Review Article

Waldenström Macroglobulinemia - A State-of-the-Art Review: Part 1: Epidemiology, Pathogenesis, Clinicopathologic Characteristics, Differential Diagnosis, Risk Stratification, and Clinical Problems

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Abstract. **Waldenström macroglobulinemia (WM) is an infrequent variant of lymphoma, classified as a B-cell malignancy identified by the presence of IgM paraprotein, infiltration of clonal, small lymphoplasmacytic B cells in the bone marrow, and the MYD88 L265P mutation, which is observed in over 90% of cases. The direct invasion of the malignant cells into tissues like lymph nodes and spleen, along with the immune response related to IgM, can also lead to various health complications, such as cytopenias, hyperviscosity, peripheral neuropathy, amyloidosis, and Bing-Neel syndrome. Chemoimmunotherapy has historically been considered the preferred treatment for WM, wherein the combination of rituximab and nucleoside analogs, alkylating drugs, or proteasome inhibitors has exhibited notable efficacy in inhibiting tumor growth. Recent studies have provided evidence that Bruton Tyrosine Kinase inhibitors (BTKI), either used independently or in conjunction with other drugs, have been shown to be effective and safe in the treatment of WM. The disease is considered to be non-curable, with a median life expectancy of 10 to 12 years.**

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Key Points:
- An indolent, low-grade non-Hodgkin lymphoma known as Waldenström macroglobulinemia (WM) is characterized by lymphoplasmacytic cells infiltrating the bone marrow and a monoclonal IgM paraproteinemia.
- The age-adjusted incidence of WM in the US population is 0.36 per 100,000 (or 0.63 per 100,000 for WM and LPL combined, shown as WM/LPL).
- The initial evaluation of a patient with WM can be challenging, and the clinical features of

patients can vary greatly.

- IgM abnormalities are common within WM families and merit further evaluation because they may eventually provide a basis for screening and prevention.
- A family history of WM/LPL has prognostic implications for WM patients.
- Next-generation sequencing has revealed recurring somatic mutations in WM. Common mutations include MYD88 (95%–97%), CXCR4 (30%–40%), ARID1A (17%), and CD79B (8%–15%).
- Patients diagnosed with WM or LPL should only begin treatment if they have lymphoma-related symptoms. If a patient exhibits no symptoms, we can monitor them for an extended period before initiating therapy.

Definition. According to WHO-HAEM4,[1] we can diagnose lymphoplasmacytic lymphoma (LPL) when trephine biopsies reveal an infiltration by clonal lymphoplasmacytic aggregates. These criteria are supported by WHO-HAEM5,[2] which lists two types of LPL: (1) IgM-LPL/WM (about 95%) and (2) non-IgM LPL (about 5%), which includes cases with IgG or IgA monoclonal proteins, monoclonal free light chains (FLCs), non-secretory LPL, and IgM-LPL that does not involve the bone marrow. The search for MYD88 (L265P), the driver mutation of LPL detectable in about 90% of cases in both groups, may help to distinguish LPL from nodal and extranodal MZL.[3] But the lack of a MYD88 mutation does not rule out LPL. Further, 40% of cases have CXCR4 mutations associated with hyperviscosity symptoms and resistance to BTK inhibitors.[3]

The International Consensus Classification of Mature Lymphoid Neoplasms (ICC)[4] recognizes two IgM MGUS entities: (1) IgM MGUS of plasma cell type and (2) IgM MGUS not otherwise defined (NOS), which is different from WHO-HAEM5.[4] The first is characterized by the absence of the MYD88 mutation and the growth of clonal plasma cells devoid of B cells, making it a precursor to IgM MM. The IGH:CCND1 rearrangement, t(11;14)(q13;q32), or other IGH rearrangements associated with MM may exist. IgM MGUS NOS, on the other hand, is distinguished by the growth of monoclonal B cells, which usually have the MYD88 mutation; however, these cells do not show the lymphoplasmacytic aggregates typical of LPL. WM may develop in IgM-MGUS NOS. The ICC[4] and WHO-HAEM5[2] now classify primary cold agglutinin disease (CAD) as a separate illness from LPL/WM or IgM MGUS.[5]

History. In 1943, Jan Gosta Waldenstrom (JW) observed three cases of elevated globulin levels and recurring purpura, primarily affecting the lower extremities.[6]

These patients developed unique pigmentations, leading to the designation of Purpura hyperglobulinemia of Waldenstrom. In 1944, JW documented two patients with symptoms including oronasal hemorrhage, lymphadenopathy, normochromic anemia, elevated erythrocyte sedimentation rate, thrombocytopenia, hypoalbuminemia, low blood fibrinogen levels, and an increase in lymphoid cells in the bone marrow. The patients did not show skeletal bone lesions or bone pain, distinguishing this condition from multiple myeloma. The overabundance of lymphoid cells in their bone marrow differed from plasma cells in other patients diagnosed with multiple myeloma. JW collected blood samples and sent them to KO Pedersen, the ultracentrifuge supervisor at the Svedberg Institute. In 1944, JW published the results for the unusual 19S component, known as macroglobulinemia or Waldenström disease.[7]

Epidemiology. The prevalence of WM/LPL among newly diagnosed NHL cases in the United States is approximately 2%. Surveillance, Epidemiology, and End Results (SEER) data from 2000 to 2019 shows that the age-adjusted incidence of WM in the US population is 0.36 per 100,000 (or 0.63 per 100,000 for WM and LPL combined, shown as WM/LPL).[8] Individuals under the age of 30 are rarely diagnosed with WM. The occurrence of the condition starts increasing at the age of 40, and the rates continue to increase with each successive decade. The prevalence rate of WM/LPL among White Americans is 0.74 per 100,000, which is more than twice as high as the prevalence among any other racial or ethnic group.[8] Between 2000 and 2012, the combined incidence rates of WM and LPL in northern Sweden were 50% to 75% higher (1.48 and 1.75 per 100.000, respectively, for 2 counties) than the overall incidence rate in Sweden (1.05 per 100.000).[9] This is two to three times higher than the combined rate in the United States (0.61 per 100,000) during the same period. A few studies conducted on specific Asian communities provide support for the observed differences between white individuals and Asians and Pacific Islanders in the United States.[10,11] Gender impacts the incidence. In the United States, the prevalence of WM is approximately twice as high in males (0.51 per 100,000) compared to females (0.25 per 100,000). There was a 65% increase in the yearly age-adjusted incidence from 1990 (0.3 per 100,000) to 2019 (0.5 per 100,000). The rise is more significant in males (percent change (PC) = 60.4) compared to females (PC = 47.7) and in the elderly (PC = 69.5 vs. 47.7 for ages 60+ and 60 years, respectively).[8-11]

Family History in Waldenstrom Macroglobulinemia. The medical literature reported additional families with the condition after describing the first WM family in

1962.[12-16] According to population-based registries, family members of people with WM have an increased risk of developing WM and other B-cell cancers.[17,18]

In addition, family studies provided preliminary evidence for the role of environmental exposures in WM development.[19] A comprehensive case-control analysis found that persons with a first-degree relative diagnosed with a hematologic malignancy have a 64% higher risk of acquiring WM/LPL.[20] These observations were verified by two population-based registry investigations.[21,22]

Pathogenesis. It is hypothesized that LPL/WM cells originate from B-cells undergoing the last stages of B-cell maturation.[23] Clonal B cells may be found in the peripheral blood of WM patients, but lymphocytosis is infrequent.[23,24] WM cells express monoclonal IgM, but certain clonal cells also exhibit surface IgD. WM lymphoplasmacytic cells have pan-B-cell markers like CD19, CD20 (including FMC7), CD22, and CD79. Expression of CD5, CD10, and CD23 is detectable in around 10%–20% of cases.[24] The expression of these markers does not conclusively rule out the diagnosis of WM.[25-27] Somatic hypermutation contributes to evidence supporting the notion that the WM B-cell clone in most patients originates before the germinal center stage. The presence of isotype-switching transcripts and no diversity within clones increases the likelihood of finding the VH3/JH4 gene families.[28] The predominant etiology of WM cases is likely attributed to the presence of IgM and/or IgM IgD memory B-cells.[28]

WM patients have cells showing chromosomal abnormalities even when immunoglobulin heavy chain (IgH) translocations are absent.[29] Roughly 50% of people diagnosed with WM display deletions in the chromosomal region 6q21e23.[30,31] Additionally, approximately 40% of patients with 6q deletions also exhibit simultaneous increases in the 6p gene.[32] The chromosomal region under consideration encompasses two potential genes: TNFAIP3, which functions to inhibit nuclear factor kappa B (NF-kB) signaling, and PRDM1, a pivotal regulator of B-cell maturation.[33] Getting rid of an NF-kB suppressor is very important because WM cells need NF-kB to be phosphorylated and move into the nucleus to survive.[34]

Protease inhibitor therapy may help WM patients stop the breakdown of NF-kB inhibitors of kappa B (I-B) and other harmful NF-kB regulators.[35-37]

Somatic Events. The utilization of next-generation sequencing in the study of WM has revealed a high occurrence of mutations in several genes, including MYD88, CXCR4, TP53, and others.[38]

Cytogenetic Abnormalities in WM. WM is characterized by a median of two to three chromosomal abnormalities in each patient.[38,39] There is a strong correlation between a shift from asymptomatic to symptomatic WM and the deletion of 6q, the most common chromosomal aberration occurring in thirty percent to fifty percent of patients.[40-42] Other abnormalities that are frequently seen include trisomy(tri) 4, tri18, del13q, tri12, and del17p; however, none of these abnormalities are found in more than fifteen percent of patients.[43,44] There is a correlation between the deletion of 17p/TP53 and an unfavorable prognosis, which is present in seven percent of patients with WM.[45] In contrast to MM and other B-cell lymphoproliferative disorders, there has been no consistent description of translocations in WM.[46,47]

Role of MYD88 Mutations. MYD88 mutations were initially detected in diffuse large B-cell lymphoma (DLBCL) associated with the activated B-cell (ABC) subtype.[48,49] Allele-specific polymerase chain reaction (PCR) detects MYD88 L265P expression in 90% to 95% of WM patients, including both CD19-sorted WM cells and unsorted bone marrow cells.[50,51] When comparing WM to other B-cell cancers, it is seen that MYD88 mutations occur at a low prevalence. Patients with WM have also been shown to have non-L265P MYD88 mutations, such as S219C, M232T, and S243N, observed in other B-cell malignancies with MYD88 mutations.[53]

Patients diagnosed with IgM MGUS show approximately 50% to 90% prevalence for MYD88 mutations, whereas those with IgG or IgA MGUS show no such mutations.[54-56] Individuals diagnosed with IgM MGUS and possessing a mutated MYD88 gene have a higher propensity for developing WM.[57-59] IRAK1/IRAK4 and BTK, the targets of ibrutinib, facilitate the activation of NFkB.[60] Nevertheless, it is crucial to acknowledge that BTK can activate NFkB independently of IRAK4 and IRAK1.[61] Using peptides that stop MYD88 from homodimerizing or genetically silencing the MYD88 gene can stop IRAK1/IRAK4 and BTK from recruiting and activating, which causes apoptosis in WM cells with the MYD88 mutant.[62,63] Moreover, WM patients show hyperactivation of hematopoietic cell kinase (HCK)[64] HCK activation in the signaling pathways associated with mutant WM cell proliferation and survival. These pathways include BTK, PI3K/AKT, and MAPK/ERK1/2 signaling.[64]

The Role of CXCR4 Mutations. About 30% to 40% of WM patients have point mutations in the C-terminal region of CXCR4.[58,65] So far, only marginal zone B-cell lymphoma (MZL) and activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL) have also shown CXCR4 mutations. Interestingly, CXCR4 mutations are subclonal to MYD88 mutations.[65] Patients with a wild-type MYD88 gene may also have these changes in the C-terminal domain of CXCR4.[66] Germline mutations in the C-terminal region of CXCR4 characterize WHIM

syndrome, a condition characterized by autosomal dominant warts, hypogammaglobulinemia, infections, and myelokathexis syndrome.[67,68] WM patients show a significant prevalence of nonsense and frameshift mutations within the C-terminal domain of CXCR4.[67-69] MYD88 suppression leads to the induction of apoptosis in both wild-type (WT) and mutant CXCR4-expressing WM cells, even though CXCR4 mutations often enhance cell survival. This observation illustrates the heightened importance of the survival signaling pathway, specifically mutant MYD88, in the context of WM.[67–70]

The clonality of CXCR4 mutants demonstrates significant variety, which stands in contrast to the MYD88 gene. A single patient can exhibit multiple mutations in the CXCR4 gene. The CXCR4 gene appears to be directly linked to the occurrence of clonal deletions in the 6q chromosomal region. Somatic mutations in the CXCR4 gene may influence the manifestation of WM, similar to the effects shown in MYD88 mutations.[71] People who have CXCR4 mutations are less likely to have adenopathy. On the other hand, people who have CXCR4 nonsense mutations are more likely to get bone marrow disease, high serum IgM levels, hyperviscosity, and coagulopathy.[71]

The Role of Other Somatic Events. As the aggressiveness of IgM monoclonal gammopathies grows, there is a corresponding increase in the number of detectable genetic defects. An investigation examined the 12 prevailing WM genes and revealed that 21% of individuals with IgM MGUS exhibited alterations, 35% were asymptomatic, and 50% displayed symptoms.[72] A range of somatic mutations in ARID1A, such as nonsense and frameshift variants, have been identified in approximately 3–17% of individuals diagnosed with WM.[56,73,74] When ARID1A mutations occur, individuals with WM exhibit increased bone marrow infiltration.[75] The absence of its homolog ARID1B, situated on 6q, may contribute to the unfavourable prognosis associated with 6q deletion. Around 10% of WM patients carry mutations in CD79A and CD79B.[76] The B-cell receptor (BCR) pathway comprises two components that can form heterodimers.[76,77] Consequently, activating mutations in these components may play a role in the chronic BCR signaling found in WM cells.[78,79] Changes in CD79A and CD79B were rarely found in CXCR4 mutations, suggesting that CD79A/B mutations may help WM to spread through pathways directed by mutant MYD88.[67]

Approximately 10% of newly diagnosed individuals with WM and 25% of those who have progressed to more advanced stages have TP53 abnormalities, such as mutations or deletions in the TP53 locus on chromosome 17 (17p13.1).[80,81] These abnormalities may potentially link to mutant MYD88 and CXCR4.[82] Similar to other types of lymphomas, TP53 abnormalities in WM indicate a higher likelihood of a more aggressive illness.[83] Although TP53 mutations suggest unfavorable results with immunochemotherapy in chronic lymphocytic leukemia, there is still a lack of conclusive data for WM.[84] The molecular investigation for WM now recommends TP53 mutation testing, which includes checking for 17p deletions. This is especially important for patients who experience a relapse and need treatment.[84,85]

Tumor Microenvironment. WM cells' ability to migrate to the bone marrow is a critical characteristic. The expression of stromal-derived factor-1 (SDF-1), a chemokine, influences the in vitro migration of human cells.[86] This is prominently present in WM bone marrow. Recent findings have highlighted the important role of mast cells, T-cells, monocytes, and endothelial cells in the development of WM.[87] An excessive proliferation of mast cells distinguishes WM from MZL. The role of mast cells in the bone marrow of people with WM has been shown to play a role in the excessive growth of cancerous B cells through the interaction between CD40L and CD40 molecules.[87] Researchers have focused on examining the expression of PD-1, its ligands PD-L1 and PD-L2, and the presence of T cells in WM. Both WM cell lines and patient bone marrow cells showed increased expression of the PD-L1 and PD-L2 genes after exposure to IL-21, interferon-gamma, and IL-6.[88] Patients with Waldenstrom macroglobulinemia who had more PD-L1 and PD-L2 expression in their bone marrow tend to have more aggressive disease.[88] More evidence indicates that bone marrow-derived mesenchymal stem cells (BMSCs) can regulate the proliferation of tumor cells in WM and contribute to developing resistance to treatments. Ephrin receptor B2 (Eph-B2) overexpression in WM cells enhances the adhesion and proliferation of endothelial cells.[89] Patients with WM exhibit activation of Eph-B2 receptors. The suppression of Ephrin-B2 or Eph-B2 effectively prevented increased adhesion and proliferation resulting from the interaction between the endothelium and WM cells.[91]

Clonal Hematopoiesis (CH) in WM. The expansion of somatic mutations in hematopoietic progenitor cells, known as clonal hematopoiesis (CH), has been associated with various detrimental consequences.[92-94] Researchers have identified CH clones in patients diagnosed with WM.[95] Recently, 14% of WM patients were found to carry a clonal hematopoiesis of indeterminate potential (CHIP) clone.[96] This discovery coincided with a significant increase in the probability of progressing from an asymptomatic state to a symptomatic manifestation of WM. There is no correlation between the existence of CH and decreased survival rates.[96]

Diagnostic Criteria. WM is diagnosed when patients have an IgM monoclonal protein of any size and evidence of lymphoplasmacytic lymphoma infiltration in their bone marrow, even if <10% of cellularity.[1,2,4] The immunophenotypic profile of WM cells includes the detection of surface IgM, CD5, CD19, CD20, CD22, CD79a, CD23, CD25, CD27, FMC7, CD138, and CD103. While WM is the most frequently reported kind of lymphoplasmacytic lymphoma (LPL), a small proportion (5%) of LPL cases display IgG, IgA, or non-secretory features, which have been associated with an increased likelihood of extramedullary involvement.[1,2,4]

Initial Investigation.
Medical History and Physical Examination. Clinically, WM is characterized by fatigue, discomfort, and difficulty breathing, often associated with anemia. Symptoms may also include thrombocytopenia or acquired von Willebrand disease (vWD), which can increase susceptibility to bleeding or bruising. Hyperviscosity can also be present. A funduscopic examination is recommended for evaluating hyperviscosity, especially in patients with serum IgM levels above 3,000 mg/dl. A comprehensive neurological examination is recommended to identify sensory and motor neuropathy. Physical examinations may also detect hepatosplenomegaly and lymphadenopathy. Cryoglobulinemia may be accompanied by symptoms like the Raynaud phenomenon or ulcers. Cold agglutinin anemia is rare, and familial history of WM or other lymphoproliferative diseases should be investigated.[97-100]

Laboratory Studies. Typically, the initial diagnostic workup includes several important laboratory tests.[101] These include a complete blood count (CBC), a complete metabolic panel (CMP), quantitative immunoglobulins, free light chains, and serum and urine protein electrophoresis with immunofixation. Additionally, serum viscosity, serum LDH, and beta-2-microglobulin tests are also performed.[97-101] The amount of immunoglobulin M (IgM) in the blood might be an indirect biomarker for detecting LPL in the bone marrow. Still, the association between serum IgM levels and tumor burden may not correspond. Nearly 70% of people with WM have lower than normal IgA and/or IgG levels in their serum at the time of diagnosis.[97-101] Immunofixation using the SPEP method can detect the IgM monoclonal (M) protein. Since quantitative tests may not be able to identify small levels of IgM, combining immunofixation with qualitative tests is crucial to ensure the detection of all particles. Genuine bi- or tri-clonality, class switching, and the presence of IgG or IgA M-spikes are rare.[97-101] We recommend quantifying serum-free light chains in people with WM in some cases, particularly when there is a suspicion of light chain amyloidosis. Urine electrophoresis and immunofixation techniques can detect Bence Jones proteinuria, which is less common than in multiple myeloma.[97-101] Serum viscosity can be a valuable diagnostic tool for people with hyperviscosity symptoms. For those suspected of having hyperviscosity syndrome, measuring serum immunoglobulin M (IgM) levels provides a more accurate and precise diagnostic approach.[97-101] A high serum IgM level can sometimes be associated with artificially low hemoglobin levels produced by volume expansion. When clinically necessary, we perform screening for acquired von Willebrand disease (vWD) by assessing the VW antigen, ristocetin cofactor, and FVIII level. Acquired VWD is typically seen with >5,000 mg/dl serum IgM levels. Patients with WM with elevated levels of von Willebrand factor may have a more unfavorable prognosis.[97-101]

Bone Marrow Investigations. Bone marrow biopsies reveal increased lymphocytes restricted to either kappa or lambda light chains. The trephine biopsy sections show interstitial, nodular, or diffuse infiltration patterns. Paratrabecular infiltration is a rare phenomenon. In lymphocytes and lymphoplasmacytic cells, immunohistochemistry and flow cytometry tests demonstrate the detection of IgM, kappa, or lambda light chains, CD19, CD20, weak CD22, and homogeneous CD25. WM cells can express CD5, a protein typically found among individuals diagnosed with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL).[97-101] Furthermore, WM cells may also express CD23, a protein commonly found in CLL. Approximately 10%–20% of WM cells may exhibit the presence of CD10, a protein typically linked to follicular lymphoma (FL).[102] Due to the difficult logistics of producing tumor metaphases in a laboratory setting, cytogenetic testing is typically not included in the diagnosis procedure for individuals with WM.[103] However, conventional cytogenetic or fluorescence in situ hybridization (FISH) tests can be advantageous in differential diagnosis.[104-107] We recommend testing the bone marrow aspirate for the presence of the MYD88 L265P mutation.[108-110] A large percentage (50–90%) of patients with IgM monoclonal gammopathy of unknown significance (MGUS) exhibit the MYD88 L265P mutation.[109,110] Therefore, this mutation alone cannot be considered a conclusive indicator of WM. A subset of patients, ranging from 3% to 5%, who satisfy both the immunophenotypic and clinical criteria for WM may not possess the MYD88 L265P mutation, commonly referred to as "wild-type MYD88". The absence of a MYD88 mutation has been linked to an adverse prognosis in terms of survival.[111] Approximately 30%–40% of individuals diagnosed with WM have CXCR4 mutations.[112]

Imaging. In most cases, WM is a disorder that affects

Table 1. Significant and useful investigations in the context of WM.

Studies on Waldenstrom Macroglobulinemia	
Medical records and a physical assessment	History (with regard to WM or NHL in the family), Physical Examination, Lymphadenopathy, organomegaly, skin rash, or hemorrhagic, clinical assessments of hyperviscosity symptoms.
Haematological analysis and urinalysis	Complete blood count (CBC), differential, platelet count, peripheral blood smear. Urea and electrolytes, calcium, phosphate, uric acid. Liver function tests. Iron studies with LDH and B2 microglobulin, as well as B12 and folic acid. Serum electrophoresis with immunofixation and serum immunoglobulins, PT, aPTT, HIV ab, and Hepatitis B and C serology. Cold agglutinin titers and cryoglobulins.
Examination of bone marrow	Bone marrow aspirate and trephine, Flow Cytometry, Perl's stain for iron stores Molecular studies for $MYD88^{L256P}$, CXCR4 mutations
Medical imaging techniques	Chest/abdominal/pelvic CT scan with IV contrast. PET-CT if an aggressive transformation is suspected.
Presumed Amyloidosis	Fat pad sampling and/or Congo red staining of bone for amyloid, Amyloid tissue subtyping with mass spectrometry when indicated. Echocardiogram and ECG, NT-proBNP and troponin, 24-hour urine for proteinuria and Bence Jones protein
Possible diagnosis of Haemorrhagic conditions	Von Willebrand disease testing Platelet aggregation studies, Specific Coagulative factor studies
Possible diagnosis of Neuropathy	Neurology consult, anti-myelin-associated glycoprotein (anti-MAG) and anti-ganglioside antibodies, nerve conduction study (NCS)/electromyogram (EMG)
Bing-Neel Syndrome	MRI brain and spine with gadolinium enhancement, CSF sampling for cytology, flow cytometry, protein and glucose
Hypothesised Hyperviscosity syndrome	Retinal examination (if IgM >3.0 g/dl)

Table 2. Manifestations of Waldenstrom Macroglobulinemia in a clinical setting.

Higher occurrence of lymphomas, myelodysplasia, and leukaemias
Bleeding symptoms caused by platelet dysfunction, anomalies in coagulation factors and fibrinogen, resulting from the interaction with plasma IgM.
Heightened susceptibility to infection resulting from impaired B-cell function (disease-related) or T-cell function (treatment-related, especially following nucleoside analogues).
Renal disease (less prevalent)
Diarrhoea and impaired nutrient absorption caused by gastrointestinal (GI) complications
Hyperviscosity syndrome
Visual impairments caused by hyperviscosity syndrome
Amyloidosis compromising the heart, kidney, liver, lungs, and joints.
Peripheral neuropathy
Raynaud's phenomenon caused by cryoglobulinemia
Cardiac failure
Bing Neel syndrome

bone marrow, but around 10%–15% may have extramedullary symptoms during the initial physical examination, such as lymphadenopathy, hepatosplenomegaly, or pleural effusions. CT scans of the chest, abdomen, and pelvis are necessary for the initial staging of patients with WM who are being considered for therapy initiation. In cases of aggressive transformation, PET/CT scanning is very helpful because DLBCL histology is often present.[97-101]

Differential Diagnosis. All IgM-secreting lymphomas show similarities to WM.

IgM MGUS-NOS. Patients have IgM MGUS-NOS if they show an IgM monoclonal gammopathy without any apparent evidence of bone marrow structural involvement with lymphoplasmacytic lymphoma. Additionally, these patients may exhibit a MYD88 mutation, and there is no indication of any other B-cell neoplasms.

IgM MGUS, Plasma Cell Type (IGM MGUS-PC). Plasma cell type IgM MGUS (IGM MGUS-PC) is classified as a precursor to MM. It is characterized by the presence of clonal plasma cells (<10%) without a

detectable B-cell component and with wild-type MYD88 and includes patients who have t(11;14) (q13;q32) or other cytogenetic abnormalities that are characteristic of multiple myeloma (MM).

IgM-Related Disorders/ Monoclonal Gammopathy of Clinical Significance (MGCS). Certain patients exhibit clinical characteristics linked to the monoclonal IgM paraprotein, but they fail to meet the diagnostic criteria for WM. These patients are classified as IgM-associated diseases, aligning with the monoclonal gammopathy of clinical significance (MGCS) category in the updated ICC classification.[4]

IgM Multiple Myeloma. IgM-MM is distinguished from WM by the presence of plasmacytic infiltration in the bone marrow. Compared to WM, IgM-MM is frequently associated with osteolytic lesions and renal insufficiency. Cytogenetic abnormalities such as 13q deletion, 11:14 translocation, or 4:14 translocation can distinguish MM and WM. Identifying mutations in MYD88, present in WM but absent in MM, significantly enhances the distinction between the two entities.

Marginal Zone Lymphoma (MZL). Differentiating between WM and MZL, especially splenic marginal zone lymphoma (SMZL), may pose a challenge. Pan-B-cell markers for immunophenotyping, such as CD19, CD20, CD22, and surface Ig, are always present in WM and SMZL. Individuals with SMZL demonstrate higher CD22 and CD11c expression levels than individuals with WM. Conversely, CD25 positivity is more common in patients with WM (88% vs. 44%). Between SMZL and WM, the k/L ratio varies, with a ratio of 1.2:1 for SMZL and 4.5:1 for WM. In WM, the CD103 antigen always shows a negative result. However, in 40% of patients with SMZL, it demonstrates a positive result. Both diseases commonly show a positive presence of the monoclonal antibody FMC7, with a heterogeneous distribution in WM and a homogenous distribution in SMZL. By utilizing the combination of CD25 and CD22, it is possible to differentiate between WM and SMZL. Analysis of the MYD88 mutation may serve as a reliable indicator for differentiating WM from other comparable conditions.

Mantle Cell Lymphoma (MCL). The invasion of the bone marrow by uniform, small to medium-sized lymphoid cells with irregular nuclei can differentiate MCL from WM. MCL primarily impacts the bone marrow, lymph nodes, and extranodal regions such as the gastrointestinal tract and spleen. Most cases of mantle cell lymphoma consistently exhibit the t(11;14)(q13;q32) chromosomal translocation.

Follicular Lymphoma. Follicular lymphoma is distinct from WM because it involves the invasion of tiny, cleaved cells into the paratrabecular region of the bone marrow. Furthermore, cytogenetic investigation demonstrates t(14;18) in 70–90% of cases.

Chronic Lymphocytic Leukemia (CLL). CLL with an IgM monoclonal protein may be similar to WM. In CLL, lymphocytes are usually tiny and fully developed, lacking visible nucleoli and exhibiting the distinctive smudge cells on a blood smear with a positive expression of CD5 and CD23 while showing negative expression of cytoplasmic immunoglobulin (Ig). On the other hand, in WM, the lymphocytes are negative for CD5 and CD23 but significantly positive for cytoplasmic Ig.

Risk Stratification.
Asymptomatic Disease. Patients can meet the diagnostic criteria for WM and have no symptoms of the illness, also called "asymptomatic WM" or "smoldering WM".[113] Patients who do not show symptoms should not be treated. An observation-based approach is suitable, as no evidence demonstrates that immediate therapy is more effective than an observation-based approach. The likelihood of disease progression in asymptomatic WM patients was 6% after 1 year, 39% after 3 years, 59% after 5 years, and 65% after 10 years.[114] Nevertheless, even if there are no evident symptoms present, it may be necessary to start therapy if the IgM serum concentrations are extremely high (e.g., above 60 g/l) or if there is severe anemia with levels below a certain threshold (e.g., 8 mg/dl).[114] The AWM risk score, which includes the percentage of involvement of the bone marrow by LPL and serum IgM, beta-2-microglobulin,

Table 3a. Differential diagnosis of Waldenstrom Macroglobulinemia.

IgM monoclonal gammopathies different from IgM Multiple Myeloma (IWWM-11/ICC)	IgM monoclonal protein	Bone marrow infiltration	Clonal or monotypic B-cells	Clonal plasma cells/ No clonal or monotypic b-cells	Symptoms related to monoclonal IgM or light chain	Symptoms related to tumor infiltration	Mutational landscape MYD88
IgM MGUS-NOS	Yes	No	Yes	No	No	No	Mutated
IgM MGUS-PC	Yes	No	No	Yes	No	No	Wild-type
IgM related disorders/ MGCS	Yes	No	Yes	Yes/No	Yes	Yes	Mutated
WM asymptomatic	Yes	Yes	Yes	Yes	No	No	Mutated
WM symptomatic	Yes	Yes	Yes	Yes	Yes	Yes	Mutated

Table 3b. Outline the criteria differentiating those diseases from WM.

Disease	Clinical Presentation	Immunophenotype	MYD88[L265P]	Cytogenetics	Bone marrow
Waldenstrom Macroglobulinemia	Hyperviscosity syndrome, lymphadenopathy, splenomegaly, bleeding, neuropathy, constitutional symptoms	CD20$^+$, CD22$^+$, CD25$^+$, CD27$^+$, cd52$^+$, FMC7$^+$, BCL2$^+$, slgM$^+$, CD5$^{+/-}$, CD10$^{+/-}$, CD23$^{+/-}$, CD103$^-$	80-90%	Del6q (30%-50%)	Morphology: lymphoplasmacytes or cells with lymphoplasmacytic differentiation, together with a small population of clonal plasma cells even with <10% LPL
MGUS IgM	No symptoms or IgM-related, <3g/dl IgM, no end-organ damage	PC:CD138+, CD38+, CD19$^-$ CD20$^{+/-}$, cyclin D1 +/-	30-60%		No LPL infiltrate
Multiple Myeloma IgM	Diffuse bone pain for lytic lesions, hypercalcemia symptoms, neurological symptoms, Constitutional symptoms	PC: CD138$^+$, CD38$^+$, CD19$^-$, CD20$^{+/-}$, cyclin D1$^+$	0	t(11;14) or other IgH translocations	>10% Neoplastic Plasma cells
Follicular Lymphoma	Predominant Lymphoadenopathy, Constitutional Symptoms.	CD5$^-$, CD10$^{+/-}$, CD11c$^{-/+}$, CD103$^-$, CD25$^-$, CD138$^-$, CD38$^+$, CD45$^+$, bcl2$^+$, bcl6$^+$	0	Translocations involving BCL-2 (70-90%)	Small cleaved lymphocytes, paratrabecular localization in the BM
Mantle cell lymphoma	Common nodal and extranodal involvement	CD5$^+$, CD10$^-$, CD23$^-$, CD25$^-$, CD45$^+$, CD103$^-$, CD138$^-$	0	t(11;14)(q13;q32)	Monomorphous, small medium lymphoid cells With irregular nuclei
Splenic Marginal Zone Lymphoma	Common Splenomegaly, circulating cells with a distinctive morphology may be present.	CD19$^+$, CD20$^+$, CD22$^+$, CD79a+, cd79b$^+$, FMC7$^+$, IgM$^+$, CD5$^-$, CD10$^-$, CD43$^-$, BCL6$^-$, cyclin D1$^-$, CD103$^-$, CD11c$^{-/+}$, CD25$^{-/+}$, CD11c$^+$	10%	Del7q (19%), +3q(19%), +5q(10%)	Nodal non paratrabecular, Intrasinusoidal infiltration by CD20+ cells

and albumin levels, can be used to classify asymptomatic WM patients into low, intermediate, and high risk for treatment initiation.[115]

Symptomatic Disease. We classify patients with WM as symptomatic if they display signs or symptoms associated with tumor infiltration. Some of these signs are constitutional symptoms, cytopenias, infiltration of the central nervous system, organomegaly, and/or symptoms caused by the IgM or light chain monoclonal protein itself, such as hyperviscosity syndrome, cryoglobulinemia, cold agglutinin syndrome, light chain deposition disease, amyloidosis, IgM demyelinating peripheral neuropathy, and IgM deposition disease. Any of the above constitute criteria for treatment initiation based on the recommendations by the 2nd IWWM.[114-115] The International Prognostic Scoring System for WM (IPSSWM) can help categorize patients who will start frontline therapy into different risk groups.[116] The updated version of the prognosis scoring system (revised IPSSWM) includes factors such as age (65 vs. 66–75 vs. > 76 years), beta-2-microglobulin levels of 4 mg/L, serum albumin levels <3.5 g/dl, and LDH≥250 IU/L.[116] This classification enables the identification of both an extremely low-risk and extremely high-risk cohort. The

3-year mortality rate associated with WM was seen to be 0%, 10%, 14%, 38%, and 48% (p < 0.01) for these prognostic groups, whereas the 10-year survival rate was established to be 84%, 59%, 37%, 19%, and 9% (p < 0.001). The IPSSWM and its variants serve as prognostic tools and should not be used to determine the necessity of therapy.

Table 4. Revised International prognostic score system for Waldenstrom macroglobulinemia. Adapted from reference 150.

Criteria	Points
Age less <65	0
Age 66-75	1
Age >75	2
B2-microglobulin >4 mg/L	1
LDH >250 UI/L	1
Serum albumin <3.5 g/L	1

Table 5. Outline the Revised International prognostic score system for Waldenstrom macroglobulinemia.

Score	Stage	3-year WM related death rate (%)	10-year survival rate (%)
0	Very low	0	84
1	Low	10	59
2	Intermediate	14	37
3	High	38	19
4-5	Very High	48	9

Immunoglobulin M-Mediated Morbidity

Hyperviscosity Syndrome. WM patients can experience symptomatic hyperviscosity due to elevated serum IgM levels. Individuals with IgM levels below 3,000 mg/dL do not require viscosity testing, as clinical hyperviscosity is infrequent in such a group.[82] We often observe nosebleeds, bleeding gums, and changes in vision due to bleeding in the retina.[117] Individuals suspected of having hyperviscosity should evaluate and analyze the possible influence of cryoglobulins on the viscosity of their blood serum. The existence of cryoglobulins can result in falsely decreased levels of IgM in the serum. For this specific situation, we recommend placing the serum sample in a warm bath at a temperature of 37°C.[118-121] This could result in a more accurate measurement of the serum IgM concentration. It is advised that patients diagnosed with WM and having serum IgM levels above 3000 mg/dL receive a thorough examination of the fundus by a skilled ophthalmologist once a year.[122,123]

Cryoglobulinemia. Patients with WM may have monoclonal IgM that can display cryoglobulin-like properties. Type I is usually the predominant type of cryoglobulinemia, but the exact prevalence and incidence have not been determined.[124] The WMUK Rory Morrison national registry, which includes over 1300 cases, reported a prevalence rate of 7%.[125] Another study in Greece found that 5.5% of a group of 595 WM patients had cryoglobulins.[126] Recently, in a study of 102 patients with WM, a high percentage of them exhibited cryoglobulinemia and experienced cryoglobulin symptoms.[124] Of note, even a small concentration of detectable cryoglobulin could trigger symptoms.[124-126]

Immunoglobulin M-Associated Neuropathy. The estimated incidence rate of IgM-related peripheral neuropathy in patients with WM varies from 5% to 40%. Approximately 8% of idiopathic neuropathy cases are associated with monoclonal gammopathy.[127,128] Among these cases, IgM accounts for 60%, IgG for 30%, and IgA for 10%. Several mechanisms lead to nerve damage, including (a) the effects of IgM antibodies against nerve components, resulting in demyelinating polyneuropathies; (b) the presence of IgM deposits in the endoneurium without antibody activity, leading to axonal polyneuropathy; (c) the formation of sporadic tubular deposits in the endoneurium, associated with IgM cryoglobulin; and (d) in extremely uncommon cases, the existence of amyloid deposits or infiltration of neoplastic cells.[129-133] About half of the people diagnosed with IgM neuropathy have antibodies against the myelin-associated glycoprotein (MAG). Anti-MAG usually causes neuropathy that results in deficiencies in both motor and sensory functions. An extended phase of stability typically marks this syndrome, which typically displays a symmetrical and distal pattern of involvement.[134-137] People who have monoclonal IgM antibodies that target gangliosides with disialosyl moieties, specifically GD1b, GD3, GD2, GT1b, and GQ1b, tend to have sensory neuropathy that is mostly caused by loss of myelin.[138-140] Antibodies targeting GD1b and GQ1b have been associated with the onset of sensory ataxic neuropathy. Monoclonal IgMs targeting antigangliosides display significant clinical symptoms of chronic ataxic neuropathy, such as ophthalmoplegia and/or cold agglutination activity that impacts red blood cells.[138-141] Miller-Fisher syndrome, a variant of Guillain-Barré syndrome, has been associated with Campylobacter jejuni lipopolysaccharides (LPS).[142] Motor neuron disease is linked to people who have WM and monoclonal IgM with anti-GM1 and sulfoglucuronyl paragloboside activity.[143,144] Only a small number of individuals diagnosed with WM exhibit symptoms of the POEMS syndrome, characterized by polyneuropathy, organomegaly, endocrinopathy, an M protein, and skin issues.[145]

Cold Agglutinin Hemolytic Anemia. The ICC[4] and the WHO-HAEM5[5] have recently differentiated primary cold agglutinin disease (CAD) from cold agglutinin syndrome (CAS), which is secondary to other conditions. CAS is often linked to cold agglutinin titers above 1:1000 and affects less than 10% of patients with WM. Monoclonal IgM, which recognizes several red cell antigens at temperatures below 37°C, is responsible for hemolytic anemia.[146-150] Monoclonal components commonly contain the IgM kappa light chain.[151] Its interactions with red cell I/I antigens lead to the binding and activation of complement. Raynaud syndrome, acrocyanosis, and livedo reticularis are other medical conditions that result from an accumulation of red blood cells in the skin's blood vessels. Both cryoglobulins and cold agglutinins, particularly those that exhibit anti-Pr specificity, can exhibit characteristics that macroglobulins can display.[151,152]

Bleeding Propensity in WM. Although the current body of literature lacks strong evidence of platelet dysfunction, specific medical conditions, such as acquired von Willebrand factor syndrome, hyperviscosity, aberrant hematopoiesis, cryoglobulinemia, and amyloidosis, have been identified as potential factors that can interfere with coagulation pathways and result in bleeding. Furthermore, many people diagnosed with WM are typically elderly and experience one or several comorbidities. Understanding the processes that cause bleeding is critical since many commonly used treatments for WM, like chemoimmunotherapy and Bruton tyrosine kinase inhibitors, have been linked to an increased risk of bleeding episodes.[154,155] Approximately 17% of individuals had indicators of bleeding. Nevertheless, the severity of these symptoms was not

adequately characterized.[156,158]

AL Amyloidosis. Individuals diagnosed with WM have a greater risk of developing amyloidosis, which includes both AL amyloidosis and the apparently but potentially coexisting transthyretin (ATTR) amyloidosis.[159-166] WM-associated AL amyloidosis occurs in approximately 7.5% of patients with WM.[159] We should prioritize the precise identification of amyloid deposits using mass spectrometry-based techniques, immunoelectron microscopy, and immunohistochemistry. Due to its rarity, extensive, high-quality trials to guide treatment decisions for WM-associated AL amyloidosis are lacking.[159-166] Measuring the 24-hour urinary albumin concentration or the urinary albumin/creatinine ratio annually, along with the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and alkaline phosphatase concentrations, may allow for the early detection of AL amyloidosis in patients with IgM MGUS or WM with early signs of renal, cardiac, and liver amyloid involvement. Patients who have incidentally discovered amyloid deposits, such as through bone marrow biopsy or other biopsies, but do not show any signs of organ damage should undergo regular monitoring. A level of NT-proBNP below 180 ng/L argues against the presence of cardiac amyloidosis.[159-167] If there is a documented increase in either biomarker over these criteria throughout the follow-up period, it may be appropriate to explore using cardiac magnetic resonance or echocardiography to confirm the presence of cardiac involvement.

Lymphoma Cell-Mediated Morbidity.

Anemia. Anaemia is the most common reason for medical intervention and therapy in patients with WM. Many factors, such as the invasion of malignant cells in the bone marrow, iron deficiency, and hemolysis, can trigger anemia in people with WM. Increased levels of IgM can cause fluid accumulation in the body, leading to dilutional anemia. Patients diagnosed with absolute iron deficiency anemia as the only criteria for starting therapy in the setting of WM should have a physical exam to exclude gastrointestinal bleeding as an alternative explanation. Given the old age of many individuals with WM, it is plausible that a secondary malignancy, such as colon cancer, could be present simultaneously. Data also suggests that WM cells have increased hepcidin synthesis and secretion. Because hepcidin inhibits iron absorption, intravenous iron supplementation may be beneficial in some cases.[167] To evaluate warm or cold autoimmune hemolytic anemia, an in-depth investigation of hemolysis is required.[168] It's crucial to consider potential cobalamin and folate insufficiency, chronic renal, hepatic, or thyroid dysfunction, and inadequate nutrient intake.[168]

Extramedullary disease. Extramedullary WM is characterized by a clonal lymphoplasmacytic infiltrate in anatomical locations different from bone marrow. Case reports have documented lung manifestations such as masses, nodules, diffuse infiltrates, or pleural effusions resulting from WM.[169] Also, malabsorption, diarrhea, bleeding, or obstruction may suggest that the gastrointestinal system, specifically the stomach, duodenum, or small intestine, is affected. In some WM patients, cancer cells infiltrating the kidneys may cause renal failure.[170] Typically, cases arise after treatment rather than at the initial diagnosis, suggesting the possibility of clonal evolution or heterogeneity.[170] Recent case series revealed a median overall survival of 10 years, with a 79% survival rate (95% CI: 57-90%) for patients with WM with extramedullary diseases.[170,171] Individuals with WM that include all IPSS risk variables also have a similar survival rate.[171] These studies suggest that extramedullary WM, in contrast to multiple myeloma, remains treatable and may not result in a poor prognosis for these patients.[171]

Bing-Neel Syndrome (BNS). BNS is a disorder characterized by migrating and accumulating clonal lymphoplasmacytic cells (LPCs) in the central nervous system (CNS). In 1936, doctors Jens Bing and Axel Neel documented two individuals with neurological issues, hyperglobulinemia, and LPCs in their cerebrospinal fluid (CSF).[172] Only 1-2% of people with WM develop BNS.[173] Patients frequently exhibit a wide range of neurological abnormalities, including balance difficulties, ataxia, sensory and motor impairments, headaches, and cognitive impairments. Imaging studies, investigations of CSF fluid, and biopsies are all viable methods to definitively establish a clinical diagnosis of BNS. The first assessment should include gadolinium-enhanced magnetic resonance imaging (MRI) scans of the brain and the entire spine.[174-176] The leptomeningeal type, which results from the infiltration and migration of LPCs within the CNS, is the predominant form of CNS involvement in individuals with BNS, while the presence of brain masses is less frequent.[174-176] The detection of IgH locus rearrangements and MYD88 L256P gene mutations may serve as effective diagnostic methods for BNS.[177]

Young Patients with Waldenström Macroglobulinemia. WM is a cancer that primarily affects older patients. However, one in four people with WM are younger than 60, and one in ten are 50 or younger.[179-181] WM can potentially cause significant harm to this young patient population (50 years of age), which has a long-life expectancy and no significant comorbidities. Recent research examined the clinical traits and prognoses of a significant young WM (50-year-old) patient population encompassing more than five decades (1960–2013).[181] This study compared the long-term outcomes of a

significant cohort of young WM patients to those of a paired older WM patient cohort (65 years). When compared to older patients (>65 years) at the time of diagnosis, younger patients with WM had an estimated 10-year OS rate of 74%, with a higher percentage of deaths being attributed to WM (91% vs. 58%, p<0.0001). Consequently, despite the disease's slow progression, nearly all young patients succumb to it, resulting in an estimated loss of 11.2 years of life after diagnosis. The prevalence of lymphadenopathy, splenomegaly, hyperviscosity symptoms, and serum IgM levels were all higher in younger patients with WM at the time of diagnosis.[178-181] Interestingly, WM caused almost all WM-related deaths in younger patients but only about half in the older WM group. The DSS of older patients has improved due to advances in non-WM-related care,

such as supportive care and comorbidity management, as well as a rise in life expectancy due to improved WM-directed therapies. Younger patients with lower mortality and comorbidities may benefit less from these factors and die from WM-related causes.[181,182]

Conclusions. This first section of the state-of-the-art review presented a comprehensive description of the pathophysiology, clinicopathologic features, differential diagnosis, risk stratification, and clinical difficulties associated with WM. In the second section of this review, we will focus primarily on the treatment of MW. More specifically, we will investigate both the traditional, consolidated method and the novel therapeutic strategy, paying special emphasis to the utilization of genomics and novel targeted agents.

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