WM Basics Diagnostics, Understanding Lab Tests and Symptoms

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WM Basics
Diagnostics, Understanding Lab Tests and Symptoms

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Case 1

- A farmer with no significant personal medical history or family history
- Presented with pain in the shoulders and left wrist
- Had several severe nose bleeds which caused anemia

- Returned one year later with joint pains and severe nosebleeds

- Returned 5 years later with pneumonia, swelling of the feet, eczematous changes in the trunk, urine had albumin but no bence jones proteinuria
- Enlarged lymph nodes, *bled from the wound for more than a fortnight*

- He returned two years later with severe abdominal pain, still had albuminuria.
- Ocular exam showed multiple bleeds
- Still had symptoms of gingival bleeding and nosebleeds

Case 2

- Farmer with past medical history notable for **left** eye trauma 13 years prior, no family history
- Presents now with decreasing vision in the **right** eye, no longer able to read
- Has had bleeding from the nose and gingiva
- Examination notable for enlarged lymph nodes in the neck and mandible

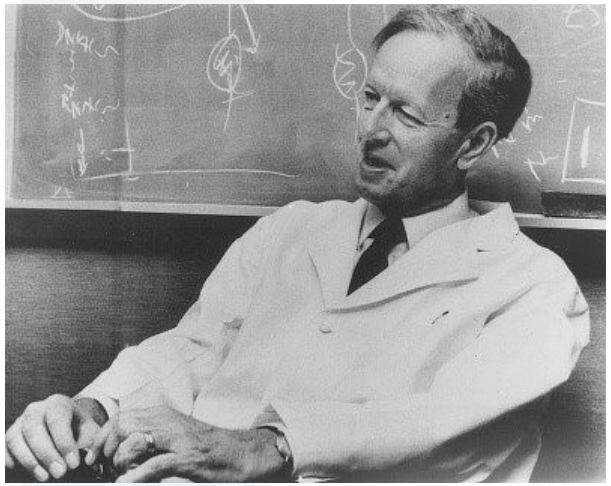
- Has had multiple recent admissions for bleeding, felt better after transfusions

- Returned 2 years later with fatigue, ongoing gingival and nasal bleeding
- Bone marrow biopsy (sternal) attempted but sample not obtained, bled for >12 hours after the procedure
- Labs notable for anemia (hemoglobin is 20) and low platelets (115)

- The two patients seem to suffer from the same malady
- Both anemic with tendency to bleed
- Slight enlargement of lymph nodes
- Anemia does not seem to be due to hemolysis (breaking of red blood cells)
- Bone marrow has the same appearance – **chiefly lymphocytoid cells.** Plasma cells at the upper limit of normal.

Acta Medica Scandinavica. Vol. CXVII, fasc. III—IV, 1944.

(From Med. Clin. Akad. Hospital, Upsala (Sweden). Chief: Prof. G. Bergmark).



Incipient myelomatosis or «essential» hyperglobulinemia with fibrinogenopenia — a new syndrome?

By

JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.

The real nature of myelomatosis.

The title of this paper may at first seem somewhat surprising. The myeloma has of old had a reputation as a well defined clinical entity. With the aid of the typical changes on the X-ray film and guided by the examination of the cells from a sternal puncture the diagnosis should therefore be easy and there ought not to be found

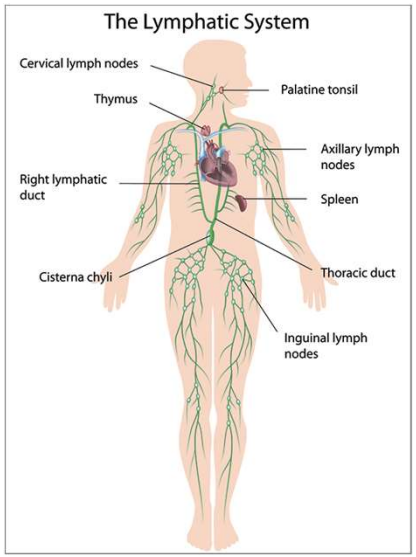
Waldenstrom J. Acta Medica Scandinavica. January/December 1944. 117(3-4):216-247.

Overview

- Incidence and brief epidemiology of WM and IgM MGUS
- What are the risk factors for WM
- Understand how WM is diagnosed
- How do we stage WM?
- Who needs treatment?
- How do we monitor when you don't need treatment?

What is Waldenstrom's Macroglobulinemia?

- WM is a type of non-Hodgkin lymphoma, characterized by:
  - **Lymphoplasmacytic lymphoma (LPL)** in the bone marrow
  - **IgM monoclonal gammopathy** in the blood

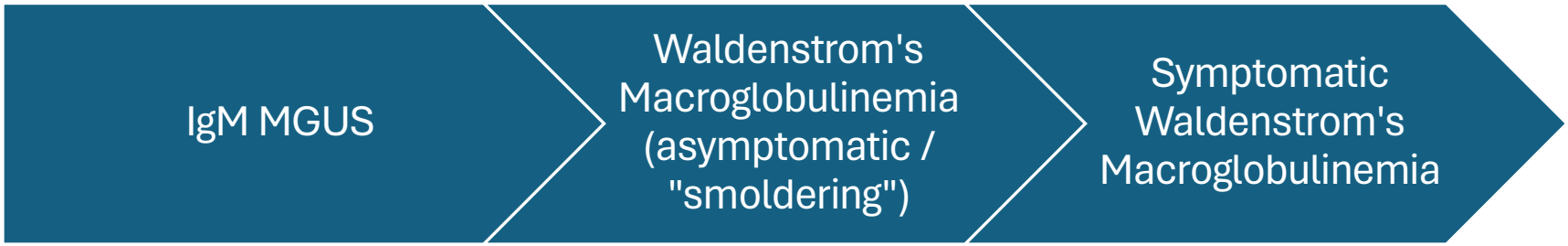


Alaggio R, et al. Leukemia. 2022 Jul;36(7):1720-1748.
https://iwmf.com/what-is-wm-lpl/

What is Waldenstrom's Macroglobulinemia?

- It is preceded by a precursor condition called an IgM MGUS (monoclonal gammopathy of undetermined significance)

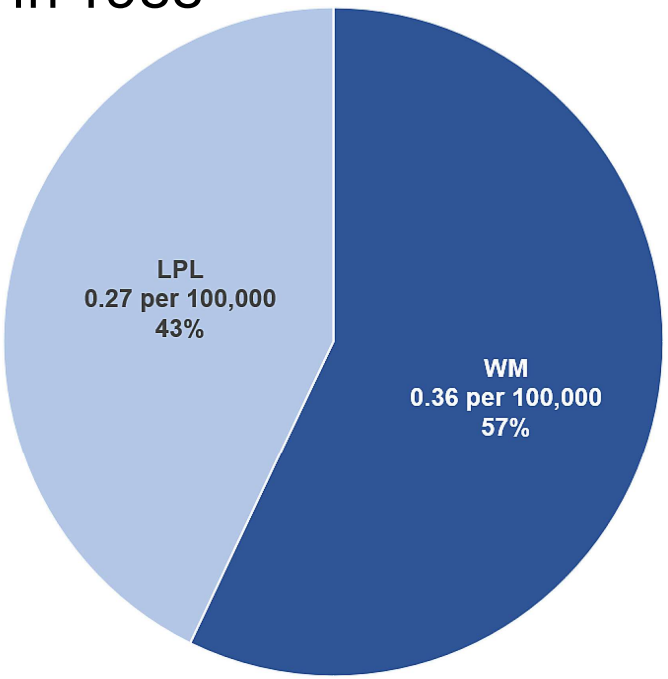
- WM can be either symptomatic or asymptomatic at initial diagnosis



What do we know about the incidence of WM?

- WM was first described in 1944
- Became reportable in the US as a malignancy in 1988
- IWWM first met in 2000

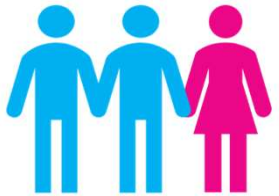
- It is rare, incidence is 3 per million, about **1000-1500 cases in the US per year**
- WM and LPL represent **2% of newly diagnosed non-hodgkin lymphoma**



McMaster M. The epidemiology of Waldenstrom Macroglobulinemia. Seminars in Hematology. 2023. 60:65-72.

Where did it come from?
What are the risk factors?

- Older age
- White race/ethnicity
- Males are affected more than females
- Chronic immune stimulation
  - Hepatitis C or HIV
  - Autoimmune conditions
- Family history
  - Clustering has been observed for over 60 years
  - Relatives with WM or B-cell malignancies or IgM MGUS
  - 64% increased risk for developing WM/LPL in individuals with a first degree relative



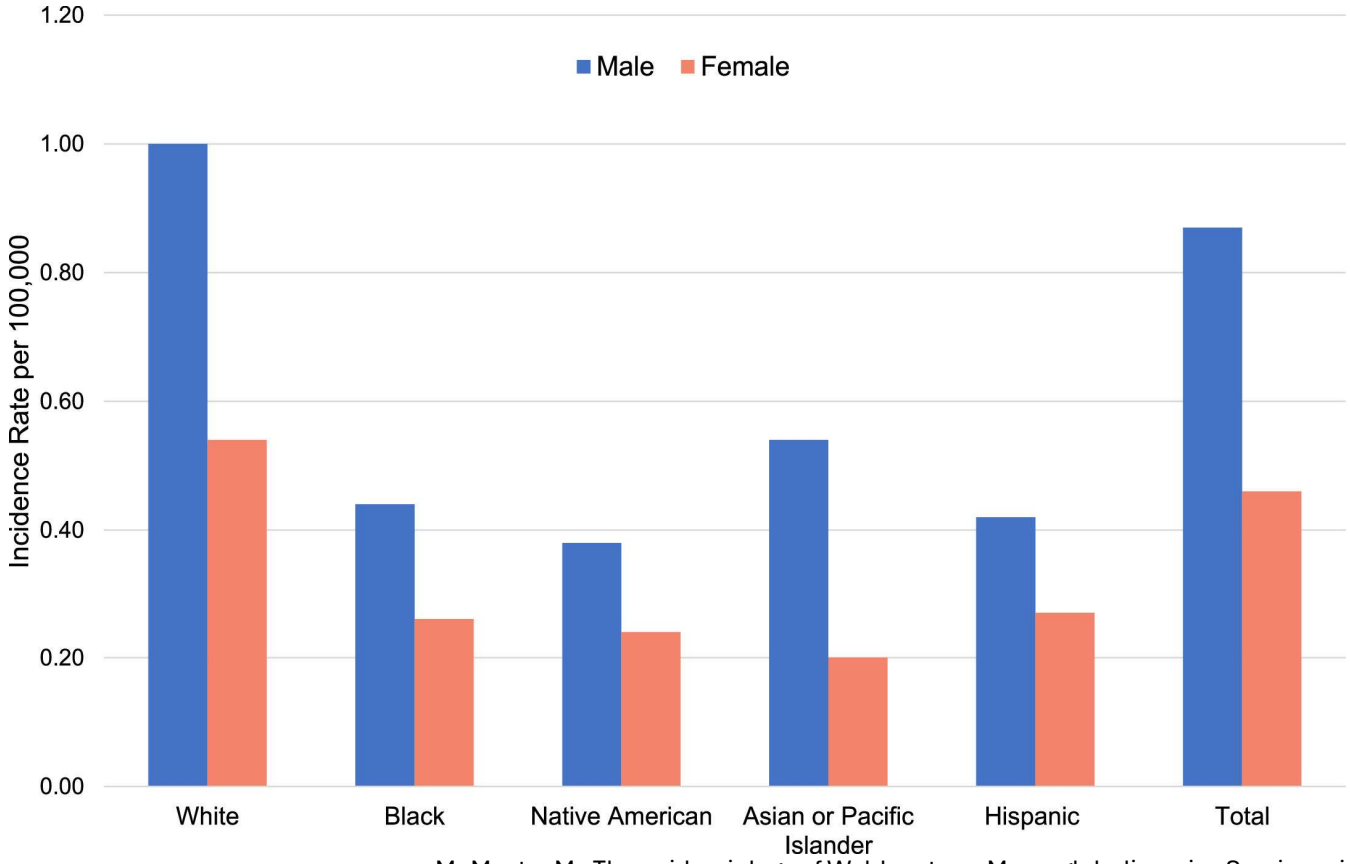
CM Vajdic, O Landgren, ML McMaster, *et al*. Medical history, lifestyle, family history, and occupational risk factors for lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia: the InterLymph non-Hodgkin lymphoma subtypes project. J Natl Cancer Inst Monogr, 48 (2014), pp. 87-97
KMcMaster M. The epidemiology of Waldenstrom Macroglobulinemia. Seminars in Hematology. 2023. 60:65-72.
oshiol J, et al *Arch Intern Med*. 2008;168(17):1903-1909

What if I have a family history?

- 4.3% of patients with WM have a positive family history of LP or WM
  - First degree relatives with WM have 20 x higher incidence of WM (but still rare overall)
  - First degree relatives are also at higher risk for non-hodgkin lymphoma, MGUS, CLL
- No role for screening asymptomatic relatives
  - Currently no preventative measures

Kristinsson SY, Björkholm M, Goldin LR, McMaster ML, Turesson I, Landgren O. Blood. 2008;112(8):3052

Incidence Rates of WM and LPL in the USA (2000-2019)



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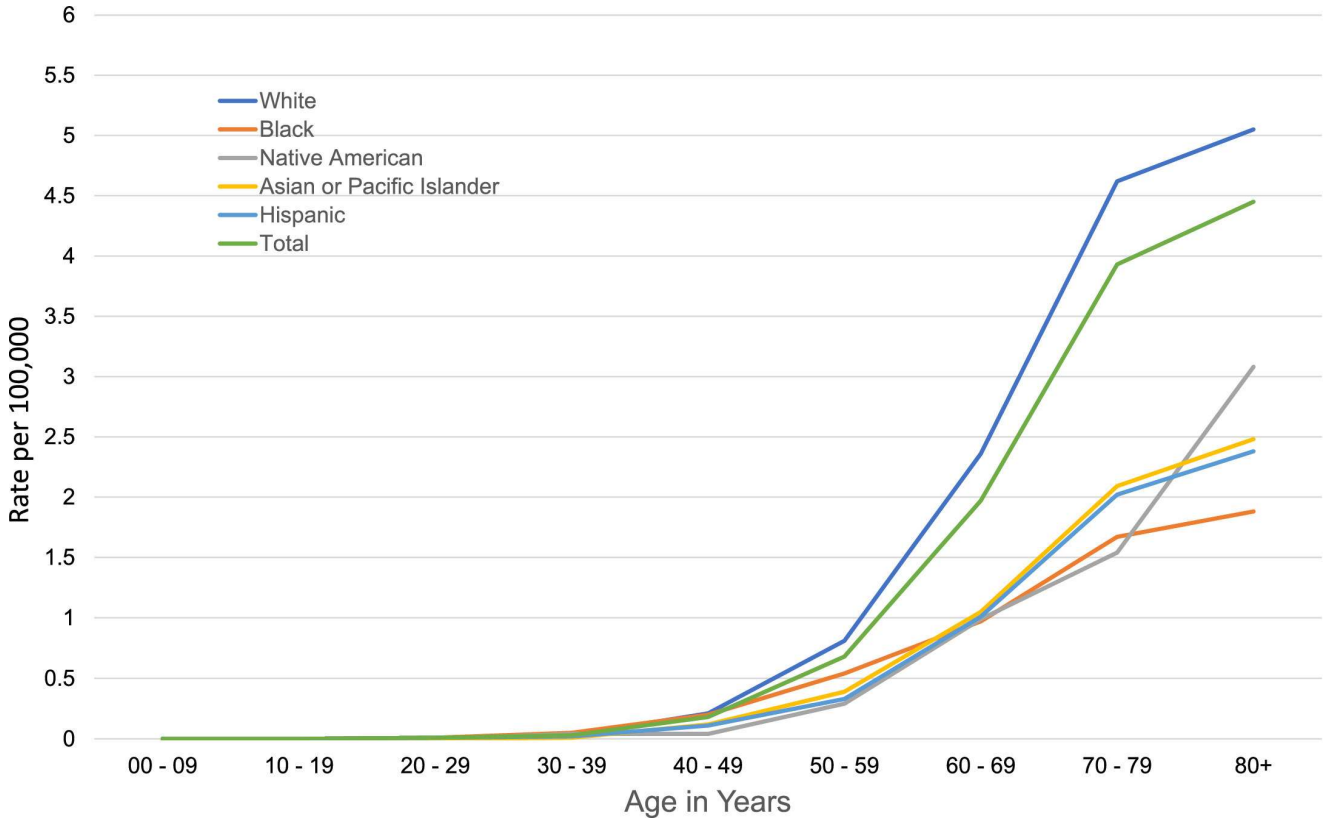

McMaster M. The epidemiology of Waldenstrom Macroglobulinemia. Seminars in Hematology. 2023. 60:65-72.

What about outside of the US?

Country/Region	Rate per 100,000		Period	Reference
	WM only	WM/LPL		
US Whites, 22 SEER registries	0.43	0.74	2000-2019	[20]
Olmsted County, MN, USA	0.57	–	1961-2010	[21]
South East England	0.55	–	1999-2001	[22]
Sweden – Norrbotten County	–	1.75	2000-2012	[17]
Sweden – Västerbotten County	–	1.48	2000-2012	[17]
Sweden	–	1.05	2000-2012	[17]
US Blacks, 22 SEER registries	0.16	0.33	2000-2019	[20]
US Asian or Pacific Islanders, 22 SEER Registries	0.18	0.35	2000-2019	[20]
Japan	–	0.28	2016	[19]
Japan	–	0.043	1996-2003	[18]
Taiwan	–	0.031	1996-2003	[18]
South Korea	0.03 (2003)			
	0.10 (2016)	–	2003-2016	[23]
US Hispanics, 22 SEER registries	0.17	0.33	2000-2019	[20]

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How about IgM MGUS?

- IgM MGUS is found in 1 in 600 persons over age 50
  - 3x more common than WM
- IgM MGUS is more common in the elderly
  - Most will not progress to WM or another disorder
- Patients with IgM MGUS require lifelong monitoring

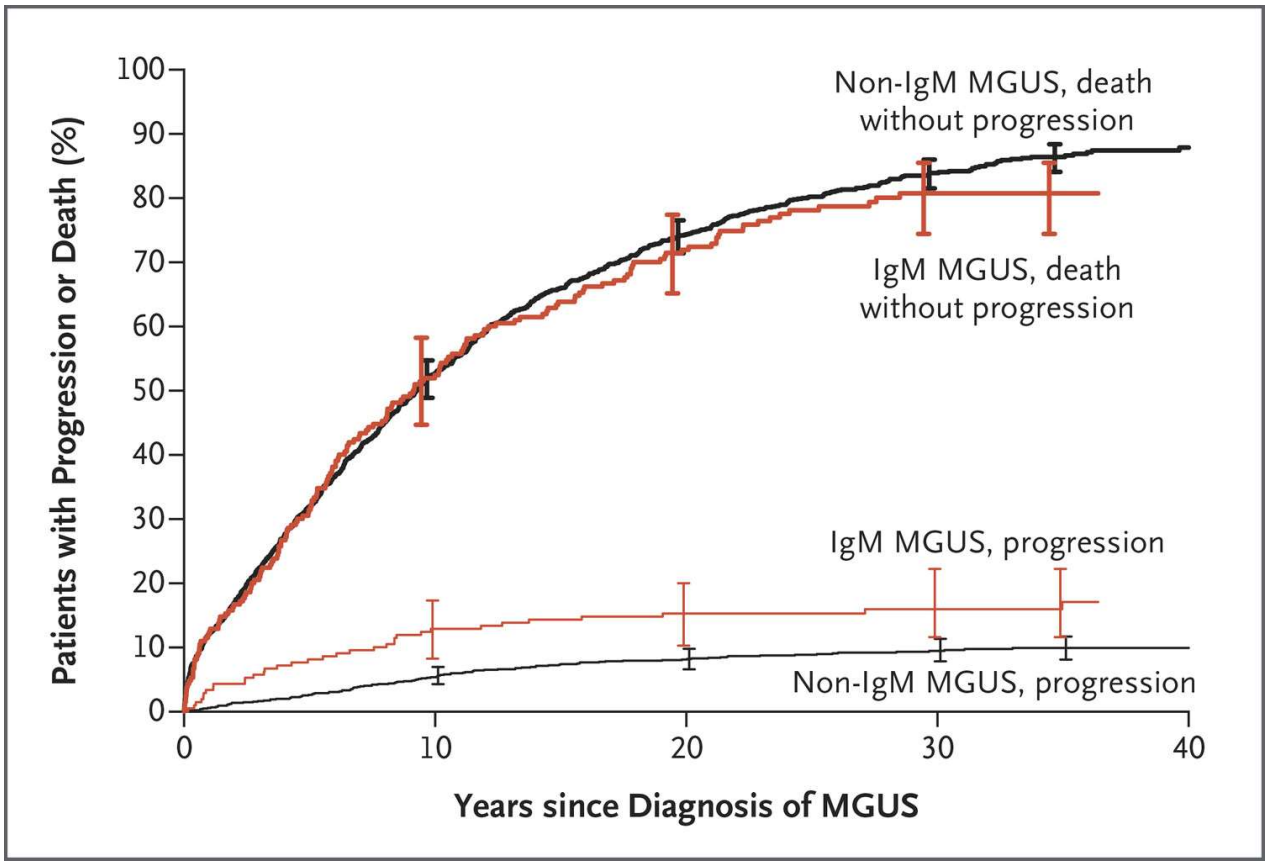
Gertz M.

IgM MGUS

Risk factors:

- Abnormal kappa/lambda ratio
- M-spike >1.5 g/dL

- Risk for progression at 20 years
  - 2 risk factors: 55%
  - 1 risk factor: 41%
  - 0 risk factor: 19%



Kyle RA. NEJM. **2018;378:241-249**

How is it diagnosed (what are the tests)?

Labs

For diagnosis:

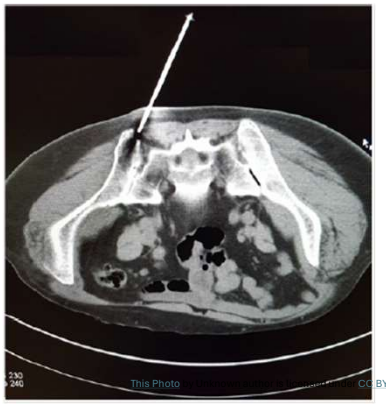
CBC with differential
Chemistries
IgM, IgG, IgA levels
SPEP
Serum immunofixation
Free light chains
UPEP

For prognosis:

Serum β2 microglobulin
LDH

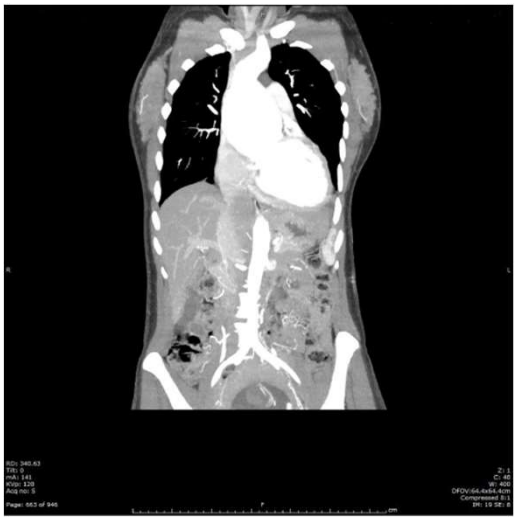
Bone marrow biopsy

Diagnose LPL
% bone marrow involvement
Molecular studies
(MYD88, CXCR4, TP53)



Imaging

CT scan of the chest, abdomen, pelvis



Treon SP, et al. Semin Hematol. 2023;60(2):97.

Other tests

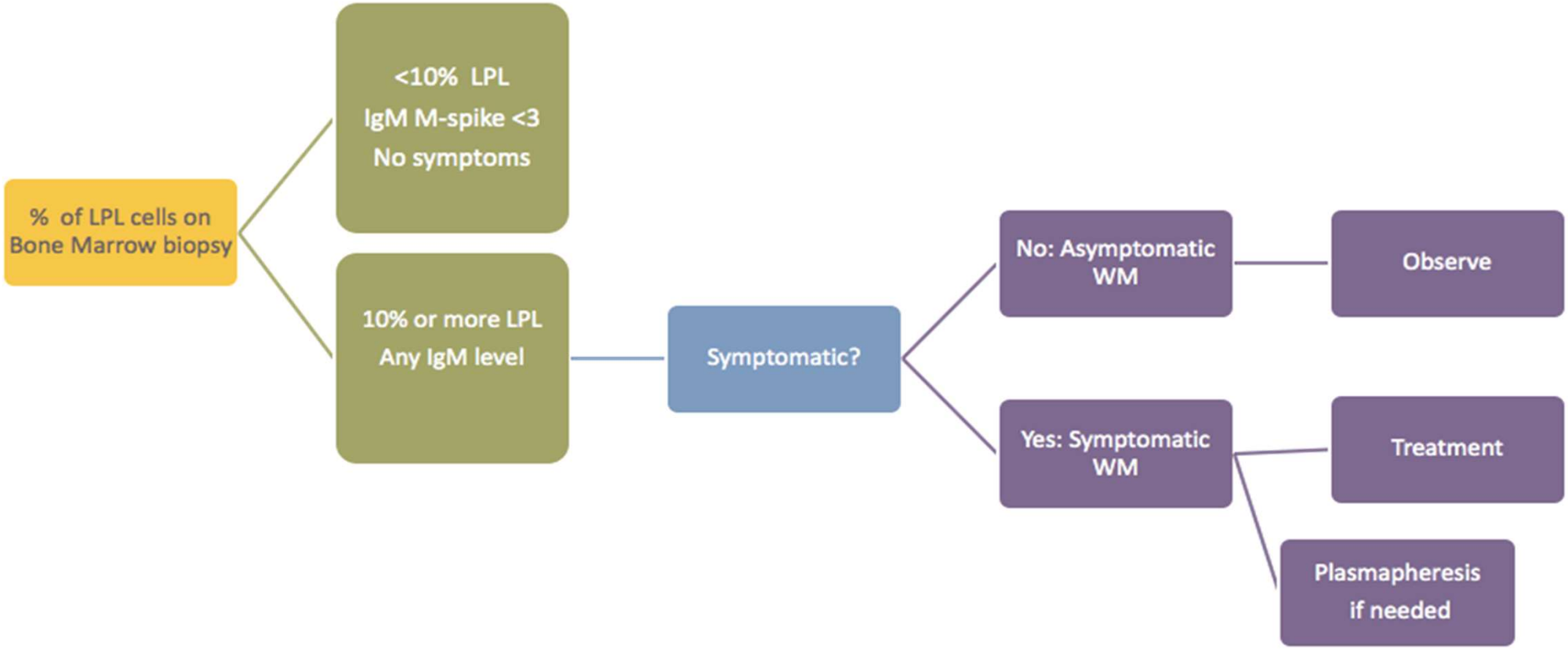
- Serum viscosity
  - If hyperviscosity syndrome symptoms present or when IgM >4000 mg/dL
- Ophthalmologic evaluation
- Coombs test
- Cryoglobulin
- Von Willebrand Ag
- Factor VIII
- Tissue stains for amyloid deposits.
- Testing for IgM myeloma (rare)
- Hepatitis B and C screening if rituximab therapy is planned
- Brain or spine imaging (if neurological symptoms)

How is it diagnosed
(i.e. how do I make sense of all this testing?)

- Diagnostic criteria for WM
  - **IgM monoclonal gammopathy** of any concentration
  - **Bone marrow infiltration by small lymphocytes** showing plasmacytoid/plasma cell differentiation
  - **Intratrabecular pattern of bone marrow infiltration**
  - Surface IgM+, CD5±, CD10−, CD19+, CD20+, CD22+, CD23−, CD25+, CD27+, FMC7+, CD103−, CD138− immunophenotype

Owen RG, et al. Clinicopathologic definition of Waldenstrom's macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Seminars in Oncology. April 2003. 30(20):110-115.

What can this tell us?



MYD88 L265P mutation

- Is seen in ~90% of patients with WM

- *MYD88 L265P* mutation is associated with response to BTKi therapy
  - Does not appear to impact chemo-immunotherapy or BCL2 inhibitor therapy
- Impact on survival is debated

- *MYD88 WT* status is associated with a higher risk for transformation to an aggressive lymphoma
- *MYD88 WT* status also has a shorter time from smoldering WM to development of active disease

Zanwar S, Abeykoon JP. Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond. Ther Adv Hematol. 2022 Apr 29;13:20406207221093962.

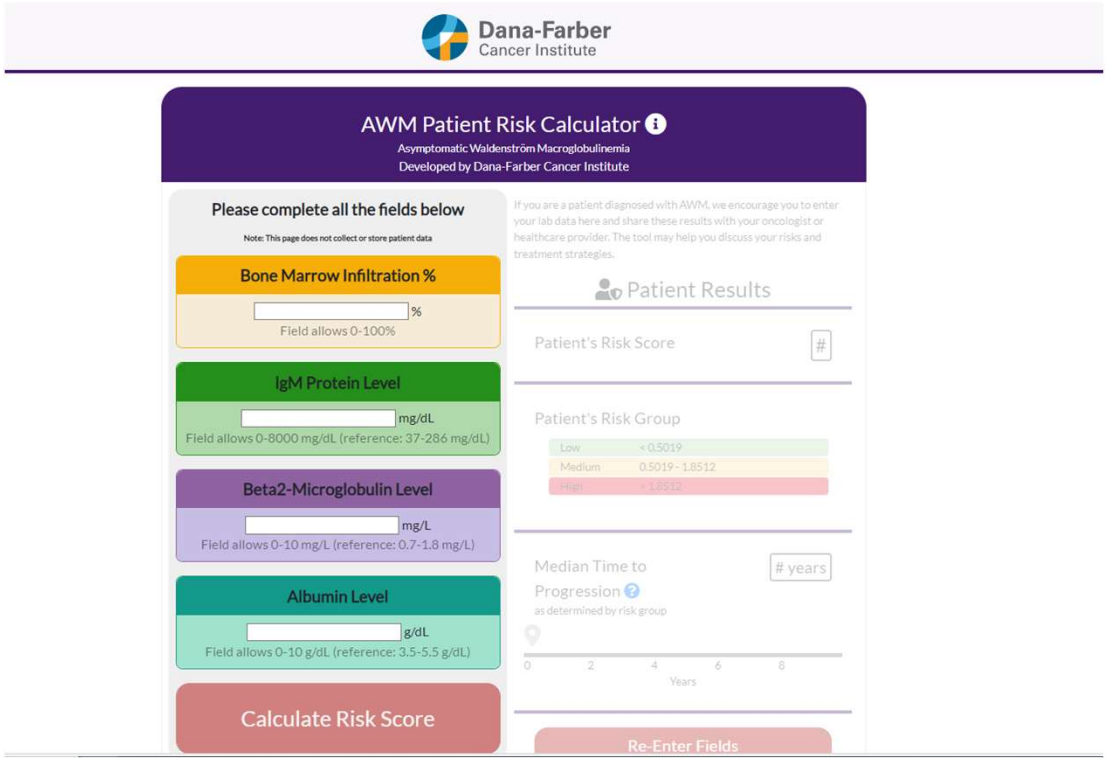
Asymptomatic (smoldering) WM

- Patients can fulfill diagnostic criteria for WM without symptoms related to disease

- Some patients with asymptomatic WM may not require therapy for prolonged periods of time
  - 6% at 1 year
  - 39% at 3 years
  - 59% at 5 years
  - 65% at 10 years

Treon SP, et al. Seminars in Hematology. March 2023. 60(2):97-106

Asymptomatic WM risk stratification tool



https://awmrisk.com

Watch and Wait

- Monitoring with clinic visits and labs
  - CBC with diff
  - IgM
  - Symptoms
  - Chemistries

- Imaging if needed

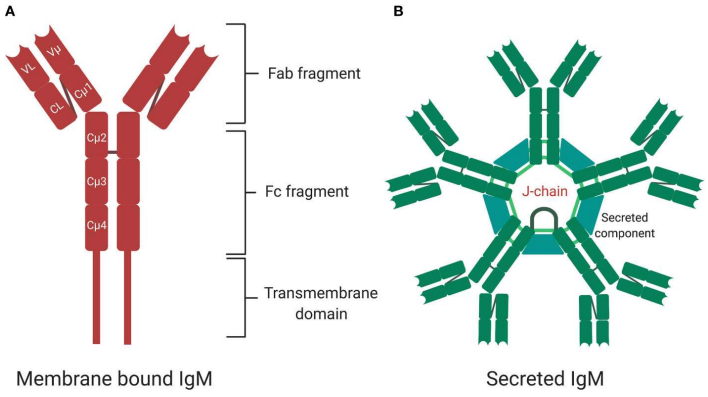
What are the symptoms to look for?

- Symptoms due to
  - High levels of IgM (hyperviscosity syndrome)
  - Symptoms of tumor mass or infiltration
  - Effects from the IgM itself

Hyperviscosity syndrome

- Rare with IgM <4000 mg/dL
- Symptoms are due to shear forces that rupture venous channels

- Nosebleeds
- Gingival bleeding
- Visual changes (retinal hemorrhage)
- Dizziness
- Lightheadedness
- Fatigue
- Sudden hearing changes

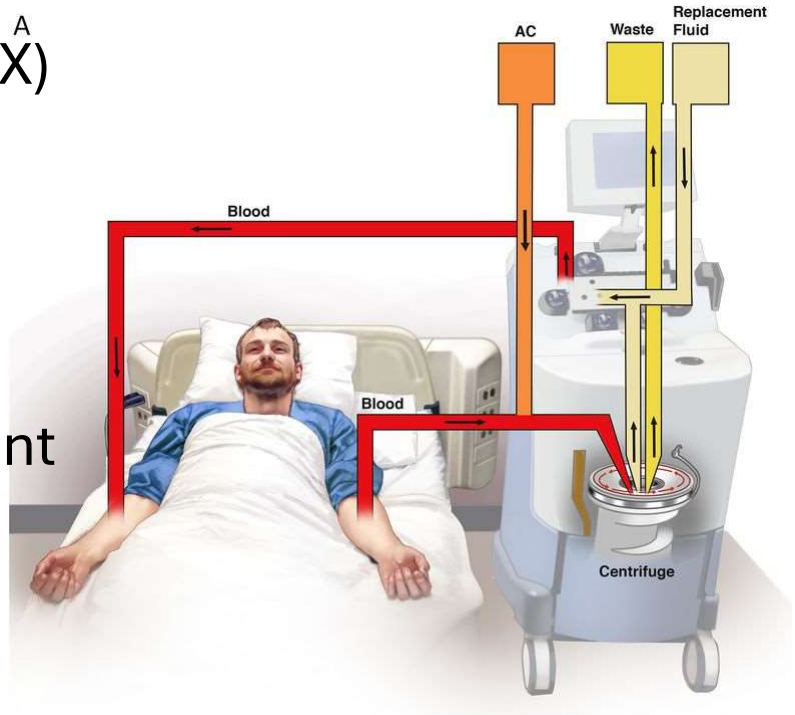


Membrane bound IgM

Secreted IgM

Plasma exchange temporizes hyperviscosity

- Plasma exchange (plasmapheresis, PLEX)[A]
- Removes excess IgM
  - To relieve hyperviscosity symptoms
  - To bring IgM to <4000 mg/dL prior to planned rituximab
- Single plasma exchange is often sufficient



Abeykoon JP, Zanwar S, Ansell SM, et al. Predictors of symptomatic hyperviscosity in Waldenstrom macroglobulinemia. *Am J Hematol*. 2018; **93**(11): 1384-1393.

What are the symptoms to look for?

- Symptoms due to
  - High levels of IgM (hyperviscosity syndrome)
  - Symptoms of tumor mass or infiltration
  - Effects from the IgM itself

Symptoms due to tumor mass or infiltration

- Constitutional symptoms (weight loss, fatigue, fevers, night sweats)
- Low blood counts
- Central nervous system infiltration (Bing Neel Syndrome)
- Enlarged organs
  - Lymph node enlargement
  - Spleen enlargement
  - Mass infiltrating another organ

Treon SP, et al. Seminars in Hematology. March 2023. 60(2):97-106

What are symptoms related to IgM itself?

- Too much IgM = Hyperviscosity syndrome

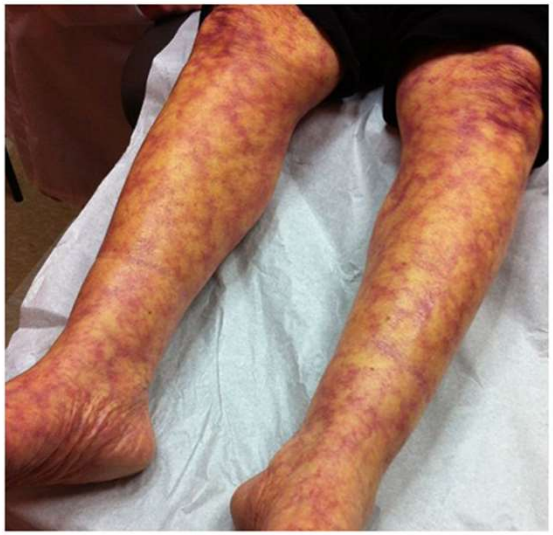
- IgM causing direct effects (even at a low level)
  - Cryoglobulinemia
  - Cold agglutinins
  - Light chain deposition disease
  - Amyloidosis
  - IgM demyelinating peripheral neuropathy
  - IgM deposition disease

- Monoclonal gammopathies of clinical significance

Treon SP, et al. Seminars in Hematology. March 2023. 60(2):97-106

Cold agglutinin disease

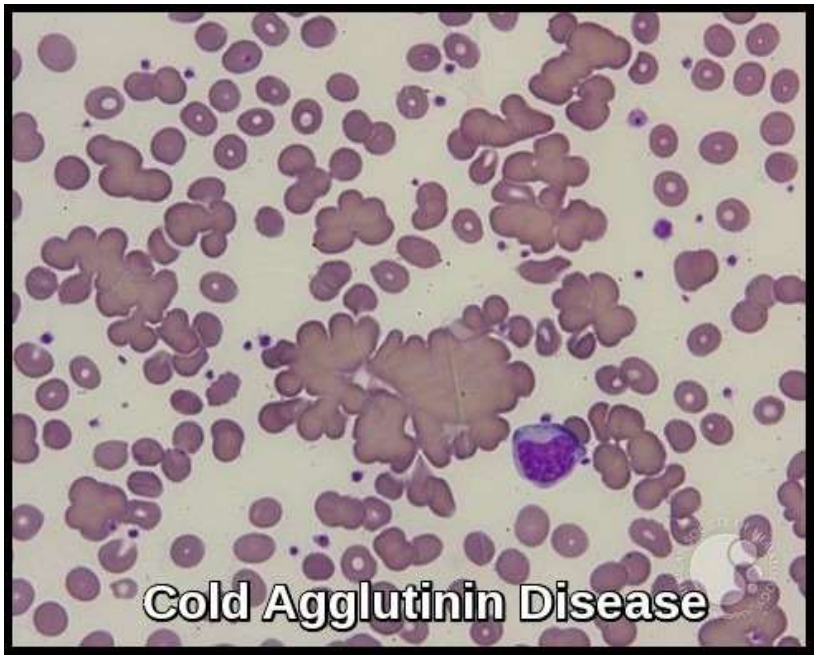
Livedo reticularis in cold agglutinin disease



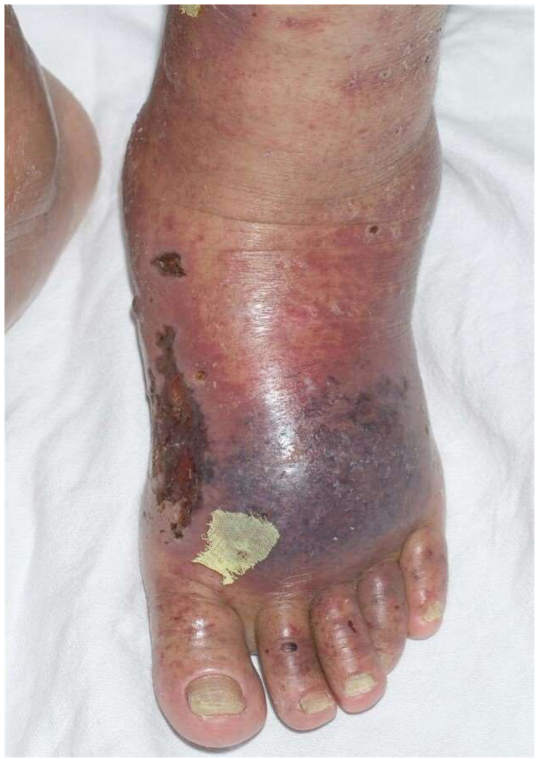
This photograph demonstrates a severe degree of livedo reticularis in a patient with cold agglutinin disease following exposure to cold. The patient's skin changes disappear completely without residua within several minutes following warming.

Photo courtesy of Dr. Jason Gotlib, Stanford University School of Medicine.

UpToDate®



Type I cryoglobulinemia



Purpura and stellate ulcerations of the foot.

- Cryoglobulins precipitate at temperatures below 37 C

- Type 1: occur in monoclonal gammopathies (MM, WM, CLL)
- Type 2: mixture of monoclonal Ig's in combination with RF and polyclonal IgG. Associated with hepatitis C, lupus
- Type 3: purely polyclonal, typically associated with hepatitis C or autoimmune disease

- inflammatory macules or papules
- hemorrhagic crusts
- Scarring
- Acrocyanosis
- livedo reticularis

Claveau JS, Wetter DA, Kumar S. Cutaneous manifestations of monoclonal gammopathy. Blood Cancer J. 2022 Apr 11;12(4):58.

IgM monoclonal gammopathies of clinical significance

- What if there are symptoms but does not meet criteria for WM?
- The monoclonal IgM protein leads to unique immunological or biochemical manifestations
- Indication for treatment is based on circulating IgM

Cold agglutinin disease	Acquired von Willebrand syndrome
Cryoglobulinemia (Type 1 or Type 2)	Acquired C1 inhibitor deficiency
IgM related neuropathy	Monoclonal gammopathy of renal significance
• IgM-associated AL amyloidosis	Pure red cell aplasia
• Schnitzler syndrome	IgM POEMS

Khwaja J, D'Sa S, Minnema MC, Kersten MJ, Wechalekar A, Vos JM. Haematologica. 2022 Sep 1;107(9):2037-2050.

How do I treat it?

- Chemo-immunotherapy (bendamustine and rituximab)
- Targeted agents (BTK inhibitors)

- Many other agents which will be discussed in this meeting!

Conclusions

- WM is diagnosed when there is a clonal IgM population and bone marrow infiltration by a lymphoplasmacytic lymphoma
- WM is preceded by IgM MGUS
- Not all patients who are diagnosed with WM have findings that require treatment initially
- Symptoms requiring treatment in WM are due to symptoms related to hyperviscosity, tumor mass/infiltration or direct effects from IgM

Special Thanks

- To the IWMF for their advocacy, education and getting us all together!
- To the many WM researchers globally who brought us to where we are today
- To the patients who participate in clinical trials
- To the patients and their families who are living with WM, allowing us to participate in their care

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