Diagnosing Waldenström's macroglobulinemia (WM) in your patients

A diagnosis of WM can involve several stages and a range of investigative procedures. Here, we will explore these stages in more detail.

Risk stratification and prognosis in patients

WM risk factors in accordance with the International Prognostic Scoring System for Waldenstrom macroglobulinemia (IPSSWM)*[1]:

WM patients can be categorised into three stages[1]:

Stage 1 (low risk): 0–1 risk factors, except age; **5-year OS: 87%**
Stage 2 (intermediate risk): 2 risk factors, OR age; **5-year OS: 68%**
Stage 3 (high risk): ≥ 3 risk factors; **5-year OS: 36%**

Hb=haemoglobin, IgM=immunoglobulin M; OS=overall survival.

*The IPSSWM is a collaboration between 7 international cooperative groups, sharing collective data to create a prognostically meaningful international scoring system for patients with WM requiring therapy because of a symptomatic disease, according to the Athens workshop recommendations.[1]

Asymptomatic patients

At diagnosis, **30–50% of patients with WM are asymptomatic** and do not require therapy. The risk of progression to symptomatic disease is 59% at 5 years.[1,2]

Features of IgM monoclonal gammopathies*[4]

Characteristics	IgM MGUS	Smouldering WM (SWM)	Symptomatic WM
Serum IgM gammopathy	<3 g/dL	≥3 g/dL	Any level
Bone marrow LPL infiltrate	<10%	≥10%	≥10%[1]
Terminal damage/symptoms	No	No	Yes[1]
Hyperviscosity	No	No	Yes
Genetic characteristics and markers	Absence of 6q deletion, MYD88 L265P (up to 80%)	6q deletion, MYD88 L265P (90%), CD56–	6q deletion (30%–50%), translocation of IgH absent, MYD88 L265P (90%) CD56– CD25+ (88%) CD103–
Transformation risk	1.5% per year	12% per year for the first 5 years, 68% for the next 10 years	5%–10% risk of DLBCL

DLBCL=diffuse large B-cell lymphoma; IgH=immunoglobulin heavy locus; IgM=immunoglobulin M; LPL, lymphoplasmacytic lymphoma; MGUS=monoclonal gammopathy of undetermined significance; WM=Waldenström's macroglobulinemia.

*The table lists some important differential features of IgM monoclonal gammopathies. IgM paraprotein can be present in virtually all B-cell lymphoproliferative disorders.[3] Mayo clinical criteria require at least 10% bone marrow involvement by LPL, while the Second International Workshop on WM (IWWM-2) eliminated the requirement for a minimal amount of spinal cord involvement.[1] Constitutional symptoms: hepatosplenomegaly, lymphadenopathy, anaemia, hyperviscosity, solid organ involvement and rarely lytic lesions.

Table adapted from Paludo, *et al.* 2016.

Symptoms of WM

The most common initial symptom of WM is progressive asthenia due to anaemia[3]

Progressive asthenia

Other common symptoms are[5]:

Bleeding

Neurological manifestations

Lymphadenopathy

In addition to symptoms associated with other types of NHL, WM has additional symptoms:[3,6]

Implication of other organs

Production of excessive monoclonal IgM

Excessive monoclonal IgM results in further symptoms[3]:

Cryoglobulinaemia

Peripheral neuropathy

Hyperviscosity syndrome

Diagnostic pathway

Journey from non-specific symptoms to specialist referral

Non-specific symptoms

Symptomatic

Patient presents with persistent symptoms, such as fatigue, night sweats, and fever.[6,5]

Asymptomatic

Patients with no symptoms may be diagnosed as a result of incidental findings.[6]

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Primary care physician (PCP)

Testing

The PCP will conduct initial history check and physical examination, and then may request initial blood tests (complete blood count, serum immunoglobulin levels).[6,5]

Referral

If WM is suspected from the results of the tests, PCP will refer the patient to a specialist.[6]

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Specialist

Testing

Will carry out two essential tests: bone marrow biopsy and MYD88 L265P mutation test[6]

May also carry out further testing: CXCR4 mutation test, serum viscosity test, radiological test and CT scans[6,9]

Evaluation

Will perform prognostication using the IPSSWM (International Prognostic Scoring System for WM).[6]

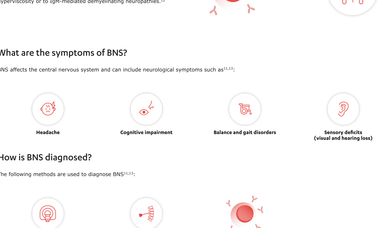
Treatment options will be symptom dependent:

Asymptomatic patients are not treated but should be followed up every 3–6 months; watch and wait[6]

Symptoms of hyperviscosity require urgent plasmapheresis, followed by first-line therapy choice[6]

No hyperviscosity leads to further assessment of tumour burden, followed by first-line therapy choice[6]

Testing in Waldenström's macroglobulinemia



Bone marrow aspiration and biopsy

A diagnosis of WM requires histopathological confirmation of bone marrow (BM) infiltration by monoclonal lymphoplasmacytic cells and the presence of any amount of monoclonal IgM protein, confirmed by immunofixation.[3]

The presence of monoclonal IgM without bone marrow infiltration does not fulfil the diagnostic criteria for WM, as this could also correspond to monoclonal gammopathy of undetermined significance (MGUS).[7] Differential diagnosis is crucial, as elevated IgM is also a feature of marginal zone lymphoma and IgM multiple myeloma, which constitutes approximately 1% of all multiple myeloma cases.[10] Please refer to "Immunophenotypic evaluation."

Immunophenotypic evaluation

Bone marrow infiltration by clonal lymphoplasmacytic cells can be confirmed by immunophenotypic studies, showing expression of CD19, CD20, CD22 and CD79a.[3]

About 90% of patients with WM harbour the myeloid differentiation primary response MYD88 $^{(L265P)}$ gene mutation in their lymphoplasmacytic cells, which may support a differential diagnosis from other morphologically similar conditions.[8]

However, MYD88 $^{(L265P)}$ is also found in 50%–80% of patients with IgM MGUS and may also be found in other lymphomas, such as marginal zone lymphoma. In addition, patients may fulfil the immunophenotypic and clinical criteria for WM but have other MYD88 mutations or wild-type MYD88.[3]

Approximately 30% of patients with WM have activating CXCR4 mutations. Clinical testing for CXCR4 mutations is not routinely recommended beyond the scope of clinical trials.[3]

Sensitive assay methods, such as allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), are recommended for immunophenotypic assessment.[3]

Bing-Neel syndrome

Bing-Neel syndrome (BNS) is a rare complication of WM that occurs in intracranial tissues, mainly causing neurological and ocular involvement.[4]

Bing-Neel syndrome (BNS) occurs when lymphoplasmacytic cells infiltrate different areas of the central nervous system, such as the brain parenchyma, leptomeninges, dura, or cerebrospinal fluid.

Normally, the nervous symptoms derived from WM are due to hyperviscosity or to IgM-mediated demyelinating neuropathies.[12]

What are the symptoms of BNS?

BNS affects the central nervous system and can include neurological symptoms such as[11,12]:

Headache

Cognitive impairment

Balance and gait disorders

Sensory deficits (visual and hearing loss)

How is BNS diagnosed?

The following methods are used to diagnose BNS[11,12]:

MRI of the brain and spinal cord

Lumbar puncture for analysis of CSF

CSF analysis

CSF is analysed by flow cytometry and cytology to determine the presence of lymphoplasmacytic cells and their morphology and the presence of markers, such as IgM.[11]

MYD88 e ICH

Additionally, PCR of the CSF could be used to determine if the patient has the MYD88 $^{(L265P)}$ mutation and rearrangement in the *IGH* gene.[11,14]

BM=bone marrow; BMB=bone marrow biopsy; CBC: BNS=Bing-Neel syndrome; CBC=complete blood count; Add: CSF=cerebrospinal fluid; CXCR4=C-X-C chemokine receptor type 4; DLBCL=diffuse large B-cell lymphoma; IgH=heavy chain immunoglobulin (immunoglobulin heavy locus); IgM=immunoglobulin M; LPL: IPSSWM=International Prognostic Scoring System for Waldenström's macroglobulinemia; LPL =lymphoplasmacytic lymphoma; MGUS=monoclonal gammopathy of undetermined significance; MRI=magnetic resonance imaging; PCP=primary care physician; PCP: PCR=polymerase chain reaction; WM=Waldenström's macroglobulinemia.

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