

# Clinicopathological Definition of Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations From the Second International Workshop on Waldenstrom's Macroglobulinemia

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This presentation represents consensus recommendations for the clinicopathological definition of Waldenstrom's macroglobulinemia (WM), which were prepared in conjunction with the Second International Workshop held in Athens, Greece during September 2002. WM is an uncommon lymphoproliferative disorder characterized primarily by bone marrow infiltration and IgM monoclonal gammopathy. It should be considered a distinct clinicopathological entity rather than a clinical syndrome secondary to IgM secretion. The underlying pathological diagnosis in WM is lymphoplasmacytic lymphoma as defined by the World Health Organization (WHO) and Revised European-American Lymphoma (REAL) classification criteria. The concentration of monoclonal IgM can vary widely in WM and it is not possible to define a concentration that reliably distinguishes WM from monoclonal gammopathy of undetermined significance (MGUS) and other lymphoproliferative disorders. A diagnosis of WM can therefore be made irrespective of IgM concentration if there is evidence on a bone marrow trephine biopsy of bone marrow infiltration by lymphoplasmacytic lymphoma with predominantly an intertrabecular pattern, supported by appropriate immunophenotypic studies. Simple criteria to distinguish patients with symptomatic WM who require therapy from those with asymptomatic WM and MGUS were also proposed. Patients with clinical features attributable to IgM monoclonal gammopathy but no overt evidence of lymphoma are considered to constitute a distinct clinical group and the term "IgM-related disorders" is proposed.

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THERE ARE CURRENTLY no universally accepted criteria for the diagnosis of Waldenstrom's macroglobulinemia (WM), a factor which has hindered our understanding of the disease. WM is a chronic lymphoproliferative disorder characterized by bone marrow infiltration and IgM paraproteinemia.<sup>1-3</sup> However, opinions vary as to the true nature of WM; some suggest that it is a distinct clinicopathological entity, while others argue that it is a clinical syndrome associated with monoclonal IgM secretion irrespective of the underlying pathological diagnosis.<sup>4-6</sup> The majority of clinical studies to date have accepted the presence of IgM monoclonal gammopathy in the context of an apparently indolent lymphoproliferative disorder as sufficient evidence for the diagnosis of WM. This is unsatisfactory, and diagnostic criteria incorporating clinical, morphological, immunophenotypic, and ultimately genotypic parameters are needed for the accurate diagnosis of WM. A consensus panel of interested investigators was therefore convened with the aim of resolving these difficulties and proposing reproducible diagnostic criteria that may be applied to future clinical trials. These statements are the result of extensive discussions that were held and subsequently refined at the Second International Workshop on Waldenstrom's Macroglobulinemia held in Athens, Greece during September 2002. The faculty of the International Workshop proposed that the consensus panel resolve a number of specific questions in formulating their proposal for a clinicopathological definition of WM.

## What Pathological Entities Should be Included in the Clinicopathological Definition of WM?

### Statement I

WM is an uncommon B-cell lymphoproliferative disorder characterized primarily by bone marrow infiltration with a predominately intertrabecular pattern along with demonstration of an IgM monoclonal gammopathy. WM should be regarded

as a distinct clinicopathological entity and not a clinical syndrome secondary to IgM secretion irrespective of the underlying pathological diagnosis. In WM this is considered to be lymphoplasmacytic lymphoma as defined by the Revised European-American Lymphoma (REAL) classification and World Health Organization (WHO) criteria.<sup>7,8</sup>

***Should IgG- or IgA-Secreting Lymphoplasmacytic Lymphomas be Considered in the Clinicopathological Definition of WM?***

**Statement 2**

The clinicopathological definition of WM should be confined to those patients with lymphoplasmacytic lymphoma who have demonstrable IgM monoclonal gammopathy.

***Discussion***

Statement 2 is primarily based on the unique role that the IgM monoclonal protein sustains in the clinical presentation of many patients with WM. Individuals with IgG or IgA monoclonal proteins or indeed nonsecretory lymphoplasmacytic lymphoma undoubtedly exist and they present similar clinical problems to those seen in WM.<sup>9-11</sup> However, their relationship to WM is unclear at present and requires further study.

***Is the Secretion of IgM Sufficient for Inclusion Into the Clinicopathological Diagnosis of WM? Is There a Minimum Threshold of IgM Required to Define WM?***

**Statement 3**

The demonstration of an IgM monoclonal protein is not synonymous with a diagnosis of WM as they are demonstrable in other lymphoproliferative disorders and monoclonal gammopathy of undetermined significance (MGUS). The concentration of IgM varies widely in WM and it is not possible to define a concentration that reliably distinguishes WM from MGUS and other lymphoproliferative disorders. A diagnosis of WM can therefore be made irrespective of IgM concentration if there is evidence of bone marrow infiltration by lymphoplasmacytic lymphoma and this is supported by immunophenotypic studies.

***Discussion***

The secretion of monoclonal IgM may be seen in most forms of B-cell lymphoproliferative disorder, as well as in MGUS,<sup>12-15</sup> and therefore the demonstration of an IgM monoclonal protein per se is not synonymous with a diagnosis of WM. IgM concentrations tend to be higher in WM but there is considerable overlap. The concentration of monoclonal protein rarely if ever exceeds 3 g/dL in MGUS and other lymphoproliferative disorders. However, the majority of patients with WM have IgM concentrations less than 3 g/dL and it is not possible to define an IgM concentration that consistently distinguishes WM from MGUS and other lymphoproliferative disorders.<sup>15</sup> The panel therefore considered that a diagnosis of WM could be made irrespective of IgM concentration if there was evidence of bone marrow infiltration by lymphoplasmacytic lymphoma and this was supported by immunophenotypic studies (see below). This statement is further supported by data from several large studies, which have demonstrated that the concentration of monoclonal protein has little or no prognostic relevance in patients with WM.<sup>16-21</sup> They do not appear to accurately reflect disease bulk and merely represent a continuous variable that does not correlate with the extent of bone marrow infiltration.<sup>22</sup>

**CRITERIA TO DISTINGUISH WM FROM OTHER IgM-SECRETING B-CELL MALIGNANCIES**

**Statement 4**

Central to the diagnosis of WM is the demonstration of bone marrow infiltration by lymphoplasmacytic lymphoma. This is defined as a tumor of small lymphocytes showing evidence of plasmacytoid/plasma cell differentiation without any of the clinical, morphological, or immunophenotypic features of other lymphoproliferative disorders.<sup>7,8</sup> A trephine biopsy should be regarded as a mandatory requirement for the assessment of patients while lymph node biopsies are encouraged in patients with accessible nodes. Immunophenotypic studies are strongly recommended for routine clinical practice and clinical trials.

***Discussion***

WM is characterized by bone marrow infiltration in virtually all cases.<sup>1-3,7,8,19,22-24</sup> It is therefore

clear that the demonstration of bone marrow infiltration by lymphoplasmacytic lymphoma (as defined by the REAL and WHO criteria) should be regarded as an absolute requirement in the diagnosis of WM. WM may very rarely occur in the context of extramedullary lymphoplasmacytic lymphoma but it is essential in such cases to satisfactorily exclude other lymphoproliferative disorders, particularly marginal zone lymphoma.

The panel considered that a trephine biopsy was a mandatory requirement for the assessment of patients and that the pattern of infiltration was usually intertrabecular.<sup>8,19,22,23</sup> A solely paratrabeular pattern of infiltration is unusual and should raise the possibility of follicular lymphoma particularly in a patient with lymphadenopathy. The panel considered that the presence of bone marrow infiltration should routinely be confirmed by immunophenotypic studies (flow cytometry and/or immunohistochemistry) and that such studies should also be encouraged for use in clinical trials. The combination of cytomorphology, pattern of infiltration, and immunophenotype (see below) should allow a definitive diagnosis of WM to be made in most instances.

#### **CRITERIA TO DISTINGUISH IGM MGUS, ASYMPTOMATIC WM AND SYMPTOMATIC WM**

##### **Statement 5**

Clearly defined and reproducible criteria that distinguish MGUS and WM are required to facilitate a better understanding of the outcome and natural history of the IgM gammopathies. Patients with an IgM monoclonal protein and unequivocal evidence of bone marrow infiltration by lymphoplasmacytic lymphoma should be considered to have WM irrespective of the IgM concentration. Patients should be considered to have MGUS if they have IgM monoclonal gammopathy but no morphological evidence of bone marrow infiltration by lymphoma. Patients with WM may be considered symptomatic if they have features attributable to tumor infiltration, eg, constitutional symptoms, cytopenia(s), and organomegaly and/or symptoms attributable to the monoclonal protein (eg, hyperviscosity syndrome, cryoglobulinemia, amyloidosis, or autoimmune phenomena such as peripheral neuropathy and cold agglutinin dis-

ease). It is also well recognized that some patients have clinical features attributable to the IgM monoclonal protein but no overt evidence of lymphoma. It is considered that these patients constitute a distinct clinical group, and the term "IgM-related disorders" is proposed. These criteria are summarized in Table 1.

##### *Discussion*

The panel considered that it would be inappropriate to suggest disease definitions based on arbitrary values for laboratory parameters such as IgM concentration and percentage of bone marrow lymphocytes. Patients with an IgM monoclonal protein and unequivocal evidence of bone marrow infiltration by lymphoplasmacytic lymphoma should be considered to have WM irrespective of the IgM concentration. It is acknowledged that some patients have equivocal evidence of bone marrow disease. This may manifest in a number of ways and includes the demonstration of clonal B cells by flow cytometry or polymerase chain reaction in the absence of morphologically detectable disease.<sup>24</sup> Similarly, patients may have equivocal bone marrow infiltrates without confirmatory phenotypic studies. It is proposed that these patients be classified as MGUS until further data become available.

#### **CONSIDERATIONS ON THE NEED AND USE OF A STAGING SYSTEM FOR WM**

##### **Statement 6**

The faculty supported the position that the development of a prognostic scoring system for WM was more appropriate than the adoption of a staging system and deferred considerations to Consensus Panel 2.

#### ***Immunophenotypic Definition of WM. Can WM Patients Express CD5?***

##### **Statement 7**

Immunophenotyping is of great value in the differential diagnosis of B-cell lymphoproliferative disorders and its application in all cases of suspected WM is strongly recommended. The characteristic immunophenotypic profile for lymphoplasmacytic cells in WM should include the expression of the pan B-cell antigens CD19, CD20, CD22, and CD79, as well as the expression

Table 1. Classification of WM and Related Disorders				
	IgM Monoclonal Protein*	Bone Marrow Infiltration†	Symptoms Attributable to IgM	Symptoms Attributable to Tumor Infiltration§
WM				
Symptomatic	+	+	+	+
Asymptomatic	+	+	-	-
IgM-related disorders‡	+	-(b)	+	-
MGUS	+	-(b)	-	-

\* The panel considered it to be inappropriate to define an IgM concentration to distinguish MGUS from WM. However, it is important to note that the IgM concentration rarely if ever exceeds 3 g/dL in MGUS.

† Patients with unequivocal bone marrow infiltration by lymphoplasmacytic lymphoma will be considered to have WM, while patients without evidence of infiltration will be considered to have MGUS. However, it is acknowledged that in some patients equivocal evidence of bone marrow infiltration is demonstrable. This may be manifest in a number of ways and includes the detection of clonal B-cells by flow cytometry or polymerase chain reaction in the absence of morphological evidence of bone marrow infiltration. Alternatively, patients may have equivocal bone marrow infiltrates without confirmatory phenotypic studies. It is considered that these patients should be classified as MGUS until further data become available.

‡ It is well recognized that a population of patients exist who have symptoms attributable to the IgM monoclonal protein but no overt evidence of lymphoma. Such patients may present with symptomatic cryoglobulinemia, amyloidosis, or autoimmune phenomena such as peripheral neuropathy and cold agglutinin disease. It is appropriate to consider these patients as a clinically distinct group and the term "IgM-related disorders" is proposed.

§ Symptoms attributable to tumor infiltration will include any of the following manifestations: constitutional symptoms, cytopenia(s), or organomegaly.

of light chain-restricted surface IgM. The majority of cases do not express CD10 or CD23, but a proportion of patients (5% to 20%) appear to express the CD5 antigen; however, the significance of this has not been established and warrants further study.

#### Discussion

There are relatively few published studies of immunophenotypic analyses in WM.<sup>19,24-28</sup> It would appear that the pan B-cell antigens CD19, CD20, CD22, and CD79 are expressed in virtually all cases, while CD10 and CD23 expression is rarely encountered. CD5 expression is uncommon, but this should not preclude a diagnosis of WM. However, care should be taken in CD5<sup>+</sup> cases to satisfactorily exclude chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. Expression of CD25, CD27, FMC7, BCL-2, and CD52 is seen in the majority of cases, but CD103 and CD138 expression is rarely if ever encountered.<sup>27,28</sup>

The degree of plasma cell differentiation can also vary considerably from case to case and may be extreme in some rare instances. In such circumstances it is essential to demonstrate that at least a proportion of cells express surface immunoglobulin

and/or B-cell antigens. Cases consisting entirely of plasma cells (cytoplasmic IgM<sup>+</sup>, CD20<sup>-</sup>, CD138<sup>+</sup>) do not fulfill the WHO criteria for lymphoplasmacytic lymphoma and should be considered as part of the spectrum multiple myeloma. This is also supported by a number of studies that have demonstrated a high incidence of lytic bone disease in such patients and the presence of chromosomal abnormalities more characteristic of multiple myeloma such as the t(11;14).<sup>29-34</sup>

#### PROGRESS ON CHARACTERISTIC CHROMOSOMAL ABNORMALITIES TO DEFINE WM

##### Statement 8

There are currently no disease defining cytogenetic abnormalities in WM. Cytogenetic criteria cannot therefore be included in the clinicopathological definition of WM at this time.

##### Discussion

There have been a number of published series of cytogenetic analyses in WM.<sup>35-39</sup> It is evident that many patients appear to be karyotypically normal, which reflects in part the low proliferative activity

Table 2. Proposed Diagnostic Criteria for WM

<ul style="list-style-type: none"> <li>● IgM monoclonal gammopathy of any concentration</li> <li>● Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation</li> <li>● Intertrabecular pattern of bone marrow infiltration</li> <li>● Surface IgM<sup>+</sup>, CD5<sup>+</sup>, CD10<sup>-</sup>, CD19<sup>+</sup>, CD20<sup>+</sup>, CD22<sup>+</sup>, CD23<sup>-</sup>, CD25<sup>+</sup>, CD27<sup>+</sup>, FMC7<sup>+</sup>, CD103<sup>-</sup>, CD138<sup>-</sup> immunophenotype*</li> </ul>
<p>*Variations from this immunophenotypic profile can occur. However, care should be taken to satisfactorily exclude other lymphoproliferative disorders. This is most relevant in CD5<sup>+</sup> cases, for which chronic lymphocytic leukemia and mantle cell lymphoma require specific exclusion before a diagnosis of WM can be made.</p>

of the clonal cells in WM. When clonal karyotypic changes are detected, the karyotypes of individual patients may be complex. Indeed, a plethora of numerical and structural abnormalities have thus far been described but to date no disease-defining abnormalities exist. Translocations into the immunoglobulin heavy chain (IgH) locus at 14q32 are a defining feature of many B-cell lymphomas and multiple myeloma and might therefore be an important oncogenic event in WM. Initial reports suggested that "lymphoplasmacytoid" lymphoma was associated with the presence of a t(9;14) that deregulates the PAX-5 gene.<sup>40,41</sup> However, none of the cases included in these analyses had demonstrable monoclonal proteins and they could not therefore be defined as WM. In a more recent analysis Schop et al were unable to demonstrate (by fluorescent in situ hybridization [FISH]) the t(9;14) in 48 patients with WM. Intriguingly, none of these cases had additional 14q32 signals indicating the absence of alternative IgH translocations in WM.<sup>39</sup> This observation has been confirmed in two subsequent studies,<sup>28,34</sup> and it seems likely that the absence of immunoglobulin translocations is a characteristic feature of WM. However, further analysis is required to identify "positive" genetic markers that may ultimately be used in the routine diagnostic setting.

### CONCLUSIONS

WM is a distinct entity characterized by bone marrow infiltration by lymphoplasmacytic lymphoma and IgM monoclonal gammopathy. It can be confidently diagnosed through a combination of clinical features, cytomorphology, pattern of bone marrow infiltration, and immunophenotype. It is to be hoped that the proposed diagnostic criteria (summarized in Table 2.) will be incorpo-

rated into future clinical trials and that they will be refined as more phenotypic and genotypic data become available.

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