Waldenstrom's Macroglobulinemia

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Abstract

Waldenstrom's macroglobulinemia is an uncommon lymphoplasmacytic lymphoma presenting with hyperviscosity and autoimmune phenomenon. Disease is characterized by bone marrow infiltration by lymphoplasmacytic cells and raised IgM. Bone marrow morphology and immunohistochemistry is important for diagnosis. Course is indolent and anemia and age are most important prognostic factors. Treatment options include alkylating agents, anti-purine anti-metabolites, which though not curative but offer valuable responses. Newer agents like Rituximab and autologous transplant are being tried.

Incidence

The disease is quite uncommon with a risk of 1.7 per million person years in females and 3.4 per million person years in males.

Etiology

Etiology is largely unknown. Familial clustering has been seen, suggesting a genetic cause. 12 families containing 31 cases of WM have been reported so far. Prevalence of IgM monoclonal gammopathy in first degree relatives is around 3.2 to 6.3%.

Pathology

WM is a B cell lympho-proliferative disorder characterized by bone marrow infiltration and IgM paraproteinemia. It is placed under lymphoplasmacytic lymphoma category in WHO/REAL classification.

Malignant cell in WM is a lymphoid cell that has undergone somatic hyper-mutation. These cells express somatically mutated variable region suggesting their origin from post germinal cell. But their consistent expression of IgM suggests that they may have failed to undergo Ig isotype class switching.

Bone Marrow

Bone marrow is infiltrated with small lymphocytes showing evidence of plasmacytoid/plasma cell differentiation with a predominant inter-trabecular pattern (diffuse, interstitial, nodular). Para-trabecular pattern of involvement is rare and suggests an alternate diagnosis as follicular lymphoma. Degree of plasma cell differentiation can vary considerably.

Immunophenotyping

Immunophenotyping is important for diagnosis and differential diagnosis of WM. WM cell express pan B cell antigen CD_{19}, CD_{20}, CD_{22}, CD_{23}, CD_{45} (RA+/RO-) is present in all cases. Other antigens, which are expressed, include dim CD_{25}, CD_{27}, FMC7, BCL-2, CD_{22}, PAX-5, and dim CD_{35}. Cells are sIg (K:λ = 5:1) and cIg positive. Expression of CD_{5}, CD_{10}, CD_{11c}, CD_{23}, CD_{103}, CD_{138} is rare and uncommon.

Expressions of CD_{5}, FMC7-, CD_{25}-correlate with symptomatic disease, higher M component, and greater bone marrow infiltration.

Cytogenetics

Many patients are karyotypically normal which in part reflects the low proliferative activity of the clonal cells in WM. When clonal karyotype changes are detected, the karyotype is frequently complex. 6q deletion is the most common recurring abnormality. IgH translocation is characteristically absent. WM cells lack aneuploidy.

Paraprotein

WM cells secrete IgM paraprotein, which is hallmark of the disease. Level of IgM monoclonal protein though does not correlate with disease burden. Previously a cut off of 3gm/dL of IgM was proposed for the diagnosis but subsequently it was shown that majority of WM patients have IgM levels less than 3gm/dL. Hence presence of IgM para-protein is sufficient for the diagnosis. Serum IgM is measured by densitometry method. Presence of cryoglobulins/
cold agglutinins may affect the determination of IgM levels hence serum levels can be re-evaluated in warm conditions.

**Clinical Features**

The median age of presentation is 67 years. The clinical features of WM can be due to infiltration by malignant cell or due to the presence of monoclonal protein.

1. **Features attributable to tumor infiltration**
   a. Constitutional symptoms - recurrent fever, night sweats, weight loss, fatigue.
   b. Cytopenias due to bone marrow infiltration resulting in anemia, neutropenia and thrombocytopenia.
   c. Organomegaly - lymphadenopathy, hepatosplenomegaly.
   d. Occasional lung, GIT and skin infiltration.

2. **Feature attributable to monoclonal protein**
   a. Hyper-viscosity (6%) - oro-nasal bleeding, blurred vision, headache, dizziness, vertigo, ataxia, altered sensorium, and encephalopathy.
   Fundus examination shows retinal vein engorgement with ‘sausage formation’ hemorrhages and exudates with or without papilloedema.
   Serum viscosity can be measured by densitometry. Correlation between serum viscosity level and symptoms is poor, though symptoms are infrequent below 4 cp (normal level = 1.8cp).
   b. Cryoglobulinemia (4%).
   c. Amyloidosis.
   d. Autoimmune phenomenon (14%) - results in peripheral neuropathy and cold agglutinin disease.
   e. Nephropathy.

**Smoldering/Asymptomatic WM**

Patients with diagnosis of WM without symptoms or signs listed above are said to have asymptomatic/smoldering WM. Probability of transformation into a symptomatic disease at 5 and 10 years is 5% and 8% respectively. Levels of IgM, B2 microglobulin (B2M), anemia and lymphocytosis predict for malignant evolution.

**Diagnosis**

- Diagnosis of WM requires all of the following:
  1. IgM monoclonal protein of any concentration.
  2. Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation.
  3. Inter-trabecular pattern of bone marrow involvement.
  4. sIgM+, CD5−, CD10+, CD19+, CD20+, CD23−, CD27+, FMC7+, CD103−, CD138− immuno-phenotype.

**Prognostic Markers**

Median survival is 5-7 years. Anemia and age are the most important prognostic factors. Three different investigators (Table 1) have given three different prognostic variables.
Level of IgM is not determinant of disease burden.

**Differential Diagnosis**

Basically, WM should be distinguished from following using Tables 2 and 3.

a. IgM secreting lympho-proliferative disorders as B-CLL(chronic lymphocytic leukemia), SLL (small lymphocytic lymphoma), Marginal Zone Lymphoma (MZL), Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Multiple Myeloma (MM).

b. Lympho-proliferative disorders with lymphoplasmacytic differentiation - B-CLL, MZL, lymphoplasmacytic lymphoma (LPL).

Other differential diagnosis include:

1. Monoclonal gammopathy of uncertain significance (MGUS). This disorder is characterized by IgM monoclonal protein, which is generally <3 gm/dl. It can be easily distinguished from WM by absence of BM infiltration by lymphoplasmacytic lymphoma and absence of symptoms attributable to IgM.

2. IgM multiple myeloma. Presence of myeloma cells in BM, suppression of normal IgG and IgA levels, presence of osteolytic bone lesions and presence of 14q32 translocation (IgH translocation) differentiate WM from Multiple Myeloma.

**Table 1: Prognostic variables**

<table>
<thead>
<tr>
<th>Prognostic Features</th>
<th>No. of groups</th>
</tr>
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<tbody>
<tr>
<td><strong>1. Gobi et al</strong></td>
<td></td>
</tr>
<tr>
<td>Hb &lt; 9 gm/dl</td>
<td>0-1 prognostic factors</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>2-4 prognostic factors</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
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<tr>
<td>Cryoglobulinemia</td>
<td></td>
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<tr>
<td><strong>2. Morel et al</strong></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>0-1 prognostic factors</td>
</tr>
<tr>
<td>Albumin &lt; 4 gm/dl</td>
<td>2 prognostic factors</td>
</tr>
<tr>
<td>Hb &lt; 12 gm/dl</td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 4 x 10^9/L</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt; 150 x 10^9/L</td>
<td>3-4 prognostic factors</td>
</tr>
<tr>
<td><strong>3. Dhodakpar</strong></td>
<td></td>
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<tr>
<td>β2 microglobulin &gt; 3 mg/L</td>
<td></td>
</tr>
<tr>
<td>Hb &lt; 12 gm/dl</td>
<td>βb M&lt;3+Hb ≥ 12 gm/dl</td>
</tr>
<tr>
<td>IgM &lt; 4 gm/dl</td>
<td>βb M&lt;3+Hb&lt;12</td>
</tr>
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<td>βb M&gt;3+IgM&lt; 4 gm/dl</td>
<td>βb M&gt;3+IgM&lt; 4 gm/dl</td>
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</tbody>
</table>
CD38++, CD138+, CD56+, CD20-, FMC7-. Cytogenetic studies reveal t(11;14), del 13q which is absent in WM.

**RESPONSE CRITERIA**

Responses criteria to treatment are as follows.  

**Complete response**
1. Complete disappearance of serum/urine monoclonal IgM by immuno-fixation.
2. Resolution of adenopathy and organomegaly on CT scan.
3. Absence of signs and symptoms attributable to WM.
4. Absence of malignant cells by bone marrow histologic evaluation.

Complete response should be maintained for at least 6 weeks.

**Partial response**
1. \( \geq 50\% \) reduction in level of serum monoclonal IgM concentration on protein electrophoresis.
2. \( \geq 50\% \) improvement in bulky adenopathy/organomegaly on CT scan.
3. No new signs, symptoms or other evidence of disease.

**Progressive disease**
1. \( > 25\% \) increase in serum IgM monoclonal protein levels from the lowest attained response as determined by serum electrophoresis.
2. Progression of clinically significant disease related symptoms.

Not evaluable
Insufficient data/time for determination of response to treatment.

**TREATMENT**

The treatment of WM has not been standardized as yet, mainly due to rarity of disease.

Asymptomatic/smoldering WM needs close follow-up every 3-6 months with treatment only for progression.

When to initiate treatment?
Cytopenias attributable to disease, bulky adenopathy or organomegaly, constitutional symptoms or symptoms attributable to monoclonal protein needs treatment. Adverse prognostic markers or serum Ig levels should not be considered for initiating or selecting treatment.

Immediate plasmapheresis is needed for symptomatic hyperviscosity, moderate to severe neuropathy, symptomatic cryoglobulinemia and light chain cast nephropathy.

**DRUG THERAPY**

1. Alkylating agents: Chlorambucil at the dose 0.1mg/kg has produced response rate in various studies from 31-100%.
2. Nucleoside analogues.
   i. Fludarabine 30 mg/m2 d1-5 every 4 weeks has

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Table 2: Differential diagnosis of Waldenstrom’s macroglobulinemia from other lymphoproliferative disorders

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic</th>
<th>LN</th>
<th>Spleen</th>
<th>Anemia</th>
<th>Lympho-cytosis</th>
<th>Para-protein</th>
<th>BM</th>
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<tr>
<td>WM</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>DP</td>
</tr>
<tr>
<td>LPL</td>
<td>++</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+++</td>
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<tr>
<td>CLL</td>
<td>++</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>FL</td>
<td>-</td>
<td>+++</td>
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<td>±</td>
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<tr>
<td>SLVL</td>
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<td>-</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>±</td>
<td>+++</td>
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<tr>
<td>MCL</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>NMZL</td>
<td>-</td>
<td>+++</td>
<td>±</td>
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<td>±</td>
</tr>
</tbody>
</table>

\( \pm 10\% ; + 10-25\% ; ++ 25-50\% ; +++ 50-75\% ; ++++ 75-99\% ; DP = Defining criteria.\)

LN (lymph node), LPL (lymphoplasmacytic lymphoma), CLL (chronic lymphocytic leukemia), FL (follicular Lymphoma), SLVL (splenic villous lymphocytic lymphoma), MCL (Mantle cell lymphoma), NMZL (Nodal marginal zone lymphoma). Table reprinted from reference 19 with permission from Elsevier Publications.

Table 3: Differential diagnosis of Waldenstrom’s Macroglobulinemia from other lymphoproliferative disorders using immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>CD5</th>
<th>Slg</th>
<th>CD20</th>
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<th>CD10</th>
<th>FMC7</th>
<th>CD22</th>
<th>CD13</th>
<th>CD25</th>
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<tr>
<td>CLL</td>
<td>+</td>
<td>Dim</td>
<td>+Dim</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>Del(13)(q14)</td>
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<tr>
<td>PLL</td>
<td>±</td>
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<td>+</td>
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<td>-</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>trisomy 12, del 11q, del 6q, del (17p)</td>
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<tr>
<td>WM/ LPL</td>
<td>±</td>
<td>I</td>
<td>+I</td>
<td>±</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>t(11;14)</td>
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<tr>
<td>MCL</td>
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<td>I</td>
<td>+</td>
<td>±</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>t(11;14)</td>
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<td>FL</td>
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<td>B</td>
<td>+I</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>t(14;18)</td>
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<tr>
<td>MZL</td>
<td>±</td>
<td>B</td>
<td>+I</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>t(11;18), +3,+18</td>
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</table>

CD5++, CD10++, CD23++, CD13++, FMC7+. Cytogenetic studies reveal t(11;14).del 13q which is absent in WM.

Table reprinted from reference 19 with permission from Elsevier Publications.
produced response rates in 38% as 1st line and 33% as 2nd line treatment. 5 year overall survival was 62% and progression free survival in 49% was achieved. Low β2M and IgM<4gm/dl were predictors for poor overall survival. Myelosuppression and impaired cell mediated immunity were major toxicities observed. In a randomized trial fludarabine was found superior to combination of cyclophosphamide, adriamicin and prednisolone (Response Rate=30% versus 11% and Duration Of Response 19 versus 3 months).

ii. Cladribine was evaluated in 90 patients at the dose 0.1mg/kg. 94% patients responded with median survival of 73 months. Low Hb was the only predictor of poor response.

3. Immunotherapy : Rituximab, the chimeric humanized antibody against CD20 antigen was tried in heavily pretreated WM patients. A response rate of 57% was achieved in that population. It can lead to abrupt and transient increase in serum viscosity due to release of IgM in circulation following cell lysis. Ibritumomab, a radio-immunoconjugate against CD20 antibody has also been tried in WM patients in a phase I trial.

4. Thalidomide : It is an anti-angiogeneic, immunomodulator and apoptotic agent found useful in myeloma. In the dose of 200-600 mg/day, it achieved 25% partial response with median duration of response lasting 11 months in 20 WM patient. Major advantages is lack of myelo-suppression so it is useful in patients with cytopenias. Thalidomide has been combined with dexamethasone and clarithromycin to improve the results.

5. High dose chemotherapy (HDCT) with autologous transplant: Despite effectiveness of standard chemotherapy complete responses are rare. Hence next step is to try HDCT with stem cell support. In 49 patients transplanted so far, 9 achieved complete response and 39 patients had partial response. ASCT appears promising and needs further evaluation.

6. Experimental : Allogeneic transplant, IMID (immunomodulatory thalidomide derivative), BCL-2 antisense oligonucleotide, proteasome inhibitors are various experimental approaches being tried in patients with WM.

There is no randomized data yet to recommend one agent over other, or use of drugs in combination.

**Follow Up On Treatment**

Though IgM is poor indicator of bulk, serial measurements of monoclonal protein by serum electrophoresis is useful in following disease burden. Decrease in organomegaly may lag behind IgM decrease and vice versa hence it is recommended to monitor both parameters in patients on treatment.

**Conclusion**

WM is an IgM secreting lympho-plasmacytic lymphoma characterized by mucosal bleeding, hyperviscosity, organomegaly and cytopenias. Immunophenotyping is important for diagnosis and differential diagnosis. Course of the disease is usually indolent. Age and anemia are the most important prognostic factors. Various treatment options are available though not curative yields useful response rates.

**References**


