Diagnosis of Waldenström macroglobulinemia

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ABSTRACT

Waldenström macroglobulinemia is a rare disorder affecting about 1400 people annually in the United States. This case report reviews from a primary care provider's perspective the initial presentation of a patient who complained of fatigue and dizziness that ultimately led to hospital admission with a diagnosis of Waldenström macroglobulinemia. The referral to hematology/oncology prompting the bone marrow biopsy that led to the diagnosis highlights the important role of the primary care provider in the initial workup, coordination among specialists, and overall management of patients with rare disorders.

KEYWORDS Anemia; bone marrow biopsy; hyperviscosity; lymphoplasmacytosis; non-Hodgkin lymphoma; Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM) is a rare disorder.^{1,2} A recent study cited an incidence of 1400 cases per year in the USA.¹ With no clearly identified etiology, WM results in the abnormal infiltration of bone marrow with clonal lymphoplasmacytic cells, giving rise to the classic monoclonal immunoglobulin (Ig) M gammopathy. Initial clinical manifestations range from a relatively asymptomatic status to nonspecific constitutional symptoms.³ This case report reviews, from the perspective of a primary care provider (PCP), the initial presentation of a patient who was ultimately diagnosed with WM.

CASE DESCRIPTION

A 54-year-old man with prior hyperlipidemia, gout, and tobacco and alcohol abuse presented to his PCP's office with chief complaints of progressing fatigue, dizziness, and dyspnea over the past 3 months. Splenomegaly was absent and there was no obvious lymphadenopathy. A complete blood count revealed pancytopenia with a white blood count of $3.6 \times 10^9/L$, hemoglobin of 6.6 g/dL, and platelet count of $43 \times 10^9/L$. He was admitted for further evaluation and possible blood transfusion.

Upon arrival at the hospital, several tests were ordered, including comprehensive metabolic panel, vitamin B12, folate, thyroid-stimulating hormone, haptoglobin, HIV antibodies, and reticulocyte count. The normal reticulocyte

count of 1.6 (reference range 0.5–2.2) in the setting of pancytopenia reinforced the concern for a bone marrow disorder (Table 1). Given the low hemoglobin, he was given 2 units of packed red blood cells and a hematology/oncology consult was ordered. Initial recommendations included obtaining a peripheral blood smear, serum viscosity, flow cytometry, immunofixation, and bone marrow biopsy. The peripheral blood smear showed marked Rouleaux formation, with thrombocytopenia, neutropenia, and few reactive lymphocytes. Serum viscosity came back elevated at 4.2 units, prompting an ophthalmology consult for evaluation of retinal hemorrhages. A dilated funduscopic examination showed areas of vitreous heme, not likely visually significant, and no breaks or tears in the retina. The absence of retinal venous engorgement and “sausaging” was not specifically mentioned. However, given a viscosity level >4 , plasmapheresis was performed. Immunoglobulin tests showed an IgM level of 6162 mg/dL and an IgA level of 51 mg/dL. Flow cytometry showed an immunophenotype with a lambda-restricted B lymphoid population positive for CD19 and CD20 and partially positive for CD10, CD22, and CD23, with no phenotype evidence of myeloid immaturity.

The patient was started on dexamethasone and throughout his admission remained relatively asymptomatic. The diagnosis of WM was discussed in detail with the patient by hematology/oncology, along with treatment with rituximab and close outpatient follow-up. Per hematology/oncology recommendations, the patient underwent plasmapheresis prior to

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Table 1. Abnormal admission laboratory results

Test	Value	Reference range
White blood cells ($10^9/L$)	3.3	4.8–10.8
Red blood cells ($10^{12}/L$)	1.86	4.70–6.10
Hemoglobin (g/L)	6.2	14.0–18.0
Hematocrit (%)	18.0	42.0–52.0
Mean corpuscular volume (fL)	96.8	80.0–94.0
Red cell distribution width (%)	22.6	11.0–15.0
Platelet count ($10^9/L$)	43	150–450
Granulocytes ($10^9/L$)	1.22	1.92–8.64
Protein, total (g/dL)	10.4	6.0–8.0
International normalized ratio	1.2	0.9–1.1

treatment with rituximab to prevent any rituximab flare. The bone marrow biopsy result confirmed the presence of a lambda-restricted B lymphoid population, consistent with the diagnosis of WM. A major advance in WM during the past 5 years is the presence of a somatic mutation (*MDY88*) in over 90% of cases,⁴ which was not checked in our patient.

DISCUSSION

In many aspects, our patient exemplified a fairly classic WM presentation,⁵ other than the absence of symptoms secondary to hyperviscosity syndrome, the severity of thrombocytopenia, and age of diagnosis at 54 years, which is significantly lower than the reported median age of 70 years.⁶ In addition, his platelet count was $43 \times 10^9/L$, and <2% of patients have a count $\leq 50 \times 10^9/L$ at the time of presentation.⁷

In the setting of WM, hyperviscosity syndrome is likely due to the accumulation of large IgM antibodies in smaller capillaries causing vascular congestion, which produces the more frequent symptoms of visual disturbances, dizziness, and headaches. One small study found that no patient with plasma viscosity <3 had symptoms of hyperviscosity syndrome and that symptoms usually begin to develop when serum viscosity is >4.⁸ Our patient was asymptomatic despite an initial serum viscosity of 4.2. With a level >4, it was reasonable to screen for retinal hemorrhages, which prompted the ophthalmology consult and the need for the funduscopy examination. Garcia-Sanz et al reported that approximately 34% of patients with WM had funduscopy abnormalities.⁷ Though these findings likely included overt hyperviscous patients, further questions arise regarding the development of retinal pathology along the spectrum of developing hyperviscosity syndrome. This ought to prompt the PCP to have a low threshold for ophthalmology referral even in asymptomatic patients and those without definite hyperviscosity syndrome. The 2016 Annual International

Workshop on WM recommended that patients with serum IgM levels >3000 mg/dL be evaluated with funduscopy examination.⁹ For our patient, an ophthalmology referral was indicated based on a serum IgM of 6162.

Prognosis depends on the stage of the disease and treatment regimens. Several staging systems exist, including the International Prognostic Staging System, which is based on poorer prognostic factors defined as age >65 years, hemoglobin ≤ 11.5 g/dL (prompting transfusion to prevent possible tissue hypoxia), platelet count $\leq 100,000/\mu L$, beta-2 microglobulin >3 mg/L, and serum IgM >70 g/L. When this system was developed, only a small fraction of patients were being treated with rituximab, which has since become a cornerstone of treatment. Nevertheless, if applied to our patient, he would be considered “high risk” based on the presence of more than two risk factors, with an estimated 5-year survival rate of 36%.¹⁰ One study reported a 10-year survival rate of 66% for patients diagnosed from 2001 to 2010, an increase of 49% compared with patients diagnosed from 1980 to 2000.¹¹

This case report, unlike others,^{12,13} highlights PCPs’ involvement in both the clinic and hospital settings with the care of a patient from initial presentation with fatigue to final diagnosis of WM. It is important to consider hematologic/oncologic disorders as a potential etiology and thus a complete blood count should often be included in the basic laboratory evaluation. Although specific diagnosis and treatment regimens are often handled by hematology/oncology specialists, the PCP plays an important role in the initial workup, coordination among specialists, and overall management of the patient with WM.

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Avocations

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