CLINICAL REVIEW ARTICLE

Waldenstrom’s Macroglobulinemia

By Meletios A. Dimopoulos and Raymond Alexanian

WALDENSTROM’s macroglobulinemia (WM) accounts for approximately 2% of hematologic cancers and affects approximately 1,500 Americans each year. The disease is more frequent among older persons and there may be a genetic predisposition, as suggested by family clusters. The original description of WM focused on bone marrow infiltration by plasmacytoid lymphocytes and a high level of circulating macroglobulin (IgM). Many aspects of the biology and clinical features of this disease were summarized recently. This review focuses on recent advances in the pathogenesis of complications caused by the elevated IgM and on the treatment of macroglobulinemic lymphoma.

DISEASE FEATURES

The most common clinical features of WM are depicted in Fig 1. Among large series of patients, the median age is 63 years. 55% are male, and lymphadenopathy or splenomegaly occurs in 20% to 40% of patients, especially when computed tomography or magnetic resonance imaging of the abdomen has been performed. Unusual sites of tumor infiltration include the lungs, the gastrointestinal tract, and the skin. Lytic bone lesions were present on standard radiographs in 2%, but bone marrow involvement was shown by magnetic resonance imaging in more than 90% of patients. Hypercalcemia occurred in 4% of our patients, with values ranging between 11.6 and 12.2 mg/dL, and increased calcitriol levels are the likely cause as in other types of lymphoma. Anemia, monoclonal blood lymphocytosis, and Bence Jones proteinuria occur in the majority of patients. Bence Jones proteinuria of more than 10 mg/d was present in 55%, but exceeded 1.0 g/d in only 3% of our patients. Serum β2-microglobulin exceeded 4.0 mg/L (normal, <3.0 mg/L) in 17 of 46 patients (37%) and C-reactive protein was greater than 4.0 mg/L (normal <4.0 mg/L) in 8 of 12 newly diagnosed patients. The hyperviscosity syndrome is the most common complication of circulating IgM, occurring in approximately 15% of patients. Other less common protein complications include cryoglobulinemia, cold agglutinin hemolytic anemia, peripheral neuropathy, and amyloidosis (AL), all of which occur more frequently in patients without lymphoma.

Biology: In most patients, the malignant B cell resembles a plasmacytoid lymphocyte, but many patients have only well-differentiated lymphocytes, as in chronic lymphocytic leukemia (CLL). Abnormal and complex karyotypes are common, most frequently consisting of a gain or loss of chromosomes 10, 12, or 20. Occasional patients have been reported with t(8;14) or t(14;18) translocations that may activate c-myc or bcl-2 oncogenes. More studies of cytogenetic abnormalities and oncogene expression may clarify the pathogenesis and implicate features of prognostic significance.

The malignant cells always express monoclonal IgM of the same light chain type as in the blood. Phenotypic markers reflect a continuum of differentiation, from small lymphocytes bearing large, focal deposits of surface Ig to plasma cells that contain only intracytoplasmic Ig (Table 1). In contrast, the cells of CLL usually show fainter and more homogeneous expression of both IgM and IgD on the cell membrane without maturation of Ig-secretory cells. In multiple myeloma, the plasma cells contain intracytoplasmic Ig and may express aberrant phenotypes. Thus, WM and chronic lymphocytic leukemia show different forms of a similar lymphoproliferative disorder, with marked leukemia uncommon in WM and monoclonal IgM uncommon in CLL.

Immunity: Normal Igs are less frequently and less markedly depressed than in multiple myeloma; thus, normal IgG exceeded 700 mg/dL in 52% and normal IgA exceeded 90 mg/dL in 41% of our previously untreated patients. Cellular immunity appears to be preserved in most patients; consistent with a previous report, CD4+ lymphocytes exceeded 0.5 × 10^9/L in 75% of our patients at diagnosis.

Macroglobulinemia without lymphoma. Many patients with monoclonal IgM and without symptoms are diagnosed by chance or while being assessed for a complication caused by the macroglobulin. Some patients have monoclonal lymphocytosis of bone marrow and/or blood, and it may be difficult to distinguish between asymptomatic WM and monoclonal IgM gammopathy of unknown significance. Asymptomatic patients should be monitored without treatment until a complication of circulating IgM or overt lymphoproliferative disease becomes evident.

COMPLICATIONS OF CIRCULATING MACROGLOBULIN

Hyperviscosity syndrome. Hyperviscosity syndrome caused by IgM virtually always occurs in patients who have an underlying lymphoma and is characterized most often by fatigue, dizziness, blurred vision, and easy bleeding of mucous membranes. The fundi may have distended, sausage-shaped retinal veins, hemorrhage, and papilledema. The plasma volume is moderately expanded, may reduce
Table 1. Phenotypic Features of Bone Marrow Malignant Cells

<table>
<thead>
<tr>
<th></th>
<th>CLL</th>
<th>WM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ig</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Cytoplasmic</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>T-cell–associated antigens</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>CD5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell–associated antigens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD10</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD19</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CD20</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>CD21</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>CD22</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>CD38</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>PCA 1</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviation: MM, multiple myeloma.
complement-dependent demyelination with conduction block, implying that the IgM causes human neuropathy. Most patients do not have evidence of lymphoma but clonal growth may occur later, indicating the importance of a screening electrophoresis in all patients with unexplained polyneuropathy. Immunocytochemical studies on sural nerve biopsies have shown the monoclonal IgM (usually of κ type) deposited on the outer layer of the myelin sheath, a sign suggestive of IgM anti-myelin antibody activity. In approximately one-half of the patients with neuropathy, the IgM is an antibody against carbohydrate epitopes of myelin-associated glycoprotein (MAG), as demonstrated by the immunoblotting technique. The presence of anti-MAG antibodies can be detected and quantified by enzyme-linked immunosorbent assay (ELISA), but their specificity is confirmed with immunoblots. When the IgM monoclonal protein immunoreacts with MAG it also reacts with the sulfate-3 glucuronyl paragloboside (SGPG), the principal antigenic acidic glycolipid in the ganglioside fraction of peripheral nerve. Because the amount of MAG within peripheral nerves is small, but abundant in the central nervous system, which is not affected, SPGP may be the main antigenic target. Intraneural injection of monoclonal IgM from patients into feline peripheral nerves induces a complement-dependent demyelination with conduction block, implying that the IgM causes human neuropathy.

A high proportion of IgM monoclonal Igs that do not react with MAG or SPGP immunoreact with other glycolipid antigens, such as GM₁, GD₁₇, asialo GM₁, or GM₂ gangliosides. In some patients, the IgM may react with chondroitin sulfate or sulfatides.

Although the clinical features of neuropathy are variable, patients with anti-MAG antibodies usually have a sensory or ataxic polyneuropathy. In contrast, patients with non-MAG-reacting IgM often have a mixed sensorimotor neuropathy. Electromyographic studies are needed to determine if the neuropathy is demyelinating, as seen in the majority of patients, or axonal.

Approximately one-third of patients with macroglobulinemia, but without neuropathy, demonstrate low titers (<1:400) of anti-MAG and SGPG antibodies by ELISA. Whether prospective screening of such patients for IgM anti-MAG antibodies would identify those at risk for future neurologic complications is unclear.

Renal disease. The renal complications of WM are less common and less severe than those of multiple myeloma because of the lower frequency and severity of hypercalcemia and Bence Jones proteinuria. A nephrotic syndrome is the most common renal complication, usually caused by complicating amyloidosis. Nephrosis may also result from the aggregation and precipitation of IgM molecules on the endothelial side of the glomerular basement membrane and their occlusion of the capillary lumen; the proteinuria is usually mild and reversible and most patients are asymptomatic. Usually, no antibody activity or glomerular proliferation is evident, although rare cases of cryoglobulinemia or an immune-mediated glomerulonephritis have been described. Approximately 5% of patients with monoclonal IgM do not react with MAG and SGPG antibodies by ELISA. The presence of anti-MAG antibodies can be detected and quantified by enzyme-linked immunosorbent assay (ELISA), but their specificity is confirmed with immunoblots. When the IgM monoclonal protein immunoreacts with MAG it also reacts with the sulfate-3 glucuronyl paragloboside (SGPG), the principal antigenic acidic glycolipid in the ganglioside fraction of peripheral nerve. Because the amount of MAG within peripheral nerves is small, but abundant in the central nervous system, which is not affected, SPGP may be the main antigenic target. Intraneural injection of monoclonal IgM from patients into feline peripheral nerves induces a complement-dependent demyelination with conduction block, implying that the IgM causes human neuropathy.

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thus, treatment has been adapted from established programs for CLL and low-grade lymphoma. Macroglobulinemia has been treated most commonly with a combination of an alkylating agent and a glucocorticoid, usually chlorambucil and prednisone. Both daily low-dose schedules and intermittent high-dose schedules have been used.\textsuperscript{8,10,59} We have studied a combination of chlorambucil (8 mg/m\textsuperscript{2}) and prednisone (40 mg/m\textsuperscript{2}) administered orally daily for 10 days and repeated at 6-week intervals with appropriate dose adjustments. Using criteria of response based on a 75\% or greater reduction of IgM synthesis, lymphadenopathy, and splenomegaly, 57\% of newly diagnosed patients responded and an additional 15\% of patients achieved a 50\% to 74\% reduction of IgM synthesis (Table 2). Treatment was continued until a maximum reduction of IgM was induced before follow-up without treatment. Relapses were slow, disease recontrol was frequent and prolonged, approximately 20\% of patients died from unrelated diseases, and the median survival was 5 years; others have described similar survival times.\textsuperscript{8-10} Approximately 10\% of patients achieved a complete remission as defined by the disappearance of IgM by immunoelctrophoresis or immunofixation and their median survival was 11 years; complete remission should also require the elimination of monoclonal lymphocytes from bone marrow, as for patients with CLL.\textsuperscript{60} The combination of cyclophosphamide, vincristine, and prednisone or the same drugs with doxorubicin have given similar results (Table 2), as in patients with CLL.\textsuperscript{51} Combinations of multiple alkylating agents with prednisone, alleged to produce higher response rates and longer survival,\textsuperscript{62,63} have not been compared with chlorambucil-prednisone in controlled studies. Interferons \(\alpha\) and \(\gamma\), and glucocorticoids, are each active in occasional patients with resistant disease but no trials of these agents have been conducted in previously untreated patients.\textsuperscript{64-66}

Nucleoside analogues such as fludarabine and 2-chlorodeoxyadenosine (2CdA) have been studied in previously untreated patients.\textsuperscript{67,68} Fludarabine has been administered in a dose of 25 mg/m\textsuperscript{2} intravenously daily for 5 consecutive days every 4 weeks, and 2CdA in a dose of 0.1 mg/kg daily for 7 days by continuous infusion through a central venous catheter using a portable pump. For both agents, 79\% of patients responded to as few as 2 courses, 10\% of patients achieved a complete remission, and only 1 of 19 patients has died of WM after a median follow-up of 18 months (Fig 2). Repeated courses of a nucleoside analogue should be limited to prevent unpredictable occurrences of severe \(\alpha\)-chain marrow aplasia.

Intracellular phosphorylation by deoxycytidine kinase converts fludarabine and 2CdA to their active triphosphates. The ratio of deoxycytidine kinase activity to cytoplasmic 5'-nucleotidase expression correlates with subsequent sensitivity to 2CdA in patients with CLL.\textsuperscript{69} These parameters may help identify those patients with macroglobulinemia and other small cell lymphomas who are most likely to respond to a nucleoside analogue. Whether a program that alternates 2CdA with chlorambucil-prednisone would be more effective requires further study. Human macroglobulinemia tumors have been propagated in mice with severe combined immunodeficiency, providing an important model for the future study of new agents and new drug combinations.\textsuperscript{16}

**Table 2. Response and Survival of 132 Previously Untreated Patients With WM**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>Response Rate (%)</th>
<th>Median Survival (yrs)</th>
<th>Median Survival (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil-prednisone</td>
<td>77</td>
<td>57</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide-vincristine-prednisone</td>
<td>16</td>
<td>44</td>
<td>3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Cyclophosphamide-vincristine-prednisone-doxorubicin</td>
<td>20</td>
<td>65</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogues (Fludarabine, 2CdA)</td>
<td>19</td>
<td>79</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reached; NS, differences were not significant.
lated causes among older patients. Consistent standards for cause-specific survival should be applied such as deaths due to lymphoma, a complication of IgM, or a complication of therapy. Similar analyses may be useful in the study of CLL and other diseases that occur among patients of older age with a long survival time. Patients whose WM was reduced by at least 75% lived a median of 7.7 years in comparison with a median of 2.5 years for unresponsive patients \((P < .01)\), a difference that could be explained by the remission times of responding patients. A staging system has not been developed because outcome does not correlate consistently with the extent of disease as defined by available measurements.

**Alkylation agent-resistant disease.** Until recently, few effective treatments were available for patients whose WM was resistant to an alkylating agent-glucocorticoid combination. Either fludarabine or 2CdA induced responses in 54% of patients for a median duration of 30 months.²⁷,²⁸

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**Fig 3.** (A) Response rates of previously untreated patients by age \((P < .01)\). (B) Response rates to nucleoside analogues of patients resistant to alkylating agents \((P = .02)\).

**Fig 4.** (A) Cause-specific survival of previously untreated patients by age \((P < .01)\). (B) Cause-specific survival of patients with primary resistant disease or with disease in resistant relapse who received a nucleoside analogue \((P < .01)\).
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Patients in resistant relapse despite ongoing therapy were much less likely to benefit, with only 18% responding to either drug (Fig 4). This accounted for the much shorter survival of patients in relapse than of those with primary resistant disease. Thus, a nucleoside analogue is the treatment of choice for WM that has not responded to an alkylating agent-steroid combination. With resistant relapse, new agents and more intensive chemotherapy should be studied.

Myeloablative therapy with autologous bone marrow or blood stem cell transplantation has been considered useful for many patients with multiple myeloma and CLL, but no formal studies have been conducted in patients with WM. As in other lymphoproliferative diseases, the specific categories of patients (primary resistance, first remission, etc) that are most likely to benefit substantially should be identified.

Myelodysplasia and acute myelogenous leukemia have appeared after chemotherapy with alkylating agents, but it is not clear whether the use of a nucleoside analogue, Transformation of WM to large-cell lymphoma with less IgM production may also occur, consistent with clonal evolution as occurs in some patients with CLL. WM is an uncommon low-grade, small-cell lymphoma with monoclonal IgM production. Complications described in tumor infiltration, circulating or tissue-bound monoclonal protein, or a combination of features. Asymptomatic patients with smoldering IgM can be difficult to distinguish from those with monoclonal IgM protein of unknown significance. Approximately 10% of patients with monoclonal IgM have disease features due entirely to the abnormal Ig but no clear evidence of lymphoma. Plasmaphereses, interferon α, or nucleoside analogue therapy should be considered when complications are caused by circulating IgM. When overt lymphoma is present, intermittent courses of chlorambucil and prednisone have induced remissions in 40% of patients with primary resistance to chlorambucil-prednisone and in 80% of newly diagnosed patients.

CONCLUSIONS

WM is an uncommon low-grade, small-cell lymphoma with monoclonal IgM production. Complications result from tumor infiltration, circulating or tissue-bound monoclonal protein, or a combination of features. Asymptomatic patients with smoldering IgM can be difficult to distinguish from those with monoclonal IgM protein of unknown significance. Approximately 10% of patients with monoclonal IgM have disease features due entirely to the abnormal Ig but no clear evidence of lymphoma. Plasmaphereses, interferon α, or nucleoside analogue therapy should be considered when complications are caused by circulating IgM. When overt lymphoma is present, intermittent courses of chlorambucil and prednisone have induced remissions in approximately 60% of patients, resulting in a median survival of approximately 5 years. Nucleoside analogues (fludarabine, 2-chlorodeoxyadenosine) are promising new agents that have been effective in 40% of patients with primary resistance to chlorambucil-prednisone and in 80% of newly diagnosed patients.

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