Lymphoplasmacytic Lymphoma versus IGM Multiple Myeloma

The Spectrum of Plasma Cell Dyscrasias

Are you sure this is Waldenström macroglobulinemia?

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Hematology fellows’ conference 4/12/2013
Christina Fitzmaurice, MD, MPH
• 48 yo woman presents to ER with nonspecific complaints: diffuse body aches, LE edema, mild confusion

• ER LABS: Total protein 14.7, albumin 1.8, Hgb 7, PLT 132

• CT CAP: no LAD or splenomegaly
Hematology clinic

- SPEP: monoclonal IgM kappa 8.7 g/dl
- Beta-2 MG 10.2 mcg/ml
- Calcium (c): 11.3 mg/dl
- Creatinine 0.65 mg/dl
- Skeletal survey: negative
- Rouleaux formation on blood smear
- Viscosity 10.1 cp (1.4-1.8 cp)

ADMISSION FOR URGENT PLASMAPHERESIS
Viscosity

Viscum alba – Mistletoe

Viscometer

Water: 1 centipoise at 20°C


Hyperviscosity

• IgM>>IgG>IgA
• Incidence in WMG is 40-90%, 2-6% in MM
• Symptoms start at 4-5 cp (IgM>3 g/dl, IgG>4 g/dl, IgA>6 g/dl)
• Plasmapheresis most successful in IgM
• Variability between patients at what level of hyperviscosity symptoms develop
• Threshold for individual patient usually stable

Symptoms and exam findings

- Bleeding (skin and mucosal): Protein coating of platelets, interaction with coagulation factors, endothelial disruption
- Blurred vision
- HA
- Vertigo
- Lightheadedness
- Deafness
- Nystagmus
- Ataxia
- Stroke
- Coma
- Heart failure (plasma volume expansion)
- Polyneuropathy

“hot dogs on a string” or “sausaging”
Hematology consult patient

- Plasmapheresis x 2 inpatient
- Decrease in viscosity to 3.4 cp with improvement in symptoms
- Bone marrow biopsy was done
IgM monoclonal gammopathy
Retrospective analysis of 3176 patients with paraproteins

Annibali et al: Leukemia & Lymphoma, August 2006; 47(8): 1565 – 1569
WHO diagnostic criteria

- Lymphoplasmacytic lymphoma (LPL): Neoplasm of small B-lymphocytes, plasmacytoid lymphocytes and plasma cells
- WMG: LPL with bone marrow involvement and IgM monoclonal gammopathy
- Immunophenotype: Surface and cytoplasmic Ig expressed (IgM>IgG>>IgA)
- B-cell: IgD-, positive for pan-B antigens (CD19, CD20, CD22, CD79a, PAX5), negative for CD5, CD10, CD103, often CD 25+, CD23+-/−, CD38+
- Plasma cells: CD19+, MUM1+, CD138+
Diagnostic summary for WMG

• Lymphoplasmacytic lymphoma must be present
• Monoclonal IgM must be present
• Other lymphoproliferative or plasma cell disorders must be excluded
LPL/WMG cell of origin

Etiology
Development from a post-germinal center cell after somatic hypermutation but prior to class switch recombination

Merchionne et al: Waldenström’s macroglobulinemia. An overview of its clinical, biochemical, immunological and therapeutic features and our series of 121 patients collected in a single center; Critical Reviews in Oncology/Hematology 80 (2011) 87–99
LPL/WMG

• Genome-based comparative genomic hybridization showed chromosomal abnormalities in 83% of WMG patients

• Cytogenetic abnormalities are rare and non-specific: del6q (21-55%), trisomy 4, trisomy 5, monosomy 8, trisomy 12, del13q14, trisomy 14, del17p, del20q

Ghobrial: Are you sure this is Waldenstrom macroglobulinemia? ASH Education Book 2012
Mutations found by WGS in LPL

- MYD88 (91%)
- CXCR4 (27%)
- ARID1A (17%)
- MUC16 (13%)
- TRRAP (10%)
- TRAF2 (10%)
- Other

Xu et al: MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. BLOOD, 14 MARCH 2013 x VOLUME 121, NUMBER 11
MYD88

• Single nucleotide change on 3p22.2: L265P
• Protein adaptor through which Toll-like receptors (TLRs) and IL1 receptor signal
• Mutation leads to IRAK (interleukin-1 receptor associated kinase) 1/4 stabilizations promoting NF-κB and JAK-STAT3 signaling

Xu et al: BLOOD, 14 MARCH 2013 x VOLUME 121, NUMBER 11
# AS-PCR for MYD88

<table>
<thead>
<tr>
<th>237 patient cohort</th>
<th>Positive for MYD88 (%)</th>
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<tbody>
<tr>
<td>WMG</td>
<td>97/104 (93%)</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>13/24 (54%)</td>
</tr>
<tr>
<td>MZL</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>CLL</td>
<td>1/26 (4%)</td>
</tr>
<tr>
<td>MM (including IgM MM)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>IgG MGUS</td>
<td>0/9 (0%)</td>
</tr>
<tr>
<td>Healthy donors</td>
<td>0/40 (0%)</td>
</tr>
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Xu et al: MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. BLOOD, 14 MARCH 2013 x VOLUME 121, NUMBER 11
Significance of MYD88 mutation

- Therapeutic target: In vitro inhibitor of MYD88 showed decrease in nuclear staining of NF-κB
- Possible biomarker to differentiate WMG from other IgM paraproteinemias
- Possibly predicts transformation from IgM MGUS to WMG

Xu et al: MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. BLOOD, 14 MARCH 2013 x VOLUME 121, NUMBER 11
IgM monoclonal gammopathy
Retrospective analysis of 3176 patients with paraproteins

Annibali et al: Leukemia & Lymphoma, August 2006; 47(8): 1565 – 1569
IgM monoclonal gammopathy
Retrospective analysis of 382 patients with IgM paraprotein and lymphoid neoplasm (MM excluded)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total (%)</th>
<th>Range (g/dl)</th>
<th>Median (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL/WMG</td>
<td>225 (58.9)</td>
<td>0.2-10.9</td>
<td>2.2</td>
</tr>
<tr>
<td>CLL</td>
<td>77 (20.2)</td>
<td>0.1-2.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>18 (4.7)</td>
<td>0.1-1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>16 (4.2)</td>
<td>0.2-2.1</td>
<td>0.5</td>
</tr>
<tr>
<td>SMZL</td>
<td>11 (2.9)</td>
<td>0.1-2.4</td>
<td>0.4</td>
</tr>
<tr>
<td>MCL</td>
<td>11 (2.9)</td>
<td>0.2-1.3</td>
<td></td>
</tr>
<tr>
<td>CD5+/CD23- low-grade B-cell lymphoma</td>
<td>8 (2.1)</td>
<td>0.3-2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>DLBCL</td>
<td>7 (1.8)</td>
<td>0.2-1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>DLBCL concurrent with low-grade B-cell lymphoma</td>
<td>5 (1.3)</td>
<td>0.4-3.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>4 (1.0)</td>
<td>0.8</td>
<td>0.8</td>
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## Differential diagnoses

<table>
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<tr>
<th>Disease entity</th>
<th>Characteristics and how to differentiate from WMG</th>
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<tr>
<td>IgM-MGUS</td>
<td>-&lt;10% plasma cells cells in BM and &lt;3g of monoclonal Ig with no symptoms related to WM</td>
</tr>
<tr>
<td>MZL</td>
<td>-Morphology of lymph nodes (nodal MZL) or spleen (SMZL). Can be impossible to distinguish if only bone marrow samples are available</td>
</tr>
</tbody>
</table>
| Mantle cell lymphoma    | -Involves LNs and extranodal sites  
-t(11;14)/CyclinD1                                                                                                                                                                    |
| Follicular lymphoma     | -Small cleaved lymphocytes with Bcl-2 (t14;18) rearrangement                                                                                                                                                     |
| CLL/SLL                 | -Immunophenotype (positive for CD5, CD19, CD20, CD23)  
-peripheral lymphocytosis                                                                                                                                                          |
| IgM-MM                  | -Monoclonal plasma cells in the BM  
-Cytogenetics and FISH with MM-related abnormalities, specifically t(11;14)  
-Presence of lytic lesions                                                                                                                                                    |
Bone marrow aspirate/biopsy
Consult patient

• **Morphology:** involvement by clonal plasma cell process, no increase in B-cells (only few CD20 positive cells, cyclin D1 negative)

• **Flow cytometry:** abnormal plasma cell population with absent CD19, decreased CD45, monoclonal kappa cytoplasmatic light chain restriction, normal expression of CD38, CD138 without CD56. *No abnormal B-cell population is present.*

• **Cytogenetics and MM iFISH:** normal
Consult patient

- Diagnosed with IgM MM
- Currently undergoing treatment with VCD with plan for autologous stem cell transplant
Conclusions

• IgM paraprotein can be found in LPL, MGUS and various lymphoproliferative diseases
• IgM MM and WMG are two distinct disease entities
• MYD88 is a potential new biomarker with diagnostic, prognostic and possible therapeutic implications
Thank you