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 calciotriol 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 lg-secretory cells. In multiple myeloma, the plasma cells contain intracytoplasmic Ig and may express aberrant phenotypes. In all three diseases, monoclonal cells are also present in the blood, even though the absolute lymphocyte count may be normal. There is controversy on whether circulating monoclonal cells represent a spillover of differentiated cells with a limited lifespan or include primordial cells capable of sustaining the dissemination, as proposed for multiple myeloma. 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 × 10⁷/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

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the hematocrit by as much as 6 vol% less than predicted from the measured red blood cell (RBC) volume, and may contribute to high output cardiac failure, especially after RBC transfusions. Hyperviscosity results from a combination of the increased concentration and more asymmetric shape of the large, pentameric IgM molecule. Symptoms usually occur when the measured viscosity is at least four times that of normal serum when monoclonal IgM concentration usually exceeds 3.0 g/dL; in contrast, symptomatic hyperviscosity in myeloma usually requires monoclonal IgA or IgG levels of at least 5.0 g/dL.25,26 Measurements of whole blood viscosity do not provide better insight than those of serum.27

The easy bleeding of patients with WM has not been well explained. The cause appears to result from abnormal platelet function induced by the circulating IgM molecule by mechanisms that remain unclear. Interference with coagu-

Table 1. Phenotypic Features of Bone Marrow Malignant Cells

<table>
<thead>
<tr>
<th>Ig</th>
<th>CLL</th>
<th>WM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<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>
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<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.

Cryoglobulinemia. Cryoglobulins undergo reversible precipitation at low temperatures and consist of either monoclonal IgM (type I) or mixed Ig complexes in which monoclonal IgM behaves like an antibody against polyclonal IgG (type II).29 Type I cryoglobulins are detected in approximately 15% of patients with overt WM, but less than 5% have symptoms or complications; type II cryoglobulins are usually not associated with any evidence of lymphoma, but clonal growth may become manifest with time. For proper diagnosis, blood should be collected, transported, and separated at 37°C before refrigeration. The precipitate should be redissolved and electrophoreses conducted to determine the presence of monoclonal and/or polyclonal Igs and complexes. Cryoglobulinemia may produce Raynaud’s syndrome, arthralgia, purpura, peripheral neuropathy, liver function abnormalities, and renal failure.29,30 The mechanism of cryoprecipitation is not clearly understood, and the occurrence of symptoms does not correlate with the temperature at which the cryoprecipitate forms. The cryoprecipitate may activate complement sequences and thus create an immune complex vasculitis resulting in ischemia of skin, nerve, and renal tissues. Type II cryoglobulinemia is usually idiopathic, but is often associated with hepatitis C virus. These observations suggest a role for hepatitis C in the pathogenesis of some cases of type II cryoglobulinemia, and explain the response of some patients to interferon.31-33

Cold agglutinin hemolytic anemia. In approximately 10% of patients with monoclonal IgM, the abnormal protein reacts with specific RBC antigens at temperatures less than 37°C to produce a chronic hemolytic anemia. The hemolysis is usually mild, extravascular, and associated with a markedly elevated cold agglutinin titer (>1:1,000), espe-
cially when tests are conducted at low temperatures. The protein is usually IgM α and its most common target is the la antigen. The best explanation for the pathogenesis is that conformational changes that occur in the RBC membrane at low temperatures allow epitopes invisible at 37°C to become more accessible to IgM antibodies. The degree of cell lysis is in proportion to the amount of complement activation induced by the low temperature and the IgM concentration. Thus, RBCs may fix complement and agglutinate in colder areas of the circulation, producing Raynaud’s syndrome, acrocyanosis, and livedo reticularis. When the RBCs return to warmer parts of the body, the cold agglutinin dissociates, but C3d complement remains on the RBCs and can be shown by the Coombs test. The presence of C3d complement protects older RBCs from phagocytosis by macrophages in comparison with younger or transfused cells.

COMPLICATIONS OF TISSUE DEPOSITION

Peripheral neuropathy. Approximately 5% of patients with a sensorimotor peripheral neuropathy have a monoclonal gammopathy, and 5% to 10% of patients with macroglobulinemia develop a chronic, predominantly demyelinating sensorimotor peripheral 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 immunoabsorbent 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, GD1a, 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.

Amyloidosis (AL). AL has developed in less than 5% of patients with monoclonal IgM. The clinical features are similar to those of patients with AL associated with IgG, IgA, or light chain production, and the light chain type has been κ in 76% of patients. Cardiac, renal, hepatic, and pulmonary complications are common and one or more of these features are usually the cause of death. The incidence of cardiac and pulmonary involvement was higher in patients with monoclonal IgM than with other Ig types. AL should be suspected in all patients with neuropathy, nephrosis, cardiomyopathy, or purpura concurrent with any monoclonal gammopathy.

TREATMENT

IgM-induced complications. When circulating IgM has caused such clinical features as hyperviscosity, cryoglobulinemia, or peripheral neuropathy, plasma exchange transfusions should be considered. Because 80% of IgM is intravascular, plasmaphereses may be conducted expeditiously on an automatic blood cell separator using albumin and saline replacement to reduce transfusion-related risks. Although this procedure rapidly reduces the level of IgM, patients with hyperviscosity syndrome also require effective chemotherapy for the underlying lymphoma to maintain control. In patients who have symptomatic cryoglobulinemia or neuropathy but no evidence of lymphoma, the level of the pathogenetic IgM molecule should be reduced for at least 3 months to assess the effects of therapy. A sequence of plasma exchange followed by chemotherapy (eg, 2 courses of a nucleoside analogue) is the best means of ensuring sustained IgM reduction. Patients with symptomatic cryoglobulinemia and without lymphoma should be assessed for the presence of hepatitis C and considered for a trial of interferon α.

Lymphoma. Standard criteria for remission after chemotherapy have not been defined and controlled therapeutic trials have not been conducted for patients with WM;
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.\(^5\)\(^\text{10, 59}\) We have studied a combination of chlorambucil (8 mg/m\(^2\)) and prednisone (40 mg/m\(^2\)) 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 control 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.\(^8\)\(^\text{10}\) Approximately 10% of patients achieved a complete remission as defined by the disappearance of IgM by immunoelectrophoresis 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.\(^6\)\(^\text{0}\) The combination of cyclophosphamide, vincristine, and prednisone or the same drugs with doxorubicin have given similar results (Table 2), as in patients with CLL.\(^5\)\(^1\) Combinations of multiple alkylating agents with prednisone, alleged to produce higher response rates and longer survival,\(^62\)\(^\text{63}\) 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.\(^64\)\(^\text{-66}\)

Nucleoside analogues such as fludarabine and 2-chlorodeoxyadenosine (2CdA) have been studied in previously untreated patients.\(^67\)\(^\text{68}\) Fludarabine has been administered in a dose of 25 mg/m\(^2\) 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 bone 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.\(^6\)\(^9\) 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.\(^1\)\(^\text{6}\)

**Prognostic factors.** Analyses have indicated that age greater than 60 years, male gender, and hemoglobin less than 10 g/dL were associated with a shorter survival in WM.\(^1\)\(^\text{1}\) Our analysis of 132 previously untreated, symptomatic patients showed age as the only significant prognostic factor. Patients older than 60 years had a lower response rate (Fig 3) and a significantly shorter cause-specific survival time (Fig 4). In the series of Facon et al.,\(^1\)\(^\text{1}\) 23% of their patients died of unrelated causes, a figure similar to the 16% among our patients. Such observations indicate that cause-specific survival is the appropriate endpoint in these studies because it controls for the many deaths due to unre-

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (yr)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil-prednisone</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide-vincristine-prednisone</td>
<td>3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Cyclophosphamide-vincristine-prednisone-doxorubicin</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogues (Fludarabine, 2CdA)</td>
<td>7.9</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.

**Alkylating 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.67,68

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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 ($P = .02$).

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**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 ($P < .01$).
WALDENSTRÖM'S MACROGLOBULINEMIA

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 myelogeneous leukemia have appeared after chemotherapy with alkylating agents, but this complication has not yet followed 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.

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 WM 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. Plasmaphereeses, 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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