Florida 101
Epidemiology

- Estimated prevalence 8,000 individuals in U.S (compare with ≈ 80,000 MM patients)
- Annual age adjusted incidence ≈ 3-8/million-year\(^1\)
- More common among older white men\(^1\)
- Familial predisposition with ≈ 20% of patients have a first degree relative with WM or a B cell disorder\(^2\). Familial WM usually diagnosed at an earlier age and with greater BM involvement.
- Risk factors: IgM MGUS (Relative Risk=46)

a. By sex and race

b. By age group
Epidemiology

Incidence of WM in Florida

Florida Cancer Data System.
http://fcds.medmiami.edu
Age Adjusted Incidence
Outline

• General hematology and immunology
• What is Waldenstrom’s Macroglobulinemia
• Understanding your lab work and response assessment
Hematology: The Study of **Blood**, Bone Marrow and Blood Diseases

- **Plasma**: mostly water with proteins (albumin) and nutrients, ions and hormones...
- **Serum**: plasma from which the clotting proteins have been removed (contains mainly albumin and immunoglobulins)
- **Cellular components of blood** are produced in the bone marrow

Hematocrit: Percent of red blood cells in blood
Cellular Component of Blood

• White blood cells: cells which are part of the immune system
• Red blood cells: contains hemoglobin, which transport oxygen
• Hemoglobin: main transporter of oxygen and carbon dioxide in the blood
• Platelets: small corks in the blood that stop bleeding
• Neutrophils: “infection fighting cells”... elevated with some infections (bacterial) and some cancers. Low after chemotherapy
• Lymphocytes: elevated with some viral infections and some lymphomas. Low in some viral infections, after some chemotherapy
Hematopoiesis: The formation of Blood Elements

Multipotential Hematopoietic Stem Cell

Myeloid Progenitor
- Megakaryocyte
  - Platelets
- Erythrocyte
- Myeloblast
  - Neutrophil
  - Basophil
  - Eosinophil
  - Monocyte
  - Macrophage

Lymphoid Progenitor
- NK cell
- Small Lymphocyte
  - B lymphocyte
  - T lymphocyte
  - Plasma cell
Types of Antibodies

- IgG (most abundant antibody produced, 4 subtypes)
- IgA (in mucosal areas, often as a dimer, 2 subtypes)
- IgM (on the surface of B cell and secreted early in the immune response as a pentamer)
- IgD (bound to B cells, antigen receptor)
- IgE (mediates allergic responses / parasitic infections)
What is Waldenstrom’s
Lymphocyte → Maturation → Plasma cell → Antibody

- Normal State
- Cancer Counterpart
  - Lymphoma
  - Waldenstrom’s Macroglobulinemia
  - Myeloma
  - M spike
The Spectrum of WM

- **IgM MGUS**
  - <10% BM involvement
  - Asymptomatic

- **Asymptomatic Waldenstrom’s**
  - ≥10% BM involvement
  - Asymptomatic

- **Symptomatic Waldenstrom’s**
  - ≥10% BM involvement
  - Any M protein
  - Symptoms present
Diagnostic Criteria for WM

- Diagnostic criteria:
  IgM Monoclonal protein of any concentration
  Bone marrow infiltration by small lymphocytes
    showing plasmacytoid/plasma cell differentiation.
    (usually intertrabecular) usually greater than 10%
  Immunophenotype: sIgM+, CD5 (+/-), CD10-, CD19+, CD20+, CD22+, CD23-, CD138+

*JCO. 2005;23(7):1564-77*
Symptoms of WM

Related to tumor infiltration

- Cytopenias (anemia)
- Constitutional Symptoms (fevers, sweats, weight loss)
- Lymphadenopathy (enlarged lymph glands)
- Organomegaly (enlarged liver, spleen)
- Infiltration of virtually any organ

Related to monoclonal protein

- Hyperviscosity (more viscous (thick) serum because of high protein)
- Cryoglobulinemia (antibodies that precipitate with cold exposure: ear lobes, feet)
- Cold Agglutinin (antibodies that result in destruction of red blood cells in cold)
- Neuropathy (damage to nerve ending)
- Amyloidosis (characteristic deposition of usually light chains in organs)
- IgM deposits causing renal failure, macroglobulinemia cutis
Diagnosing WM

- History / Exam
- Radiology
- Laboratory
- Pathology
Diagnosing WM: Work Up

- **Laboratory**
  - Routine labs (CBC, CMP)
  - SPEP, UPEP, serum free light chains, quantitative immunoglobulins
  - β2 microglobulin
  - Viscosity testing (if indicated based on symptoms)
  - Cryoglobulins (if indicated based on symptoms)
  - Cold agglutinins (if indicated based on symptoms)
  - MAG antibody testing (if indicated based on symptoms)

- **Radiology**
  - CT / PET

- **Pathology**
  - BM aspiration and Biopsy, flow, cytogenetics
  - MYD88 mutation
  - Congo red testing if indicated
  - LN biopsy (occasionally)
Differential Diagnosis: What Else Could It Be?

• IgM MGUS: common. <10% BM involvement, asymptomatic

• Marginal Zone Lymphoma (esp. splenic): morphology and immunophenotype may help distinguish, MYD88 mutation?, some with IgM paraprotein

• IgM Myeloma: rare. based on clinical features (bone disease), molecular features (t(11;14) and / or MYD88 mutation)

• Chronic lymphocytic leukemia (CLL): based on immunophenotype
Mutation Testing

• MYD88 (L265P): in 90-95% of WM patients, and in about 50% of IgM MGUS.
  – Helpful to distinguish WM from other mature B cell lymphomas (eg marginal zone) or MM.
  – Presence associated with greater disease burden (BM involvement, M spike) and linked to prognosis

• CXCR4: in ~30% WM (First such mutation in human cancer)
  – Similar to mutations in patients with WHIM syndrome, a congenital immunodeficiency disorder characterized by chronic neutropenia
  – Might have treatment implications

• More about this in “Advances in the Management of WM Revealed by Whole Genome Sequencing” by Dr. Treon tomorrow
Understanding your lab results
The Complete Blood Count (CBC): What to Look for

- White blood cells
- Hemoglobin
- Platelets
- Neutrophils

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Red blood cell indices
- MCV
- MCHC
- RDW
Understanding the complete metabolic panel (CMP)

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<td>Calcium</td>
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<td>ALT (SGPT)</td>
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</table>

- Electrolytes
- Blood sugar
- Kidney function
- Blood proteins
- Liver function
Lymphocyte maturation produces antibody.

Normal State

Lymphocyte → Maturation → Plasma cell → Antibody

Cancer Counterpart

Lymphoma → Waldenstrom’s Macroglobulinemia → IgM M spike

Produces Tumor Marker
SPEP: Serum protein electrophoresis

Normal Pattern

M spike Present
Immunofixation
Understanding SPEP results

Immunotyping/Immunofixation electrophoresis demonstrates the presence of an IgM Lambda monoclonal gammopathy.

Monoclonal gammopathy. An abnormal protein in the form of a monoclonal peak is observed in the gamma zone.

Immunotyping/Immunofixation electrophoresis demonstrates the presence of an IgM Lambda monoclonal gammopathy.
Understanding IgM results

\[ \text{IgM} = \text{clonal IgM} + \text{non clonal IgM} \]

- **What the cancer produces**

- **Produced by the normal immune system**
  (usually small in relation to the total IgM in a patient with Waldenstrom)
## Response Criteria

(BJH 2013 Jan;160(2):171-6)

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
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<td>CR (complete response)</td>
<td>• Absence of serum monoclonal IgM protein by IF, Normal serum IgM level.</td>
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<tr>
<td></td>
<td>• Complete resolution of extramedullary disease,</td>
</tr>
<tr>
<td></td>
<td>• Morphologically normal BMBx</td>
</tr>
<tr>
<td>VGPR (very Good Partial Response)</td>
<td>• Monoclonal IgM protein is detectable.</td>
</tr>
<tr>
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<td>• 90% reduction in serum IgM level from baseline*</td>
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<tr>
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<td>• Complete resolution of extramedullary disease,</td>
</tr>
<tr>
<td></td>
<td>• No new signs or symptoms of active disease</td>
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<tr>
<td>PR (partial response)</td>
<td>• Monoclonal IgM protein is detectable</td>
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<td>• ≥50% but&lt;90% reduction in serum IgM level from baseline*</td>
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<td></td>
<td>• Reduction in extramedullary disease, i.e.,</td>
</tr>
<tr>
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<td>• No new signs or symptoms of active disease</td>
</tr>
<tr>
<td>MR (minor response)</td>
<td>• Monoclonal IgM protein is detectable</td>
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<td>• ≥25% but&lt;50% reduction in serum IgM level from baseline*</td>
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<td>• No new signs or symptoms of active disease</td>
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<tr>
<td>SD (stable disease)</td>
<td>• Monoclonal IgM protein is detectable</td>
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<tr>
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<td>• &lt;25% reduction and &lt;25% increase in serum IgM level from baseline*</td>
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<tr>
<td></td>
<td>• No progression in extramedullary disease,</td>
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<tr>
<td></td>
<td>• No new signs or symptoms of active disease</td>
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<tr>
<td>PD (progressive disease)</td>
<td>≥25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the Disease</td>
</tr>
</tbody>
</table>
Tracking Waldenstrom’s

VGPR: Very Good Partial Response: 90% decrease in tumor marker
Pitfalls in monitoring IgM / M spikes

• At low M spike concentration, IgM may be close to the normal range and difficult to interpret
• At high concentration, clumping / dilutions makes the test less precise
• Discordant Responses: In some situations, the M spike / IgM decreases whereas the BM or Lymph nodes do not improve/shrink
  – More common with newer therapies (such as bortezomib)
  – BMBx remain an important part of monitoring response to therapy (especially as part of clinical trials)
Understanding Serum Free Light Chains

Definitions:
- Involved Free Light chain: one that is produced by Waldenstrom
- Uninvolved: produced by the normal immune system
- Kappa/lambda ratio: ratio of light chains (high or low defined imbalance)

Advantages over SPEP or IgM
- Shorter half life
- Prognostic?
- IgM measurement not very accurate at high and not very indicative at low concentrations
Serum Free Light chains

In Waldenström’s macroglobulinaemia, sFLCs may be helpful:

• As prognostic markers. sFLCs >80mg/L were associated with progressive disease and a shorter time to requirement for treatment

• As an additional criteria for treatment responses or disease relapse (? faster assessment of response)

• ? To help distinguish WM from IgM MGUS.

Haematologica 2008;93:793–4
Leuk Lymphoma 2008;49:1104-7
Serum Free Light Chain (to assess response)