The ABCs of Waldenström’s Macroglobulinemia (WM)

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IWMF Ed Forum May 2017
Objectives

- Describe the roots underneath WM
- Review incidence, possible risk factors and clinical presentation of WM
- Explain diagnosis, symptoms, and treatment guidelines
- Provide a refresher course for veteran WMers and prepare the new attendees to get the most out of the rest of the Educational Forum
What is Waldenström’s Macroglobulinemia?

- WM is a **blood cancer**, a type of non-hodgkin lymphoma
  - Occurs when blood cells called **lymphocytes** and **plasma cells** reproduce out of control
  - These cells don’t die as normal cells do (More about this later, remember “bcl-2”)
  - WM cells make excess antibodies (always IgM), which are heavy proteins which can cause problems
  - Named after Jan Waldenström – Swedish oncologist (first identified in 1944)
Dr. Waldenström: I get to show this first but you’ll see it many more times.
How are blood cells produced?
What is Waldenström’s Macroglobulinemia? (cont)

- Rare cancer affecting 3 in 1 million/year
- 1500 new diagnoses in the U.S. each year
- Median age at diagnosis is 64
- 60% of patients are male
- More common in Caucasians than other ethnic groups
- Familial disposition present ~20% cases
REAL/WHO definition

- Lymphoplasmacytic lymphoma (LPL)
  - IgM secretion
  - LPL cells in the bone marrow
- Symptomatic vs. asymptomatic (smoldering)
  - Symptomatic needs to be treated
  - Asymptomatic does not need to be treated
- MGUS with IgM protein
What causes WM?

- Most cases are sporadic (occur by chance)
- I tell patients cause is “bad luck”
- About 20% are familial with at least 1 first degree relative with WM or another B cell disorder
- Main risk factor is the presence of IgM MGUS
Reported history of B-cell blood cancers among 1\textsuperscript{st} degree relatives of 257 pt with WM

Lymphoplasmacytic (LPL) cells

Aspirate from a patient with WM demonstrating excess mature lymphocytes, lymphoplasmacytic cells and plasma cells (courtesy of Marvin Stone M.D.)
WM: lymphocytes & plasma cells are both present

Figure 20.9 Waldenström. Bone marrow aspirate showing malignant cells with lymphoid and plasmacytoid morphology. (Reprinted with permission from Greer JP, et al. Wintrobe’s Clinical Hematology, 11th ed, Philadelphia, PA: Lippincott Williams & Wilkins, 2004.)
LPL cells: in WM how do they misbehave?

- They are clones of each other and try to take over the bone marrow
- The actual lymphoma cells (LPL) can cause symptoms
- The plasma cells make an abnormal type of antibody or immunoglobulin protein called IgM that can cause symptoms
- Rarely- the LPL cells, which are usually slow growing, can mutate and become fast growing
Immunoglobulin proteins (Ig’s)/Antibodies are made up of heavy chains and light chains- IgM is different than the rest
Normally we have a nice mix of all different kinds of immunoglobulins—we call this “polyclonal”

- In WM most of the IgM is completely identical, coming from clones of B cell/plasma cells
- We call this “monoclonal”
- This can be detected on a blood test known as SPEP (serum protein electrophoresis), often ordered by a doctor who notices the protein levels are too high in the blood on routine testing
- The IgM level can be determined by two different blood tests: IgM or M spike
Qigs – an important test for IgM (Quantitative Immunoglobulins)

- Measures the absolute number of IgM, IgG and IgA proteins
- In WM patients, IgM is HIGH and the other numbers are usually LOW
  - IgG (700-1600 MG/DL)
  - IgA (70-400 MG/DL)
  - IgM (40-230 MG/DL)
- Low numbers of IgA and IgG can lead to an increased risk of infection
WM occurs in phases: from MGUS to Smoldering to Symptomatic

- There are strict definitions
- We ONLY treat symptomatic WM
IgM Monoclonal Gammopathy of Undetermined Significance (MGUS)

Criteria

- Serum IgM monoclonal protein < 3.0 g/dL
- Bone marrow, lymphoplasmacytic infiltration <10%
- Absence of symptomatic anemia, lymphadenopathy, hepatosplenomegaly, or hyperviscosity
- Absence of constitutional symptoms


Chance of developing WM requiring treatment: 2%/year
Smoldering Waldenström’s Macroglobulinemia (SWM)

Criteria for Diagnosis

- Serum IgM monoclonal protein $\geq 3.0 \text{ g/dL}$ and/or
- Bone marrow, lymphoplasmacytic infiltration $\geq 10\%$
- Absence of symptomatic anemia, lymphadenopathy, hepatosplenomegaly, or hyperviscosity
- Absence of constitutional symptoms

Kyle et al., Blood 119:4462, 2012

Risk of worsening to point where symptoms are present and treatment is needed: $\sim 12\%$/yr, but risk lessens after 5-6 years
How does MGUS/Smoldering disease turn into symptomatic WM?

- Important research, here in the USA (Dr. Ghobrial) and in Iceland ongoing
- Many more patients need to be studied
Eligibility criteria

Inclusion

- Patients with Known or Suspected Precursor Hematological Cancer
  - MDS: Myelodysplastic Syndrome
  - MPN: Myeloproliferative neoplasms
  - Asymptomatic Multiple Myeloma and Waldenström Macroglobulinemia (MGUS & Smoldering)
  - MBL: Monoclonal B cell lymphocytosis

Exclusion

- Patients with Hematological Cancer or with symptomatic hematological malignancies requiring active therapy.
- Evidence of symptomatic or active hematological malignancy.

Note: Patients enrolled in a clinical trial for precursor diseases are NOT excluded from this study.
How can you help?

✓ **Step 1:** Become a Participant
✓ **Step 2:** Send in your Samples
✓ **Step 3:** Send in your clinical information
✓ **Step 4:** Complete the survey
✓ **Step 5:** Spread the word
Contact information

- Contact: Adriana Perilla-Glen
- Visit: [www.dana-farber.org/cpop](http://www.dana-farber.org/cpop)
- E-mail: precursor@partners.org
- Call: 617.582.8664
- Fax: 617.394.2603
How do WM patients present to their doctors?

- They have symptoms or signs which make the doctor suspect it (we’ll review these)

Or

- It is found incidentally by routine blood testing being suspicious
Presenting Symptoms of WM

- Weakness and fatigue 44%
- Bleeding manifestations 44%
- Weight loss 23%
- Neurologic symptoms 11%
- Visual disturbances 8%
- Raynaud's phenomenon 3%
WM Clinical Features

- **Tumor infiltration** (LPL cells)
  - Bone marrow: 90%
  - Splenomegaly: 38%
  - Lymphadenopathy: 30%

- **Circulating IgM**
  - Hyperviscosity syndrome: 15-20%
  - Cryoglobulinemia: 5-15%
  - Cold agglutinin disease: 5-10%
  - Bleeding disorders: 10%

- **Tissue IgM**
  - Neuropathy: 10-20%
LPL Cells and/or the IgM can produce symptoms:

- Adenopathy, splenomegaly ≤20%
- Fatigue, Sweats
- Hyperviscosity Syndrome: Epistaxis, HA, Impaired vision >4.0 CP
- IgM Neuropathy (22%)
- Cryoglobulinemia (10%)
- Cold Agglutinemia (5%)

Treon and Merlini, Williams Hematology 2011
What tests do we perform in a patient suspected of having WM?

- Blood work
- Urine test (looking for amyloid or other rare kidney issues)
- Bone marrow biopsy with MYD88 testing
- Sometimes CT scans

- Most important: talk to the patient!
Lab Evaluation

- Qig's
- Serum Viscosity
- SPEP + M protein
- FLC assay
- Chemistry (total protein, calcium, renal function)
- CBC (cytopenias)
- MYD88 and perhaps CXCR4
- Special tests about clotting and others
SPEP + M-protein (normal)
(serum protein electrophoresis + M)
SPEP + M-protein (abnormal)
(serum protein electrophoresis + M)
Free Light Chain Assay

- Measures kappa and lambda light chains not attached to the heavy chain (hence the term “free”)

- Lambda (3.3-19.4 mg/L)
- Kappa (5.71-26.3 mg/L)
- Ratio (0.26-1.65)
Serum Chemistry

- Total protein
- Assess for hypercalcemia
- Assess for renal disease
Complete Blood Count (CBC)

- WM patients are at risk for cytopenias (low blood counts)
  - Leukopenia (low white blood cell count)
  - Anemia
    - From underproduction of red cells secondary to a packed marrow
    - Hemolysis (destroying our own red cells)
  - Thrombocytopenia (low platelets)
    - Also important as these patients are at risk of acquired VonWillebrand disease = bleeding risk
Serum Viscosity

- Measures the resistance of fluid to flow
  - Water flows readily, less viscous = “thin”
  - Oil flows less readily, more viscous = “thick”

- IgM proteins make the blood more viscous
  - Can be mild and not cause symptoms
  - Or can thicken the blood causing headaches, nosebleeds, vision changes, or serious medical problems
  - May need plasmapheresis to remove IgM and then treat underlying production
Required to Properly diagnose WM

- A bone marrow biopsy MUST be done and show a type of non-hodgkin lymphoma called LPL
- There MUST be monoclonal IgM in the blood
- Now in newly diagnosed patients testing for a mutation in the LPL cells called MYD88
Typical BM Biopsy Report in a patient with WM

BONE MARROW BIOPSY:

Variably cellular, overall mildly to moderately hypocellular marrow (60-70% fat).

Approximately 30-40% of the cellularity and 10-20% of intertrabecular space is comprised of a predominantly nodular and interstitial population of small to intermediate sized lymphocytes, plasma cells, and lymphoplasmacytoid forms.

Mast cells are seen in association with the lymphoid aggregates.
Prognosis
Pay very little attention to what you read

- There are clinical lab features that can help with prognosis but I do not find them helpful
- In the future we’ll probably determine this by sophisticated DNA testing of the WM cells

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### Prognosis in WM

- **ISSWM**
- **587 patients at first therapy**

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<th>Risk</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tr>
<td>Age &gt; 65 years</td>
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<td>X</td>
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<td>Hb ≤ 11.5 g/dL</td>
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<td>Platelet ≤ 100 x10⁹/L</td>
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<td>≤ 1 factor</td>
<td>&gt; 1</td>
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<tr>
<td>B2M &gt; 3 mg/L</td>
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<td>2 factors</td>
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<td>IgM &gt; 7 g/dL</td>
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<table>
<thead>
<tr>
<th>N (%)</th>
<th>158 (27%)</th>
<th>223 (38%)</th>
<th>206 (35%)</th>
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<tr>
<td>Survival at 5 years</td>
<td>87%</td>
<td>68%</td>
<td>36%</td>
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Hb: hemoglobin; B2M: beta2-microglobulin; N: number of patients; %: percentage

Morel et al, Blood 2009
Treatment

- Brief review here as covered elsewhere in this forum
Consensus panel recommendations for initiation of therapy in WM.

- A high IgM level is not by itself an indication to initiate therapy.
- Hematocrit <30; Platelet count <100,000.
- Alleviate symptoms attributable to WM.
- Symptomatic Hyperviscosity (>4.0 CP).
- Moderate-Severe Neuropathies.
- Symptomatic cryoglobulinemia, cold agglutinin disease.

Semin Oncol 30: 116, 2003
Very important

- The level of IgM and/or the percentage of LPL (WM) cells in the bone marrow varies tremendously between WM patients.
- Some patients with very low IgM levels have lots of symptoms while others with very high levels may not have symptoms at all!
What on earth does this mean?
This demonstrates how the level of IgM, degree of anemia, and # of LPL cells in the marrow vary TREMENDOUSLY between patients.

Don’t worry! I’ll walk you through this.
This was a major breakthrough in WM - finding a genetic mutation picked up by chance during life which has major role in the development of WM.
What is new with diagnostics?

- MYD88 really encouraged to be tested
- Possibly CXCR4 ((another less common and more varied mutation)
- 90% WM patients have MYD88 “classic: L265P mutation
- About 10% DO NOT have it but we know they are WM – most have a different MYD88 mutation with fancier testing called sequencing
- Other non hodgkin lymphomas may have the MYD88 mutation
A Word on Familial WM (comes up every year)

- Dr. Mary McMaster at the National Cancer Institute
- They have a unit interested in families-including WM
- What may run in family?
  - WM or IgM MGUS
  - Other B cell blood cancers
  - Autoimmune diseases (especially Sjogren’s syndrome and thyroiditis)

We do not recommend routine screening of family members for WM (Dr. Kyle says “there is no risk”) - concept of relative risk versus absolute risk-that is, if your chance of getting WM is 3 times higher, it is 9 in a million, not 3.
OK let’s take some questions

And thank you!