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A Cold and Viscous Clue: Waldenström Macroglobulinemia Presenting With Secondary Cold Agglutinin Syndrome and Hyperviscosity Syndrome

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Abstract

Waldenström macroglobulinemia (WM) is an indolent mature B-cell lymphoproliferative disorder defined by bone marrow infiltration by lymphoplasmacytic lymphoma (LPL) and an associated serum monoclonal immunoglobulin M (IgM) gammopathy. In this case report, we describe a patient presenting with two serious and rare IgM-mediated complications of WM that require urgent treatment: secondary cold agglutinin syndrome and hyperviscosity syndrome. With prompt diagnosis and therapeutic plasma exchange, the patient's IgM-mediated complications improved, with a marked reduction in serum IgM and resolution of hyperviscosity-related symptoms. This highlights the importance of recognizing the possible complications of an otherwise indolent disease.

Categories: Hematology, Oncology
Keywords: hematologic emergency, hyperviscosity syndrome, lymphoplasmacytic lymphoma, secondary cold agglutinin syndrome, waldenstrom macroglobulinemia

Introduction

Waldenström macroglobulinemia (WM) is a rare disorder that accounts for approximately 2% of newly diagnosed non-Hodgkin lymphomas in the US. In the US, the population-based estimate is about three cases per million annually, corresponding to 1,000 to 1,500 new diagnoses [1]. It is predominantly a marrow-based process with symptoms arising from marrow infiltration, particularly anemia and other cytopenias. Many patients are asymptomatic at diagnosis, and fewer than 20% of cases present with lymphadenopathy and/or splenomegaly. Despite its generally indolent clinical course, WM may rarely present with clinically significant immunoglobulin M (IgM)-mediated complications that require prompt recognition and management [2,3].

In some patients, the monoclonal IgM paraprotein acts as a cold-reactive autoantibody, activating complement and causing cold agglutinin-mediated hemolysis and related symptoms [4]. Markedly elevated circulating IgM can also increase serum viscosity, resulting in hyperviscosity syndrome, with neurologic, visual, and mucocutaneous manifestations that may require urgent intervention, such as therapeutic plasma exchange [2,3]. In this case report, we describe a patient with newly diagnosed WM who presented with concurrent secondary cold agglutinin syndrome and symptomatic hyperviscosity syndrome, highlighting the importance of recognizing these potentially life-threatening IgM-mediated complications.

Case Presentation

A 46-year-old man without significant prior medical history presented to the emergency department with a two-month history of progressive fatigue and a one-day history of hematuria. He also reported intermittent drenching night sweats for approximately five years and recent cold-induced purple discoloration of his extremities consistent with acrocyanosis. On presentation, vital signs were within the normal limits. Laboratory results obtained in the weeks preceding presentation and at emergency department presentation revealed several marked abnormalities, as summarized in Table *1*. A complete blood count obtained approximately one month before presentation was unavailable because the specimen was reported as hemolyzed.

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Test	Day 1: Hospital Presentation	Day -28: Four weeks before presentation	Reference Range
White blood cell count (×10³/μL)	80.12 (High)	CBC specimen hemolyzed	4.16 - 9.95
Hemoglobin (g/dL)	7.0 (Low)	-	13.5 - 17.1
Mean corpuscular volume (fL)	120.4 (High)	-	79.3 - 98.6
Platelet count (×10³/μL)	112 (Low)	-	143 - 398
Absolute nucleated RBC count (×10³/μL)	0.49 (High)	-	0
Neutrophil (%)	4	-	-
Lymphocyte (%)	76	-	-
Monocyte (%)	20	-	-
Ferritin (ng/mL)	111	-	-
Iron saturation (%)	37	-	-
Folate, Serum (ng/mL)	9.8	-	8.1 - 30.4
Vitamin B12 (pg/mL)	374	-	254 - 1,060
Lactate dehydrogenase (U/L)	357 (High)	-	125 - 256
Haptoglobin (mg/dL)	<10 (Low)	-	21 - 210
Total bilirubin (mg/dL)	0.4	3.3 (High)	0.1 - 1.2
Total protein (g/dL)	11.7 (High)	10.5 (High)	6.1 - 8.2
Albumin (g/dL)	2.7 (Low)	3.2 (Low)	3.9 - 5
Creatinine (mg/dL)	1.3	1.11	0.6 - 1.3
Calcium (mg/dL)	9.5	9.7	8.6 - 10.4
Direct antiglobulin test (DAT)	IgG negative, C3 positive (3+)	-	-
Urine Color	Light-Red	-	-
Urine RBC	595 (High)	-	0 - 11 cells/μL
Urine RBC per HPF	108 (High)	-	0 - 2 cells/HPF

TABLE 1: Baseline Laboratory Values at Presentation and Pre-Admission

Day 1 denotes the day of hospital presentation. Day −28 denotes laboratory testing performed 28 days before presentation. CBC, complete blood count; IgG, immunoglobulin G; C3, complement component 3; HPF, high power field. Values outside the reference range are designated as (High) or (Low). A dash (-) indicates that a result was unavailable or not obtained, or that no reference range was applicable.

Laboratory evaluation demonstrated marked leukocytosis, thrombocytopenia, and severe anemia with an elevated automated mean corpuscular volume of 120.4 fL. Peripheral blood smear demonstrated moderate red blood cell agglutination and marked atypical lymphocytosis, composed predominantly of small- to intermediate-sized lymphocytes with condensed chromatin and plasmacytoid features. The observed red blood cell agglutination may have artifactually contributed to the elevated mean corpuscular volume. Anemia workup was notable for undetectable haptoglobin and elevated lactate dehydrogenase (LDH). The direct antiglobulin test (DAT) was strongly positive (3+) for complement component 3 (C3). Collectively, these findings were consistent with complement-mediated cold autoimmune hemolytic anemia and raised concern for secondary cold agglutinin syndrome in the setting of an underlying lymphoproliferative disorder. Urinalysis and urine microscopy confirmed the presence of red blood cells.

Hematology was consulted, and additional diagnostic studies were obtained. Pertinent results are reported in Table *2*.

Test	Reference Range	Results
Serum protein electrophoresis (SPEP)	-	Monoclonal protein, 6.5 g/dL (High)
Serum immunofixation (SIFE)	-	Monoclonal IgM Kappa protein present
Kappa light chain (mg/L)	3.3 - 23.22	44.93 (High)
Lambda light chain (mg/L)	4.66 - 26.3	7.91
Kappa/lambda ratio	0.26 - 1.65	5.68 (High)
Immunoglobulin G (mg/dL)	700 - 1,600	292 (Low)
Immunoglobulin M (mg/dL)	40 - 230	>5,850 (High)
Cold Agglutinin Screen (CAS)	-	Positive with incubation at 4 °C

TABLE 2: Extended Laboratory Evaluation at Presentation

SPEP, serum protein electrophoresis; SIFE, serum immunofixation; CAS, cold agglutinin screen; IgM, immunoglobulin M. Results outside the reference range are designated as (High) or (Low). A dash (-) indicates that a result was unavailable or not obtained, or that no reference range was applicable.

Although a cold agglutinin titer was requested, it could not be performed due to a preanalytical specimen issue; the specific reason was not available on retrospective review. The absence of a confirmatory cold agglutinin titer represents a diagnostic limitation. Peripheral blood flow cytometry identified a mature B-cell neoplasm that was CD11c and CD23 positive but negative for CD5, CD10, CD25, and CD103, confirming circulating involvement by a clonal B-cell lymphoproliferative disorder. In the context of marked lymphocytosis and atypical lymphocytes on the peripheral smear, the leukocytosis was attributed to circulating neoplastic B cells rather than to reactive lymphocytosis. Computed tomography (CT) scan showed marked splenomegaly, measuring 18 cm in craniocaudal dimension, and extensive retroperitoneal adenopathy. When the serum IgM level became available, the markedly elevated result raised concern for hyperviscosity syndrome. He subsequently developed epistaxis and a new-onset headache, prompting urgent therapeutic plasma exchange (TPE). Subsequent fundoscopic examination demonstrated bilateral retinal hemorrhages and microaneurysms, further supporting the diagnosis of symptomatic hyperviscosity syndrome.

The hematuria resolved spontaneously during hospitalization without specific intervention. Its relationship to the underlying lymphoproliferative disorder or its associated complications remained uncertain. Given its spontaneous resolution, subsequent evaluation and management focused on the newly diagnosed lymphoproliferative disorder and its urgent IgM-mediated complications.

Bone marrow examination was subsequently performed. It demonstrated a low-grade B-cell lymphoma with plasmacytic differentiation, involving about 70% of the marrow cellularity. Immunophenotyping identified kappa-restricted monotypic B cells with plasmacytic differentiation, positive for CD11c (partial, dim), CD23, CD38 (partial), CD138 (partial), and intracellular Vs38c (minor subset), plus PAX5, MUM1 (minor subset), and BCL2, and were negative for CD5, CD10, CD25, CD103, BCL1, SOX11, and BCL6. Biopsy of an enlarged retroperitoneal lymph node showed lymphoplasmacytic lymphoma with kappa-restricted B cells. Molecular testing showed MYD88 wild-type disease. Although the MYD88 mutation was not detected, MYD88 wild-type status does not exclude lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, as a minority of clinicopathologically confirmed cases are MYD88 wild-type [3]. In this case, the diagnosis was supported by the integrated findings of bone marrow involvement by a kappa-restricted B-cell neoplasm with plasmacytic differentiation, a retroperitoneal lymph node biopsy interpreted as lymphoplasmacytic lymphoma, and an associated monoclonal IgM-kappa gammopathy.

With five therapeutic plasma exchange sessions during hospitalization, the serum IgM level decreased from greater than 5,850 mg/dL to 1,970 mg/dL. Epistaxis and headache resolved. The patient subsequently received rituximab and bendamustine for WM and was discharged to continue lymphoma-directed therapy in the outpatient setting. Relevant laboratory trends in relation to therapeutic plasma exchange and chemotherapy are summarized in Table *3*.

Parameter	Reference range	Day 2	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Therapeutic plasma exchange	N/A	-	TPE #1	TPE #2	TPE #3	Held for retroperitoneal lymph node biopsy	TPE #4	TPE #5	-	-	-
Systemic therapy	N/A	-	-	-	-	-	-	-	-	Bendamustine 90 mg/m²	Bendamustine 90 mg/m² and Rituximab 375 mg/m²
Immunoglobulin M (mg/dL)	40 - 230	>5,850 (High)	-	>5,850 (High)	4,710 (High)	3,404 (High)	4,199 (High)	2,657 (High)	1,970 (High)	2,710 (High)	-
Hemoglobin (g/dL)	13.5 - 17.1	5.7 (Low)	8 (Low)	7.9 (Low)	8.7 (Low)	7.7 (Low)	8.5 (Low)	8.2 (Low)	7.1 (Low)	7.5 (Low)	7.6 (Low)
Total protein (g/dL)	6.1 - 8.2	10.8 (High)	12.0 (High)	9.3 (High)	8.5 (High)	7.6	8.1	7.1	6.7	6.3	7
Total bilirubin (mg/dL)	0.1 - 1.2	0.4	0.2 [a]	1.7 (High)[a]	1.2 [a]	0.9	0.5	1	1.3 (High)	0.7	0.6
Lactate dehydrogenase (U/L)	125 - 256	155	1,470 (High)[a]	1,685 (High)[a]	825 (High)[a]	299 (High)	154	126	225	169	202

TABLE 3: Laboratory Trends Relative to Therapeutic Interventions (Therapeutic Plasma Exchange and Chemotherapy)

Day numbers denote days of hospitalization, with Day 1 defined as the day of hospital presentation. TPE, therapeutic plasma exchange. On days when TPE was performed, all reported IgM measurements were obtained before the corresponding TPE session. [a] Lactate dehydrogenase and total bilirubin specimens obtained on Days 4-6 were reported by the laboratory as hemolyzed; therefore, these results may have been affected by in vitro hemolysis and should be interpreted cautiously. Bendamustine was administered at 90 mg/m² on Days 11 and 12, and rituximab was administered at 375 mg/m² on Day 12. TPE was withheld on Day 7 for retroperitoneal lymph node biopsy. Results outside the reference range are designated as high. A dash (-) indicates that a laboratory result was unavailable or not obtained, or that no intervention occurred on that day. N/A, not applicable.

Discussion

WM is a rare and indolent mature B-cell lymphoproliferative disorder. Although some patients are asymptomatic at diagnosis, most present with nonspecific manifestations, such as anemia, fatigue, and peripheral neuropathy that can be easily attributed to aging or coexisting medical conditions. These manifestations are typically related to marrow infiltration and/or the effects of the circulating monoclonal IgM protein. This case highlights the importance of recognizing hematologic emergencies in WM, which often have an indolent course. Symptomatic hyperviscosity and cold agglutinin-mediated hemolysis are recognized indications for WM-directed therapy, reflecting the clinical importance of both tumor burden and the concentration and biologic properties of the monoclonal IgM protein [3].

Although confirmatory cold agglutinin titer testing could not be completed in our patient, the combination of intermittent cold-induced acral symptoms, biochemical evidence of hemolysis, red blood cell agglutination on peripheral smear, and a strongly C3-positive DAT in the setting of newly diagnosed WM was clinically consistent with secondary cold agglutinin syndrome. Cold agglutinin-mediated hemolysis has been described in association with WM and may reflect the pathogenic activity of the monoclonal IgM paraprotein, supporting the interpretation of this patient's cold-induced symptoms and complement-mediated hemolysis [4].

In WM, the monoclonal IgM paraprotein may function as a cold-reactive autoantibody that binds erythrocyte I/i antigens and initiates complement-mediated hemolysis. Cold agglutinin binding occurs most avidly at low temperatures, typically 0-4 °C. However, clinical pathogenicity is primarily determined by the antibody's thermal amplitude, defined as the highest temperature at which the antibody remains reactive. Clinically significant IgM cold agglutinins may remain reactive at 28-30 °C, permitting binding to erythrocytes in the cooler peripheral vascular beds, including the fingers, toes, nose, and ears, particularly during colder weather. Clinical manifestations range from slight acrocyanosis to disabling Raynaud phenomenon. In rare cases, cold agglutinins retain activity at temperatures approaching 37 °C, which can lead to more extensive hemolysis. The associated hemolytic anemia may range from very mild to severe and can compound anemia caused by lymphomatous bone marrow infiltration [5,6].

In our patient, the markedly elevated IgM, together with new-onset epistaxis and headache, raised concern

for symptomatic hyperviscosity syndrome. The initial serum viscosity assay could not be completed because of a specimen-handling issue and was not repeated during this hospitalization; this is a limitation of the report. Given the compatible clinical presentation, therapeutic plasma exchange was initiated promptly and was not delayed pending serum viscosity testing.

IgM is a high-molecular-weight immunoglobulin that is predominantly pentameric in its secreted form. Its size, concentration, and polymeric structure can increase plasma viscosity, impair microcirculatory flow, and cause neurologic, visual, and mucocutaneous manifestations of hyperviscosity syndrome. These manifestations may include spontaneous or recurrent epistaxis, gingival bleeding, gastrointestinal bleeding, headache, tinnitus, hearing loss, paresthesia, blurred vision, and other symptoms. Retinal involvement may manifest as retinal venous dilation, tortuosity, classically described as “sausage-link” veins, as well as retinal hemorrhages and exudates. Severe hyperviscosity-related retinopathy may progress to retinal vein occlusion [5,7,8].

Serum viscosity can be measured with a blood test that assesses the resistance of serum to flow and is expressed in centipoise (cP). The upper limit of normal at our institution is 1.51 cP. Hyperviscosity-related symptoms are generally uncommon below 4 cP [3,8]. However, the diagnosis should be suspected based on compatible clinical manifestations in a patient with a paraprotein-secreting disorder rather than on serum viscosity measurement alone. In patients with a convincing clinical presentation, treatment should not be delayed while awaiting serum viscosity results [8].

For symptomatic hyperviscosity syndrome due to WM, urgent therapeutic plasma exchange is recommended. Plasma exchange rapidly removes circulating intravascular IgM and reduces serum viscosity. However, this effect is temporary and serves only as a bridge to disease-directed therapy that suppresses the production of the monoclonal IgM paraprotein. Systemic therapy should therefore be initiated promptly after clinical stabilization [8,9]. Common first-line treatment options for WM include bendamustine plus rituximab (BR) and Bruton’s tyrosine kinase (BTK) inhibitor-based therapy [3,9]. Rituximab should be used cautiously in patients with active or at risk for hyperviscosity syndrome because it can cause a transient IgM flare, which may exacerbate or precipitate hyperviscosity-related symptoms. In patients with serum IgM levels of approximately 4,000 mg/dL or greater, rituximab is generally withheld initially. Preemptive plasma exchange when clinically indicated and/or initial cytoreductive therapy with delayed introduction of rituximab may reduce the risk of IgM flare-associated hyperviscosity [8-10]. In our patient, five sessions of therapeutic plasma exchange were followed by bendamustine and rituximab after clinical improvement, consistent with this staged treatment approach.

Conclusions

Although WM is generally an indolent mature B-cell lymphoproliferative disorder and many asymptomatic patients can initially be managed with active surveillance, it may present with serious, potentially life-threatening IgM-mediated complications. This case underscores the importance of promptly recognizing clinical features of cold agglutinin syndrome and hyperviscosity syndrome, as early diagnosis and intervention can prevent significant morbidity. Clinicians should maintain a high index of suspicion for acute hematologic complications even in disorders traditionally considered indolent.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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