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Recommendations for the diagnosis and initial evaluation of patients with Waldenström Macroglobulinaemia: A Task Force from the 8th International Workshop on Waldenström Macroglobulinaemia

Short title

Diagnosis and initial evaluation of WM

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Abstract

The diagnosis of Waldenström macroglobulinaemia (WM) can be challenging given the variety of signs and symptoms patients can present. Furthermore, once the diagnosis of WM is established, the initial evaluation should be thorough as well as appropriately directed. During the 8th International Workshop for WM in London, United Kingdom, a multi-institutional task force was formed to develop consensus recommendations for the diagnosis and initial evaluation of patients with WM. In this document, we present the results of the deliberations that took place to address these issues. We provide recommendations for history-taking and physical examination, laboratory studies, bone marrow aspiration and biopsy analysis and imaging studies. We also provide guidance on the initial evaluation of special situations, such as anaemia, hyperviscosity, neuropathy, Bing-Neel syndrome and amyloidosis. We hope these recommendations serve as a practical guidance to clinicians taking care of patients with a suspected or an established diagnosis of WM.

Keywords

Waldenström macroglobulinaemia; anaemia; neuropathy; hyperviscosity; Bing-Neel syndrome; amyloidosis

Introduction

Waldenström Macroglobulinaemia (WM) is a lymphoplasmacytic lymphoma characterized by the accumulation of malignant immunoglobulin M (IgM)-producing B-lymphocytes, and lymphoplasmacytic and plasma cells (Swerdlow et al. 2008). WM is rare and accounts for up to 2% of all the cases of non-Hodgkin lymphoma in the United States and Europe. Despite an incurable disease course, there have been improvements in survival in patients with WM, with the median survival increasing from 5 to 8 years over the last decade (Castillo et al. 2014, Castillo et al. 2015). Some WM patients can experience prolonged survival measuring some decades. It is important to mention, however, that clinical factors, such as age and haemoglobin levels among

others, can help identifying those patients with WM who will have better and worse prognosis (Morel et al. 2009).

The clinical presentation can be highly variable in patients with WM (Treon 2015). The signs and symptoms of the disease are due to the infiltration of the bone marrow and/or other lymphoid organs by the lymphoplasmacytic cells but also due to the specific immunological and physicochemical properties of the monoclonal IgM. The clinical presentation is variable, and may include symptomatic cytopenias, peripheral neuropathy, hyperviscosity, extramedullary disease, cryoglobulinaemia and cold agglutinaemia among other clinical findings. In addition, a substantial portion of patients is asymptomatic at the time of diagnosis.

Given the heterogeneous clinical presentation, it is paramount to evaluate WM patients appropriately at diagnosis in order to guide management decisions. During the 8th International Workshop for WM (IWWM-8) in London, UK (www.wmworkshop.org), a Task Force was formed with the purpose of providing guidance for the initial evaluation of patients with suspected or established diagnosis of WM. This evaluation aims to define disease characteristics accurately and to recognize disease-related complications.

Methods

Participants of the IWWM-8 were selected as members of the Committee based on their interest and prominence in the field of WM as well as active participation in the discussions. The initial live open discussion took place during the actual IWWM-8 in London and the following questions were raised:

1. Should determination of *MYD88* mutation status be included in the diagnostic workup of patients suspected to have the diagnosis WM?
2. Should determination of *CXCR4* mutation status be included in the diagnostic workup of patients suspected to have WM?

3. What laboratory tests should be included in the workup of patients suspected to have a diagnosis of WM?
4. What workup should be included for WM patients with anaemia? Should iron deficiency workup be undertaken in anaemic patients with WM?
5. What workup should be included for WM patients with suspected hyperviscosity?
6. What workup should be included for WM patients with suspected neuropathy?
7. What workup should be included for WM patients with suspected Bing Neel syndrome?
8. What workup should be included for WM patients with suspected symptomatic amyloidosis?

After the initial live meeting, two separate teleconferences were undertaken to further discuss and refine answers to the above questions until consensus was reached. As part of the discussion process and recommendations formulation, a literature search using Pubmed and abstract presentations was performed. All the authors have reviewed the material presented here and approved the final manuscript.

Essential evaluation

A summary of the Task's recommendation for essential tests to be performed in patients with WM is shown in Table I.

History and physical

History-taking and physical examination are essential components of the initial evaluation of patients with WM. Appropriate and careful history-taking should provide valuable information regarding the presence of constitutional symptoms, such as fevers, night sweats or unintentional weight loss. Additional symptoms commonly reported by patients with WM include fatigue, malaise and shortness of breath, usually associated with anaemia, and increased bleeding or bruising that can be associated with thrombocytopenia or acquired von Willebrand disease (VWD) (Kyle et al. 2003).

Symptoms associated with hyperviscosity can include spontaneous epistaxis, new-onset headaches and blurred vision that does not correct with glasses, vertigo and tinnitus (Stone 2009). Funduscopic examination should be performed during the initial physical examination to evaluate for the presence of hyperviscosity. WM-related neuropathy is usually characterized by bilateral and symmetrical reduction of sensory function of the feet and hands and, if advanced, may contribute to gait disorder, difficulties in handling small objects or writing (Baehring et al. 2008). A history of rash or cold sensitivity may be indicative of cryglobulinaemia, while complaints of urticarial rash may also raise the suspicion of Schnitzler syndrome. A family history of WM or other lymphoproliferative disorders should also be sought as it may have negative prognostic implications (Treon et al. 2012a, Steingrimsson et al. 2015). Recommended actions based on findings in the review of systems are shown in Table II.

The physical examination may reveal lymphadenopathy as well as hepatosplenomegaly, which can produce upper quadrant abdominal discomfort and/or early satiety. Rarely, Raynaud phenomenon or ulcers of the legs or tip of the nose and ears can be manifestations of cryoglobulinaemia (Stone 2009). Also rarely, darkening of the urine after exposure to cold may be a manifestation of cold agglutinaemia (Berentsen 2009). Skin should be surveyed looking for rash, purpura or bruising. A neurological examination should be performed to evaluate for sensory and/or motor neuropathy. Funduscopic examination may reveal signs of hyperviscosity syndrome manifested by "sausaging" of engorged retinal veins. However, this task force would like to emphasize that no sign or symptom is pathognomonic of WM. Nonetheless, the presence of particular signs or symptoms can be helpful on directing additional workup.

Laboratory studies

Essential initial laboratory studies include complete blood count (CBC), complete metabolic panel (CMP), quantitative immunoglobulins, serum and urine protein electrophoresis (SPEP and UPEP) with immunofixation and beta-2-microglobulin. The CBC may identify anaemia, leucopenia/neutropenia and/or thrombocytopenia.

Thrombocytopenia can be secondary to bone marrow involvement, autoimmune destruction and/or hypersplenism. Peripheral blood evaluation shows rouleaux formation, and in some cases lymphoplasmacytoid cells can be observed. Lymphocytosis, however, is an infrequent event in WM patients. Macrocytosis may be due to rouleaux or associated with haemolysis due to cold agglutinin disease or autoimmune haemolytic anaemia. In some cases, a high IgM level can be associated with artificially low haemoglobin levels due to volume expansion (Treon 2009); transfusions of red blood cells should be avoided in these cases as it can dangerously increase serum viscosity. CMP can indicate abnormal kidney function, which can be associated with deposition of lymphoplasmacytic lymphoma (LPL) cells, IgM, light chains, cryoglobulins or amyloid (Vos et al. 2015), as well as hepatic dysfunction.

The measurement of serum IgM levels is a helpful indirect marker of LPL infiltration of the bone marrow, and can be used to follow progression or response to therapy (Treon 2015). However, serum IgM does not correlate perfectly with the tumour burden.Subnormal levels of uninvolved serum immunoglobulin (IgA and/or IgG) levels can be seen at time of diagnosis in about 70% of WM patients (Hunter et al. 2010). SPEP with immunofixation will identify an IgM monoclononal (M) protein. It is essential that immunofixation be obtained in all cases, as small quantities of IgM may be overlooked if only quantitative measurements are performed. In a few patients, two M-spikes can be identified, which may represent monomeric and pentameric forms of IgM and not necessarily true biclonality. In other cases, the IgM M-spike might migrate into the beta region rather than the gamma region and could be difficult to quantitate. Finally, in a minority of cases, true bi- or triclonality can be observed as well as class switching with corresponding IgG or IgA M-spikes. Serum viscosity can be useful in specific situations, especially in cases with high IgM or if hyperviscosity is suspected clinically (Stone and Bogen 2012). The role of serum free light chain measurement in patients with WM is under investigation (Leleu et al. 2011), and is recommended only in special situations (i.e. suspicion of light chain amyloidosis or renal failure).

A 24-h urine analysis with measurement of total protein and electrophoresis should be considered in the initial evaluation. Urine electrophoresis and immunofixation may reveal Bence Jones proteinuria (free monoclonal light chains), although this is observed less frequently than in multiple myeloma. Cases of cast nephropathy due to light chain proteinuria as well as monoclonal immunoglobulin, cryoglobulin and amyloid deposition have been described (Gnemmi et al. 2012, Vos et al. 2015). Significant albuminuria may indicate AL amyloidosis (and rarely AA amyloidosis) and serum free light chains should be measured and followed.

Serum beta-2-microglobulin level should be obtained, as it is a prognostic marker for survival and a component of the International Prognostic Scoring System for WM (IPSSWM) (Morel et al. 2009). The IPSSWM also includes age, haemoglobin, platelet count and M-spike size, and is used to classify patients with symptomatic disease requiring therapy into low, intermediate and high-risk groups. If clinically indicated, VWD screening (i.e. von Willebrand factor [VWF] antigen, ristocetin cofactor and factor VIII level) should be obtained, as acquired VWD has been identified in some cases of WM. High VWF levels have been associated with worse prognosis in patients with WM (Hivert et al. 2012).

Serum viscosity might be useful in assessing patients with hyperviscosity symptoms (Menke and Treon 2007, Stone and Bogen 2012). However, serum viscosity levels may be slow to be reported, not reproducible or lack correlation to serum IgM levels. Serum IgM levels are more expedient and reliable for assessing patients with suspected hyperviscosity syndrome. Funduscopic examination should be done in all patients with serum IgM >30 g/l and in those patients with suspected hyperviscosity syndrome.

Bone marrow aspiration and biopsy

Bone marrow aspiration and biopsy is essential for the diagnosis of WM, and should be evaluated by immunohistochemistry and flow cytometry as well as for the presence of the *MYD88* L265P gene mutation. The presence of elevated IgM

levels or an IgM M-spike is not sufficient for the diagnosis of WM (Owen et al. 2003). IgM monoclonal gammopathy of undetermined significance (MGUS), IgM myeloma, AL amyloidosis and other B-cell malignancies with plasmacytic differentiation, such as marginal zone lymphoma (MZL), chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL) or mantle cell lymphoma (MCL), are all included in the differential diagnosis of WM. Bone marrow aspiration and biopsy must be performed in all cases of IgM monoclonal gammopathy to make the diagnosis of WM and exclude other IgM-related diseases. Conversely, a diagnosis of LPL in the absence of a monoclonal IgM paraprotein does not fulfill the criteria for WM. The typical appearance of WM in a bone marrow biopsy includes the presence of an excess of kappa or lambda light chain-restricted B-lymphocytes, lymphoplasmacytoid forms and plasma cells (Swerdlow et al. 2008). The pattern of infiltration on trephine biopsy sections is typically interstitial, nodular or diffuse while a purely paratrabecular pattern is unusual. The presence of mast cells in the marrow microenvironment favours a diagnosis of WM. In addition to its use in the initial evaluation, tissue biopsy is recommended in all WM with suspected histological transformation.

Immunophenotypic evaluation must be performed on bone marrow samples. Based on immunohistochemistry and flow cytometry, which are considered complementary, lymphocytes and lymphoplasmacytic cells express IgM, kappa or lambda, CD19, CD20 and weak CD22 as well as homogeneous CD25 (Konoplev et al. 2005, Paiva et al. 2014). In approximately 10%-20% of the cases, WM cells can express CD5 (typically seen in CLL and MCL), CD23 (typically seen in CLL) or CD10 (typically seen in FL). Immunophenotyping should also demonstrate the presence of a monoclonal plasma cell component that expresses CD38 or CD138, lacks typical myelomatous antigenic aberrancies, and shows the same restricted light chain expression (kappa or lambda) as the lymphoplasmacytic component. WM plasma cells lack the phenotypic characteristics of myeloma plasma cells (e.g. WM plasma cells express CD19), which is helpful in the differential diagnosis (Morice et al. 2009). Cytogenetic analysis is not required for the routine diagnostic assessment of WM patients as it is difficult to obtain tumour metaphases *in vitro* (Schop and Fonseca 2003). There are no disease-defining

cytogenetic abnormalities. Deletion 6q and trisomy 4 are frequent cytogenetic abnormalities described in WM (Schop and Fonseca 2003, Ocio et al. 2007, Braggio and Fonseca 2013, Nguyen-Khac et al. 2013). Conventional cytogenetic or fluorescence *in situ* hybridization studies may be useful, however, in the differential diagnosis. For example, IgM myeloma is characterized by a high incidence of t(11;14) (Avet-Loiseau et al. 2003, Feyler et al. 2008).

The bone marrow aspirate should be evaluated for the *MYD88* L265P gene mutation, which is present in over 90% of patients with WM (Treon et al. 2012b), and can help in cases in which a diagnosis of WM is suspected but uncertain. The presence of the *MYD88* L265P mutation, however, is not diagnostic of WM, as approximately 50-80% of patients with IgM MGUS also carry the mutation (Jimenez et al. 2013, Poulain et al. 2013). Importantly, a minority (5-10%) of patients who fulfill the immunophenotypic and clinical criteria of WM may not have the *MYD88* L265P gene mutation (wild-type *MYD88*). In these patients, the diagnosis of WM should not be excluded based only on the absence of the *MYD88* L265P mutation. Rare *MYD88* non-L265P mutations have been reported by using *MYD88* gene Sanger sequencing (Treon et al. 2015a). The absence of *MYD88* mutation may be associated with an inferior survival outcome (Treon et al. 2014). No standardized method for the detection of the mutation yet exists. For example, allele-specific and reverse transcription polymerase chain reaction (PCR), among other methodologies, are used by different laboratories with various primers and detection limits. The use of CD19+ selected cells from peripheral blood has also been investigated but not standardized, and some false negative cases can be expected (Xu et al. 2014). Physicians should use the method with which their laboratory is most experienced, and the method and detection limits should be reported.

More recently, somatic mutations in the *CXCR4* gene, similar to the mutations seen in the Warts, Hypogammaglobulinaemia, Infections and Myelokathexis (WHIM) syndrome, have been described in approximately 30-40% of patients with WM (Hunter et al. 2014, Roccaro et al. 2014, Poulain et al. 2015, Schmidt et al. 2015). In contrast to the *MYD88* L265P recurrent point mutation, there are multiple *CXCR4*-WHIM mutations, making the

development of a PCR-based assay difficult. There is evidence that *CXCR4*-WHIM mutations can be determinant of disease presentation, i.e. association of higher serum IgM and bone marrow involvement as well as symptomatic hyperviscosity in patients with *CXCR4*-WHIM nonsense mutations, and response, i.e. resistance to ibrutinib (Treon et al. 2014, Treon et al. 2015b). The task force does not mandate routine testing for *CXCR4*-WHIM mutations at this time, but it may be helpful in the context of predicting outcome for patients on ibrutinib therapy. However, routine testing for *CXCR4*-WHIM mutations is recommended in the context of clinical trials in order to assess the impact of *CXCR4*-WHIM mutation status on treatment outcomes.

Computerized tomography (CT)

CT of the chest, abdomen and pelvis with the intravenous administration of contrast is essential for the initial staging of patients with WM who are being considered for treatment initiation. WM is typically a disease of the bone marrow. Approximately, 10-15% of patients, however, may have extramedullary disease, such as lymphadenopathy, hepatosplenomegaly or pleural effusions, on physical examination at time of diagnosis. The presence of adenopathy may be present in up to 60% of patients at time of relapse (Treon 2009). The presence of splenomegaly based on measurements using CT should be interpreted cautiously in patients with modest increases in splenic size. Baseline evaluation and re-assessment may be useful if an IgM flare needs to be differentiated from disease progression (Ghobrial et al. 2004, Treon et al. 2004). The panel recommends an initial assessment of the presence of extramedullary disease by imaging. If lymphadenopathy or organomegaly are found, then imaging during or after completion of therapy is advised. The role of positron emission tomography (PET)/CT imaging has not been established in WM and only a single published study exists (Banwait et al. 2015). Thus, the task force does not currently support the routine use of PET/CT for diagnosis or follow-up of the disease. However, PET/CT scanning can be useful in cases of aggressive transformation of WM, given that the most common histology is diffuse large B-cell lymphoma (DLBCL) (Leleu et al. 2009, Owen et al. 2011). If aggressive transformation is suspected, biopsy for

pathological evaluation is essential to exclude other pathologies, such as solid malignancies, reactive processes or clonally unrelated lymphomas (Owen et al. 2011). Staging and therapy should follow current DLBCL management guidelines.

Special situations

Anaemia

Anaemia occurring in patients with WM can be multifactorial and needs to be evaluated appropriately, with specific attention to absolute and functional iron deficiency states. Anaemia is the most common reason patients with WM seek medical attention and the most common reason to initiate treatment. In patients with WM, anaemia can occur due to the replacement of the bone marrow by malignant cells, iron deficiency and haemolysis. In some cases, high IgM levels can induce plasma volume expansion, generating a “dilutional” anaemia. In some cases of anaemia, the picture is consistent with an absolute iron deficient state (low iron saturation and low serum ferritin levels). In other cases, the picture is consistent with functional iron deficiency (low iron saturation and normal or high serum ferritin levels). When absolute iron deficiency is identified in patients with WM for whom anaemia is the only criterion for initiation of therapy, gastrointestinal or other bleeding sites should be excluded. As many patients with WM are elderly, a second malignancy (e.g. colon cancer) could co-exist. There are data describing excess secretion of hepcidin by WM cells (Ciccarelli et al. 2011). Hepcidin is a regulator of the serum iron content, and its excess results in decreased iron absorption, increased iron storage and inability to reutilize the stored iron. Given that hepcidin blocks the absorption of iron, intravenous supplementation of iron may be useful (Treon et al. 2013).

Rarely, anaemia may be due to an autoimmune haemolytic process. The Coombs test is positive in about 10% of WM patients overall, but less than 5% of patients develop significant haemolysis (Poulain et al. 2006). In such cases, performing a haemolytic workup including reticulocyte counts, lactate dehydrogenase, haptoglobin and direct

Coombs test are useful to evaluate for warm or cold autoimmune haemolytic anaemia. Cold agglutinins should also be measured, if clinically indicated by the presence of haemoglobinuria after cold exposure. Other causes of anaemia, such as cobalamin and folate deficiency, chronic renal, hepatic or thyroid dysfunction, non-autoimmune haemolytic anaemia or other primary bone marrow processes should be pursued, if clinically suspected, especially in elderly patients. Recommendations on the evaluation of anaemia in WM patients are shown in Table III.

Hyperviscosity

Symptomatic hyperviscosity can herald catastrophic events such as central nervous system (CNS) or retinal bleeding resulting in loss of vision, and should be promptly managed with plasmapheresis and WM-directed therapy. Symptomatic hyperviscosity may be present in 5-10% of newly diagnosed WM patients, and is characterized by an increased serum viscosity due to high serum IgM levels. The clinical presentation of hyperviscosity is variable but symptoms may include spontaneous epistaxis, new-onset headaches, blurred vision that does not correct with glasses, hearing loss, tinnitus and vertigo (Stone and Bogen 2012). Measurement of serum viscosity should be obtained by the Oswalt method, and carefully evaluated along with clinical symptoms and signs. However, serum viscosity levels may be slow to be reported, and often are not reproducible or lack correlation to serum IgM levels. Serum IgM levels are more expedient and reliable for assessing patients with suspected hyperviscosity syndrome. The presence of cryoglobulins (discussed below) may further aggravate serum viscosity levels, and should be examined in any patient suspected of hyperviscosity. Although routine funduscopic examination is highly encouraged in any patient with WM at first evaluation, this panel recommends that patients with WM and serum IgM levels higher than 30 g/l should also undergo a formal funduscopic evaluation by an experienced ophthalmologist to identify vessel tortuosity, “sausaging” or retinal haemorrhages. These findings would strongly suggest the need for immediate therapy. Retinal evaluation should be performed every 6-12 months as clinically indicated.

In some cases, the presence of cryoglobulins might render falsely low serum IgM levels (Stone 2009). Maintaining the blood sample in a 37^{o}C warm bath provides a more reliable serum IgM level measurement. Cryoglobulinaemia can often manifest through acrocyanosis, palpable purpura, livedo reticularis, non-healing ulcers in the lower extremities and discoloration of the tip of the nose and ears upon cold exposure. Type I cryoglobulinaemia is usually associated with lymphoproliferative disorders; Type II cryoglobulinaemia is often associated with hepatitis C virus infection. When suspected, a test for cryoglobulins should be obtained. Plasmapheresis will rapidly remove cryoglobulins and IgM and decrease the serum viscosity. Blood warmers should be used in patients with symptomatic cryoglobulins who may undergo plasmapheresis to prevent cryoprecipitation (Treon 2009).

Neuropathy

WM-associated peripheral neuropathy (PN) can have multiple aetiologies, and the panel strongly recommends consultation with a neurologist with expertise in neuropathy for evaluation and co-management of WM patients with PN. It is important to note that patients with WM can have other unrelated causes for neuropathy that need to be appropriately evaluated. The differential diagnosis for PN includes radiculopathy, diabetic neuropathy, cobalamin deficiency, thyroid dysfunction, human immunodeficiency virus infection, Lyme disease, autoimmune processes such as systemic lupus erythematosus, vasculitis or chronic inflammatory demyelinating polyneuropathy. Up to 20% of patients with WM may have PN, which may be due to lymphoplasmacytic infiltration of the nerve fibres, IgM deposition, autoantibodies, cryoglobulinaemia or amyloidosis. The most common clinical presentation is a sensory PN presenting with slowly progressing bilateral and symmetrical numbness of the feet, associated with a demyelinating process (Baehring et al. 2008). In a portion of patients with demyelinating PN, anti-myelin-associated globulin (MAG) antibodies are detectable in the serum and should be evaluated (Levine et al. 2006). Anti-GM1 antibodies should also be evaluated in WM patients with motor neuropathy (Vlam et al. 2015). Axonal

degeneration has also been described in patients with WM with sensorimotor PN, and can be secondary to long-standing demyelinating processes. Amyloidosis is typically associated with axonal degeneration. Small fiber neuropathy (SFN) can also be seen in WM patients, and is characterized by a sensation of burning or electrical shocks of soles and palms, especially at night. In these patients, physical examination and appropriate laboratory studies, neurological evaluation and electromyography/nerve conduction studies (EMG/NCS) should be performed. Skin biopsies are sometimes performed to diagnose SFN. However, these have low sensitivity, and the diagnosis of SFN remains largely clinical. Nerve biopsies are associated with permanent neurological deficits. This task force discourages clinicians from routinely performing skin or nerve biopsies in patients with WM-associated PN.

Bing-Neel syndrome (BNS)

BNS refers to involvement of the CNS with lymphoplasmacytic cells, and is recognized in approximately 1% of patients with WM. Approximately 50% of the patients diagnosed with BNS will succumb due to disease progression within 2 years of diagnosis (Simon et al. 2015, Castillo et al. 2016). BNS should be suspected in patients with WM who develop central neurological deficits. These symptoms include motor deficits, altered mental status, cranial nerve deficits, seizures, headaches and atypical PN. Hyperviscosity syndrome should be ruled out. Based on recent case series, BNS can present at any time during the course of the disease (Simon et al. 2015, Castillo et al. 2016). BNS can also present when patients are receiving WM-directed therapy, and even when in apparent complete response. BNS may rarely be the presenting symptom in newly diagnosed WM patients. The evaluation of these patients should include brain and whole spine magnetic resonance imaging with gadolinium enhancement, and lumbar puncture to obtain cerebrospinal fluid (CSF). CSF should be sent for cytology, flow cytometry and molecular studies including PCR for *IGH* gene rearrangement and *MYD88* L265P gene mutation. In patients with focal brain lesions without CSF involvement, a biopsy should be performed, whenever possible, to rule out other malignancies.

Amyloidosis

Amyloidosis is an uncommon complication seen in patients with WM and is associated with higher rates of morbidity and mortality. Amyloidosis is caused by the aggregation of misfolded proteins that deposit as fibrils in many organs, but most commonly in the kidneys, heart, liver and peripheral nerves. There are several types of amyloidosis (Sipe et al. 2014). The most commonly associated with WM is light chain amyloidosis (AL), however, although infrequently (4%), WM and other IgM-secreting lymphomas can be associated with reactive, AA amyloidosis, not AL amyloidosis, with important practical implications (Terrier et al. 2008). Amyloidosis can present as localized or systemic disease and, when suspected, material can first be obtained from a fat pad biopsy or a bone marrow biopsy and stained with Congo Red. Amyloid produces an apple-green birefringence on microscopic examination under polarized light. In a few cases, however, obtaining a biopsy of the affected organ might be necessary. With the exception of cases with a clinical presentation clearly suggesting AL-type amyloidosis (e.g. soft tissue involvement, or combination of nephrotic syndrome and heart involvement), amyloid typing is recommended. Amyloid typing should be performed preferably using mass spectrometry (Vrana et al. 2009, Brambilla et al. 2012). If mass spectrometry is not available, immunoelectron microscopy or immunohistochemistry performed in specialized laboratories may be used (Schonland et al. 2012, Fernandez de Larrea et al. 2015). Once a diagnosis of amyloidosis is obtained, appropriate workup includes 24-h urine protein analysis to evaluate for previously non-apparent renal involvement, and serum free light chain concentration, which can serve as a marker for response and/or progression. Obtaining troponin and brain natriuretic peptide levels is necessary to evaluate cardiac involvement and for prognostic assessment.

Conclusion

WM patients can have a wide variety of clinical signs and symptoms as well as laboratory findings. This Task Force aimed to present complete but concise data to help clinicians to diagnose and evaluate patients with WM. Because WM is a rare disease, most of the recommendations presented here arise from expert consensus opinion. We therefore hope that this report will instigate research focused on improving the diagnostic accuracy as well as identifying areas for improvement in the evaluation of patients with WM.

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Table I. Essential evaluation of patients with Waldenström Macroglobulinaemia (WM)

Evaluation
History and physical examination: Include familial history for WM and other B-cell lymphoproliferative disorders Include funduscopic examination Review of systems (See Table II)
Laboratory studies: Complete blood count Complete metabolic panel Serum immunoglobulin levels (IgA, IgG, IgM) Serum and urine electrophoresis with immunofixation Serum beta-2-microglobulin level If clinically indicated: Cryoglobulins Cold agglutinin titre Serum viscosity Screening for von Willebrand disease 24-hour urine protein quantification
Bone marrow aspiration and biopsy Immunohistochemistry Flow cytometry Testing for *MYD88* L265P gene mutation
Computerized tomography scans of the chest, abdomen and pelvis with intravenous contrast: In patients being considered for therapy

Table II. Review of systems in patients with Waldenström macroglobulinaemia

Symptom/Complaint	Implications	Action
Fatigue, lack of energy	Anaemia	Evaluate for anaemia, including iron, folate or cobalamin deficiency, haemolytic anaemia (warm and cold antibodies), etc. Patients with iron deficiency may benefit from parenteral iron.
Constitutional symptoms	Disease progression	Obtain serum IgM levels and SPEP. Evaluate other causes of fever, night sweats and unintentional weight loss.
Recurrent sinus and bronchial infections	Hypogammaglobulinaemia	Antibiotic support. If patient refractory to antibiotics, required hospitalization, or infections were life threatening, consider IVIG replacement.
Headaches, blurry vision or visual loss, confusion, epistaxis	Hyperviscosity	Funduscopic examination, obtain serum IgM and serum viscosity levels. Consider emergent plasmapheresis for symptomatic hyperviscosity.
Easy bruising, bleeding diathesis	Thrombocytopenia; acquired VWD; acquired coagulation factor deficiency	Complete blood count, evaluate for immune thrombocytopenia or hypersplenism if indicated; consider evaluation for VWD; consider amyloidosis. Evaluate other bleeding diathesis with INR, PTT and coagulation factor levels, as clinically indicated.
Progressive symmetrical numbness, tingling, burning, pain feet and hands	IgM-related neuropathy; amyloidosis	Obtain EMG studies and neurology consultation. Obtain anti-MAG, and if negative anti-GM1 and anti-sulfatide IgM antibody studies. Consider fat pad biopsy and Congo red stain for amyloidosis. Evaluate other causes of neuropathy: diabetes, thyroid dysfunction, HIV infection, cobalamin deficiency, etc.
Raynaud-like symptoms,	Cryoglobulinaemia; cold	Obtain cryoglobulins and cold agglutinins. In patients suspected of

acrocyanosis, ulcerations on extremities	agglutinaemia	having cryoglobulins, IgM should be obtained in a warm bath to avoid cryoprecipitation. Consider emergent plasmapheresis
Diarrhoea, gastrointestinal cramping	Malabsorption	Endoscopy to evaluate small bowel, biopsy to evaluate for amyloidosis, IgM deposition, tumour involvement. Evaluate other causes of diarrhoea.
Foamy urine, bipedal oedema	Kidney dysfunction	Obtain serum free light chains, 24-h urine protein, and consider kidney biopsy. Evaluate other causes of kidney dysfunction.
Urticaria, papules, dermatitis	Schnitzler syndrome, IgM or tumour cell infiltration, amyloid deposition	Skin biopsy, histological examination for tumour cell infiltration, stain for IgM, Congo-red staining for amyloid. Evaluate other causes of rash.

Anti-MAG, anti-myelin-associated globulin; EMG, electromyography; HIV, human immunodeficiency virus; INR, International normalized ratio; IVIG, intravenous immunoglobulin; PTT, partial thromboplastin time; SPEP, serum electrophoresis; VWD, von Willebrand disease.

Table II. Initial evaluation of anaemia in patients with Waldenström Macroglobulinaemia

Evaluation
Laboratory studies:
Iron, TIBC, ferritin*
Creatinine and estimated GFR
Liver function tests
Thyroid stimulating hormone
Cobalamin (vitamin B12)
Folate
Reticulocyte count, LDH, haptoglobin
In special situations:
Cold agglutinin titre
Direct Coombs test
Haemoglobin electrophoresis
Erythropoietin

GFR, glomerular filtration rate; LDH, lactate dehydrogenase; TIBC, total iron binding capacity.

*In iron deficiency, esophagogastroduodenoscopy and/or colonoscopy should be considered.