Initial Evaluation of the Patient with Waldenström Macroglobulinemia

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KEYWORDS

• Waldenström macroglobulinemia • Bone marrow aspiration • Anemia
• Hyperviscosity • Cryoglobulinemia • Peripheral neuropathy • Bing-Neel syndrome
• Amyloidosis

KEY POINTS

- The initial evaluation of the patient with Waldenström macroglobulinemia can be challenging.
- Not only is Waldenström macroglobulinemia a rare disease, but the clinical features of patients with Waldenström macroglobulinemia can vary greatly from patient to patient.
- The authors provide concise and practical recommendations for the initial evaluation of patients with Waldenström macroglobulinemia, specifically regarding history taking, physical examination, laboratory testing, bone marrow aspiration and biopsy evaluation, and imaging studies.
- The authors review the most common special clinical situations seen in patients with Waldenström macroglobulinemia, especially anemia, hyperviscosity, cryoglobulinemia, peripheral neuropathy, extramedullary disease, Bing-Neel syndrome, and amyloidosis.

INTRODUCTION

Given its rarity and a highly variable clinical presentation, the initial evaluation of the patient with a clinicopathologic diagnosis of Waldenström macroglobulinemia (WM) can be challenging. The clinical manifestations of WM can be associated with infiltration of the bone marrow and other organs by malignant lymphoplasmacytic cells and/or the properties of the monoclonal IgM paraproteinemia, and include anemia, hyperviscosity, extramedullary disease, peripheral neuropathy, cryoglobulinemia, cold agglutinemia, and coagulopathy, among others. It is important to note, however, that a substantial number of patients with WM can be asymptomatic at diagnosis.

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It is paramount to appropriately evaluate patients with WM to better inform the need for further evaluation, appropriateness of treatment initiation, and treatment options. The objective of this review was to succinctly summarize current recommendations with regard to initial evaluation of patients with WM. The recommendations provided herein are in line with those from the International Workshop for Waldenström macroglobulinemia and the National Comprehensive Cancer Network.

ESSENTIAL EVALUATION

The essential evaluation of the patient with a diagnosis of WM must include a history and physical examination, laboratory studies, bone marrow aspiration and biopsy, and computed tomography (CT) scans of the chest, abdomen, and pelvis with intravenous contrast.[1] It is important to note that there is no sign or symptom pathognomonic of WM. However, the presence of particular clinical findings can help to direct additional evaluation. Additionally, other causes of any sign, symptom, or laboratory or imaging finding should be further investigated to determine the likelihood of its relation to WM.

HISTORY

A careful and systematic history taking can provide information not only on the presence of constitutional symptoms such as fevers, night sweats, or unintentional weight loss, but also for potential alternative causes for these symptoms. Symptoms associated with anemia are very common in patients with WM, and include fatigue, malaise, and shortness of breath. Symptomatic hyperviscosity can induce recurrent episodes of spontaneous epistaxis, new-onset headaches, and blurred vision.[2] WM-related neuropathy is typically sensory and affects the feet more than the hands in a bilateral and symmetric pattern. If advanced and prolonged, it can manifest as muscle weakness and muscle wasting.[3] A history of skin color changes induced by exposure to cold temperatures may indicate the presence of cryoglobulins. Recurrent episodes of urticarial rash might be associated with Schnitzler syndrome.[4] Increased bruising or mucosal bleeding can be due to thrombocytopenia or acquired von Willebrand disease. Finally, recurrent upper respiratory infections might indicate secondary hypogammaglobulinemia.

PHYSICAL EXAMINATION

The physical examination can reveal lymphadenopathy and/or hepatosplenomegaly. Raynaud phenomenon or ulcers in the lower extremities or tip of the nose and ears can be manifestations of cryoglobulinemia.[2] Darkening of the urine after exposure to cold might be a manifestation of cold agglutinemia.[5] Skin examination might reveal urticarial rash, lymphomatous lesions, purpura, or bruising. A neurologic examination can reveal sensory or motor deficits in upper and lower extremities and can indicate peripheral neuropathy. Cranial nerve deficits can be a manifestation of Bing-Neel syndrome (BNS).[6] A funduscopic examination can reveal engorgement, increased tortuosity or “sausaging” of retinal vessels or retinal hemorrhages in patients with hyperviscosity.

LABORATORY STUDIES

Essential laboratory studies include a complete blood count, peripheral blood smear evaluation, complete metabolic panel, quantitative serum immunoglobulins (IgA, IgG, and IgM), serum and urine protein electrophoresis with immunofixation and beta-2-microglobulin level. The complete blood count can identify patients with WM with

anemia (common), thrombocytopenia (less common), or leukopenia (rare). Other causes of anemia, thrombocytopenia, and leukopenia should be investigated. High serum IgM levels can be associated with artificially low hemoglobin levels owing to volume expansion; transfusions should be avoided in these cases because they could increase serum viscosity.[7] Peripheral blood smear evaluation can show Rouleaux formation and, in rare cases, circulating lymphoplasmacytic cells. The complete metabolic panel can show renal dysfunction, which is rare in patients with WM, but can be associated with amyloidosis, monoclonal immunoglobulin deposition, and lymphoplasmacytic infiltration among others.[8] Rarely, WM can cause hepatic dysfunction. The serum IgM level is used to follow progression of disease or response to therapy and, in some cases, can be associated with a risk of hyperviscosity.[9] Low serum IgA and IgG levels (ie, hypogammaglobulinemia) can be seen in patients with WM at diagnosis.[10] Serum and urine protein electrophoresis with immunofixation will reveal an IgM monoclonal paraprotein, even in cases in whom serum IgM levels are normal. Beta-2-microglobulin levels can be prognostic of survival as a component of the International Prognostic Scoring System for Waldenström macroglobulinemia, along with age, hemoglobin level, platelet count, and serum IgM level.[11]

In special circumstances, additional laboratory testing can be helpful. Cryoglobulins should be obtained in patients with WM with clinical findings of cryoglobulinemia and cold agglutinins in patients with hemolytic anemia triggered by exposure to cold. However, the false-negative ratio of cryoglobulins and cold agglutinins is high, and the diagnosis is frequently made on clinical grounds. Serum viscosity can be measured in patients suspected to have symptomatic hyperviscosity.[12] Screening tests for acquired von Willebrand disease (ie, immunologic assays of von Willebrand factor [VWF], VWF ristocetin cofactor, and factor VIII procoagulant activity) should be obtained in patients suspected to have a bleeding diathesis.[13] Upon response to therapy for WM and with serum IgM levels decreasing, the levels of immunologic assays of VWF, VWF ristocetin cofactor, and factor VIII procoagulant activity do improve and, in many cases, normalize.[13] High levels of immunologic assays of VWF have been associated with worse prognosis in WM.[14] The role of serum free light chain measurements is unclear in WM and is recommended only in cases of suspected light chain amyloidosis. In cases of amyloidosis or monoclonal immunoglobulin deposition with glomerular damage, a 24-hour urine protein quantification might reveal albuminuria.

BONE MARROW ASPIRATION AND BIOPSY

A diagnosis of WM requires, in addition to a monoclonal IgM paraproteinemia, the presence of lymphoplasmacytic lymphoma in the bone marrow or other tissues.[15] A bone marrow aspiration and biopsy with immunophenotyping will help differentiate WM from IgM monoclonal gammopathy of undetermined significance, IgM multiple myeloma (MM) and IgM-secreting lymphomas such as marginal zone lymphoma.[16] The typical appearance of WM includes kappa or lambda light chain-restricted lymphocytes, lymphoplasmacytic cells, and plasma cells.[15] The malignant B-cells express CD19 and CD20 and rarely express CD5, CD10, or CD23, whereas the malignant plasma cells express CD38 or CD138 and show the same restricted light chain expression as the lymphocytic compartment.[17,18] Deletion 6q is the most common cytogenetic abnormality described in WM,[19,20] but it does not seem to have diagnostic or prognostic value. The bone marrow aspirate should be evaluated for the MYD88 L265P mutation, which is present in 90% to 95% of patients with WM,[21] and can help to further differentiate WM from other conditions. The MYD88 L265P mutation has also been described in 50% to 80% of individuals with IgM monoclonal

gammopathy of undetermined significance and in 5% to 10% of patients with marginal zone lymphoma, but not in patients with MM.[22,23] Therefore, the sole presence of the MYD88 L265P mutation is not diagnostic of WM. In contrast, the absence of MYD88 L265P mutation should not exclude the diagnosis of WM. About 5% to 10% of patients with WM will not have a MYD88 mutation, but would still meet the clinicopathologic criteria for WM and should be treated as such. Patients without MYD88 mutations have a worse outcome and have a higher risk for transformation to diffuse large B-cell lymphoma.[24] Rare cases of non-L265P MYD88 mutations have been described (approximately 2%), and should be managed as patients with MYD88 L265P mutation.[25] In about 40% of patients with WM, somatic mutations in the CXCR4 gene have been described.[26–28] Patients with WM with CXCR4 mutations tend to present with higher serum IgM levels, lower rates of extramedullary disease, and higher rates of hyperviscosity and acquired von Willebrand disease.[9,13] The presence of CXCR4 mutations have been associated with a longer time to response, lower rates of deep responses, and shorter response duration when treated with the oral BTK inhibitor ibrutinib.[29] CXCR4 mutations can also impact time to response and depth of response to ixazomib.[30] Testing for non-L265P mutations and CXCR4 mutations are not standard and not available in most laboratories.

COMPUTED TOMOGRAPHY SCANS

CT scans of the chest, abdomen, and pelvis with intravenous contrast are essential in patients with WM with suspected extramedullary disease, such as lymphadenopathy, hepatosplenomegaly, or pleural effusions, or in patients being considered for treatment initiation. If extramedullary disease is present, CT scans during and/or after treatment are advised to assess response. CT scans can be useful when differentiating an IgM flare from disease progression in patients treated with rituximab-containing regimens.[31,32] The role of PET/CT in WM is not well-established; however, it could be helpful in rare cases suspicious of transformation to diffuse large B-cell lymphoma, which can be seen in 2% to 3% of patients with WM.[33] In this context, areas of significantly higher 18F-fludeoxyglucose avidity are suspicious for aggressive transformation or other malignancies and should be biopsied accordingly.

SPECIAL SITUATIONS

This section provides guidance on the evaluation of special situations, specifically anemia, hyperviscosity and cryoglobulinemia, peripheral neuropathy, extramedullary disease and BNS, and amyloidosis.

ANEMIA

Anemia is the most common reason to initiate therapy in patients with WM. Anemia in patients with WM can be due to bone marrow replacement by the disease, iron deficiency, and/or hemolysis. In anemic patients with WM in whom the bone marrow burden of disease is low, another cause of anemia should be specifically sought. Iron studies (ie, iron, total iron-binding capacity, and ferritin) should be performed in all cases. In patients with absolute iron deficiency (low iron saturation and low ferritin level), gastrointestinal blood loss should be evaluated with upper, lower, and capsule (small bowel) endoscopies. In some patients, there can be evidence of functional iron deficiency (low iron saturation and normal/high ferritin level). WM cells can produce hepcidin, which is a regulator of serum iron content, inducing a mixture of absolute and functional iron deficiency.[34] In these cases, as long as there is no other criterion

to treat, intravenous iron supplementation can improve the anemia and delay WM-directed treatment.[35] Rarely, anemia can be secondary to hemolysis. In these patients, a hemolytic panel including reticulocyte counts, lactate dehydrogenase, haptoglobin, direct Coombs test, and cold agglutinins should be performed. In patients with severe cold agglutinemia, plasmapheresis should be started promptly to remove cold agglutinins. Other causes of anemia such as cobalamin and folate deficiency; renal, hepatic, or thyroid dysfunction; nonautoimmune hemolysis (eg, hemoglobinopathies); or other primary bone marrow processes should be ruled out.

HYPERVISCOSITY AND CRYOGLOBULINEMIA

Symptomatic hyperviscosity owing to high serum IgM levels can complicate the course of WM in 10% to 15% of patients and can have deleterious effects on the vision and neurologic function of patients.[9] The most common symptoms associated with hyperviscosity include recurrent spontaneous nosebleeds, headaches, blurred vision that does not correct with glasses, tinnitus, vertigo, and slow mentation.[12] Symptomatic hyperviscosity is rarely seen in patients with serum IgM levels of less than 3000 mg/dL.[9] In patients with serum IgM levels of 3000 or greater, obtaining serum viscosity and cryoglobulins can be helpful. Some patients are symptomatic at viscosity levels of 4 cP and most at 6 cP. A funduscopic examination must also be performed to evaluate for hyperviscosity-related changes in the retinal vessels, which can occur in asymptomatic patients. Patients with a serum IgM of 6000 mg/dL or greater have a median time to symptomatic hyperviscosity of 3 months and should be considered for therapy.[9] Plasmapheresis should be initiated promptly in patients with WM with signs and symptoms of hyperviscosity. Plasmapheresis, however, should be used only temporarily until definitive therapy for WM is instituted.[36] The most common manifestations of cryoglobulinemia include acrocyanosis, palpable purpura, livedo reticularis, nonhealing ulcers on the lower extremities, and discoloration of the tip of the nose and ears upon exposure to cold temperatures. Type I cryoglobulinemia is usually associated with WM, and type II is associated with hepatitis C infection. The presence of cryoglobulins can aggravate serum viscosity and should be evaluated while blood samples are at 37°C to prevent precipitation, which in turn can give falsely low IgM level and false-negative results.[2] Plasmapheresis will promptly remove cryoglobulins and provide symptomatic relief in these patients. Blood warmers might be needed in these patients to prevent cryoglobulin precipitation during plasmapheresis.[7]

PERIPHERAL NEUROPATHY

About 20% of patients with WM can present with symptoms of peripheral neuropathy. The most common clinical presentation of WM-related neuropathy is a sensory neuropathy characterized by a slowly progressing bilateral and symmetric numbness of the lower extremities. Nerve conduction studies typically show a demyelinating pattern.[3] In a portion of patients, antimyelin-associated globulin antibodies can be detected and would support the diagnosis.[37] In patients with atypical neuropathic symptoms or axonal patterns in nerve conduction studies, other causes of neuropathy should be evaluated. These include radiculopathy, diabetes, cobalamin deficiency, thyroid dysfunction, human immunodeficiency virus infection, Lyme disease, syphilis, autoimmune conditions (eg, lupus, vasculitis, or chronic inflammatory demyelinating polyneuropathy), and BNS. It is important to note that prolonged demyelination (ie, years) can induce axonal damage. In some cases, WM-related neuropathy may be due to lymphoplasmacytic infiltration of the nerve fibers, cryoglobulinemia, or amyloidosis. Nerve conduction studies and additional testing (ie, cryoglobulins, free light chain levels, or

nerve biopsy) might be needed to investigate these further. Nerve biopsies should not be performed routinely, because they can cause permanent neurologic deficits.[38]

EXTRAMEDULLARY DISEASE AND BING-NEEL SYNDROME

Extramedullary disease can be detected in 20% of patients with WM at diagnosis but it can be seen in up to 60% of patients at relapse. The most common sites of extramedullary disease are the lymph nodes and the spleen. Rarely, WM can affect kidneys, pleura, skeletal bone, and central nervous system. CT scans are helpful not only in identifying extramedullary disease, but also in assessing response on extramedullary sites during and after therapy. Based on CT criteria, lymph nodes above the diaphragm are considered pathologic if greater than 1.5 cm in longest diameter, whereas lymph nodes below the diaphragm are pathologic if greater than 2.0 cm. A spleen size of greater than 15.0 cm establishes splenomegaly. However, the sole presence of pathologic lymph nodes and/or splenomegaly does not constitute a criterion to initiate therapy, because they would have to be symptomatic.[39] In cases of extramedullary involvement of rare sites, a biopsy could be indicated to establish the diagnosis. Renal involvement has been reported in up to 3% of patients with WM, and can be due to amyloidosis, monoclonal IgM or free light chain deposition, light chain cast nephropathy, or lymphoplasmacytic cell infiltration, among others.[8] In patients with WM with renal involvement, monoclonal IgM deposition, and lymphoplasmacytic infiltration respond better to therapy than light chain cast nephropathy or amyloidosis. Pleural effusions are rare in patients with WM. A thoracentesis is needed to evaluate the effusion for the presence of malignant cells. The fluid should be sent for cytology, flow cytometry and polymerase chain reaction assays for IgH gene rearrangement and MYD88 L265P mutation. In some cases, the lymphoplasmacytic cells are adhered to pleural fenestrations and might not be readily identifiable by cytology or flow cytometry. In these cases, the diagnosis can be supported by the detection of IgH gene rearrangement or the MYD88 L265P mutation by polymerase chain reaction.[40] Lytic bone lesions, although common in MM, are rare in WM. Lytic bone lesions can also be due to other malignant processes, and a biopsy is advisable for proper diagnosis. The management of lytic bone lesions associated with WM should mimic the management of MM.

BNS is a rare complication of WM seen in about 1% of cases and refers to the involvement of the central nervous system by lymphoplasmacytic cells.[6] The most common manifestations of BNS include motor deficits, cranial nerve palsies, altered mental status, seizures, headaches, and atypical neuropathic symptoms.[41,42] BNS can occur at any time during the course of the disease. BNS can be the presenting symptom of WM and can also be diagnosed when in apparent complete systemic response to therapy. The evaluation of patients suspected of having BNS should include MRI studies with gadolinium enhancement of the brain and spine and a lumbar puncture for cerebrospinal fluid analysis. In most cases, the MRI shows leptomeningeal enhancement. Intraparenchymal brain lesions can be seen in a minority of cases. The cerebrospinal fluid should be sent for cytology, flow cytometry, and polymerase chain reaction assays for IgH gene rearrangement and MYD88 L265P mutation. A brain biopsy can be performed in patients with brain lesions without cerebrospinal fluid involvement. Treatment options for BNS are limited to agents with good central nervous system penetration such as methotrexate, fludarabine, bendamustine, and ibrutinib.[43]

AMYLOIDOSIS

Amyloidosis is a rare complication of WM caused by the aggregation of misfolded proteins that deposit as fibrils in several organs, including the kidneys, heart, peripheral

nerves, liver, and gastrointestinal tract. Of the several types of amyloidosis, the most commonly associated with WM is light chain (AL) amyloidosis.[44] Rare cases of IgM-related heavy chain (AH) and heavy and light chain (ALH) amyloidosis have been described in patients with WM. In patients suspected to have amyloidosis, a fat pad biopsy and/or bone marrow biopsy material should be stained with Congo red; amyloid produces a characteristic apple-green birefringence on microscopic examination under polarized light. In cases in which both fat pad and bone marrow evaluations are negative for amyloid, but a strong suspicion remains, a biopsy of the affected organ is advisable.[1] Amyloid typing is recommended in most cases and should be performed using mass spectrometry.[45,46] Immunoelectron microscopy or immunohistochemistry may also be used for this purpose.[47,48] Renal involvement by amyloid should be investigated with a 24-hour urine protein measurement and serum free light chain levels, which can be used for response assessment. Cardiac involvement should be evaluated by obtaining troponin or brain natriuretic peptide levels, which have prognostic implications. The MYD88 L265P mutation has been detected in more than 70% of patients with IgM-related amyloidosis.[49] The prognosis of patients with IgM-related AL amyloidosis might be more favorable than those with AL amyloidosis.[50]

SUMMARY

The initial evaluation of the patient with a diagnosis of WM can be challenging, but the thoughtful application of relevant data from the history, physical examination, laboratory tests, bone marrow aspiration and biopsy, and imaging studies can provide valuable insights for the management of these patients.

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