months) when compared to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in WM patients.

If the patient were to relapse, single-agent ibrutinib is highly active in WM. This Bruton tyrosine kinase inhibitor has a specific activity against MYD88 L265P expressing cells. Ibrutinib blocks NF-kb signaling by inhibiting IkB-alpha phosphorylation, a downstream target of MYD88 L265P.[3] Ibrutinib in combination with rituximab has also been shown to be effective as treatment for patients with WM. The INNOVATE trial evaluated rituximab +/- ibrutinib in those who had not received previous treatment. At 30 months, the PFS and OS for ibrutinib plus rituximab was 82% and 94% respectively versus 28% and 92% in the placebo plus rituximab group. Patients with MYD88 L265P expression also showed improved PFS in the ibrutinib plus rituximab group.[25,26]

Treatment therapies are continuously evolving. New agents and regimens are currently being studied for the treatment of WM. Carfilzomib, a proteasome inhibitor, has been studied in a trial with rituximab and dexamethasone as front-line therapy in 28 patients with WM. At 15.4 months, OR was 87% and PFS was 64.5%. Ulocuplumab, a human monoclonal antibody against CXCR4, has been tested against xenografts and has shown anti-tumor activity against leukemia, lymphoma, and myeloma. This novel agent could potentially be used as a therapeutic approach for WM. With ibrutinib's success, second-generation BTKs with greater selectivity than ibrutinib are currently undergoing clinical trials such as acalabrutinib, BGB-3111, CC292, and ONO-4059.[3]

Conclusion

This patient presented with signs and symptoms of a rare lymphoma. Recognizing a diagnosis of WM early in the disease course, which often presents with subtle and protean signs and symptoms, can be difficult. But once diagnosed, several effective, emergent, and maintenance therapies are available. As outlined above, the patient's initial presentation was characteristic for WM and he had symptoms with objective findings of retinal hemorrhage, plasmapheresis was urgently initiated. After plasmapheresis, his serum viscosity, total protein, and serum IgM level were 1.98 cP; 5.4 g/dL; and 4,170 mg/dL respectively. After completion of chemotherapy the M spike resolved, and serum IgM levels trended down to normal limits as seen in Figures 6 and 7.

Duration of disease control can be unpredictable but can often last for several years before cytotoxic therapy needs to be re-introduced. The reappearance of the monoclonal protein in-and-of-itself is not necessarily an indication to start treatment again. Instead, re-initiation of therapy can be delayed until a patient develops symptoms such as fever, weight loss, or other clinical findings related to WM.

Authors' Note

MeSH: Macroglobulinemia, Waldenstrom; Lymphoplasmacytoid Lymphoma; Paraproteinemia; Monoclonal Gammapathy; Dyscrasia, Plasma Cell

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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