Macroglobulinemia of Waldenström
Diagnosis and Management

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ABSTRACT

Waldenström's macroglobulinemia is a syndrome characterized by an IgM globulin in the blood, an infiltration of plasmacytoid lymphocytes in the bone marrow, lymph nodes and other tissues and variable symptoms related to serum hyperviscosity, hemostatic defects and tissue replacement by tumor cells. It is a disease of the older patient and commonly has a prolonged course. The median age at onset is 64 years and the median survival four years.

The circulating IgM paraprotein is usually in excess of 1,000 mg per dl. Increased plasma volume, increased blood viscosity and impairment of the hemostatic mechanism are all attributed to the abnormal protein.

The hyperviscosity of the blood results in neurologic deficits consisting of impairment of vision and hearing, cerebral dysfunction and peripheral neuropathy. Hemostatic defect resulting in mucous membrane bleeding is also associated with the hyperviscosity syndrome.

Treatment is not necessary in the asymptomatic patient. Plasmapheresis is very useful as initial therapy in severely symptomatic patients, and can be used as long term treatment if necessary in cases of failure of chemotherapy with chlorambucil. Potent combination chemotherapeutic regimens are being evaluated for treatment of refractory advanced disease. This disorder, along with others having the same histopathology, might be classified as a sub-category of plasmacytic lymphoma, as suggested by Lukes and Collins.12

Waldenström's macroglobulinemia is a malignant lymphoma of B cell origin characterized by a combination of clinical, immunologic and pathologic features which distinguish it from IgM myeloma and other diseases associated with monoclonal IgM globulin in the blood.

Clinical Features

The clinical features commonly found are related to infiltration of the bone marrow, lymph nodes, spleen, liver and occasionally other organs (lung, kidney) or more prominently, to the presence of the
MACROGLOBULINEMIA OF WALDENSTRÖM

hyperviscosity syndrome or a bleeding disorder secondary to the circulating IgM protein. The hyperviscosity syndrome includes neurologic symptoms and signs such as dizziness, vertigo, headache, impaired hearing, visual defect, ataxia, nystagmus, pyramidal tract signs and peripheral neuropathy.6,19,20,27 The clinical features of a series of 40 patients reported by MacKenzie and Fudenberg13 are shown in table I.

A study of 45 patients by Krajny and Pruzanski9 was similar, but bleeding manifestations were present in 44 percent, predominantly mucous membrane bleeding. The average age at onset of symptoms was 64 years (range 29 to 89 years). No sex predominance was found. The mean survival time was 49.5 months for those who expired and 43 months for those still living.9

Laboratory Features

Selected laboratory abnormalities9 included anemia (Hgb 8.5 to 1.5 g per dl) in 42 percent, thrombocytopenia in 34 percent, elevated sedimentation rate in most (over 80 mm per h in 56 percent), elevated BUN in 18 percent, serum protein > 8 g per dl in 42 percent cryoglobulinemia in 16 percent and cold agglutinins in 18 percent. The IgM concentration in the serum was less than 1,000 mg per dl in six of the 45 patients, and over 5,000 per dl in 14 reported. The light chain type was most commonly of the kappa type. IgG levels were subnormal in 40 percent; IgA was low in 60 percent. Bence Jones proteins were present in small amounts in 71 percent of their cases; nine patients had more than 200 mg per 24 h. Similar laboratory findings were reported in other published series.13,19,26 The Coombs' test was positive in only two cases. One patient had a high titer of cold agglutinin.

The coagulation defect appears to be in the primary hemostatic mechanism involving platelets. The bleeding time is commonly prolonged, and platelet function defects have been demonstrated by platelet factor 3 assays, prothrombin consumption and thromboplastin generation tests designed to show a platelet defect.6,10,16,17 Such a defect was not demonstrated by Perkins,18 but abnormal bleeding time, defective platelet adhesion and modest decrease in factors V and VIII were shown. Interference with polymerization of fibrin monomers resulting in prolonged prothrombin time, partial thromboplastin time or thrombin time is uncommonly seen.10,18 Inhibition of a specific clotting factor (factor VIII) has been reported by Castaldi and Perry.7

Increased plasma volume related to the IgM protein is very common, causes an "apparent anemia" by dilutional effect and may make transfusion therapy very hazardous.1

The viscosity of the serum, plasma and whole blood are, as a rule, increased. There is a rough correlation between the serum viscosity and the level of IgM, and between either of these and the symptomatic "hyperviscosity syndrome", but many exceptions to this rule have been known to occur.3,4,14,15 Interaction of the IgM molecule with the red blood cell, and the hematocrit itself are variables affecting the in vivo viscosity. In some instances, temperature has a striking effect.4,6 Quantitation of the IgM level may be complicated when viscosity is very high, or when some 7s IgM is present,9 making it difficult to predict

<table>
<thead>
<tr>
<th>TABLE I</th>
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<td>Physical Findings in 40 Patients with Macroglobulinemia</td>
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<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percent</th>
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<tr>
<td>Hepatomegaly</td>
<td>55</td>
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<tr>
<td>Splenomegaly</td>
<td>35</td>
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<tr>
<td>Adenopathy</td>
<td>45</td>
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<tr>
<td>Retinopathy</td>
<td>35</td>
</tr>
<tr>
<td>Neurologic defect</td>
<td>20</td>
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<td>Purpura</td>
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viscosity from the IgM level and hematocrit determination. Each patient has his own symptomatic threshold, and will tend to be symptomatic when that level of IgM is reached, or when that particular viscosity occurs.

Interaction of fibrinogen with the abnormal protein also affects whole blood viscosity and may also be a factor in some cases. This points out the importance of measuring whole blood viscosity, or calculating it by the method of Mannik.14,15 Although there is correlation between serum viscosity, as measured in the Ostwald viscometer or red blood cell pipet, with clinical symptoms in most instances,31 measurement of whole blood viscosity at a low shear rate in a cone-plate viscometer21,30 shows a better correlation with in vivo events. At low shear rates, the effect of hematocrit is important because the aggregation of RBC begins to occur at shear rates of 50 sec⁻¹ or less (figure 1).

A recent study using Mannik's formula:

\[
\log \eta = 0.1710 + 0.1005m - 0.0090h
\]

where \(m\) = macroglobulin concentration in g per dl and \(h\) is the hematocrit,14 showed that symptomatic patients usually had whole blood viscosity values greater than eight centipoises when calculated from the relative serum viscosity. This was a retrospective analysis of seven patients. In Mannik's study,15 there was insufficient data to permit correlation of viscosity at a given shear rate with clinical symptoms of hyperviscosity.

### Histopathology

Bone lesions are not a part of the syndrome and when found are most commonly accompanied by the histology of multiple myeloma, the predominant cell being a plasma cell, with varying degrees of differentiation and pleomorphism. Occasionally, bone lesions may be seen in malignant lymphoma, lymphocytic type, poorly differentiated in association with an IgM paraprotein.13

The usual histology of the bone marrow is that of a pleomorphic infiltrate of lymphocytes, plasma cells and plasmacytoid lymphocytes.9,26 Mast cells are occasionally present, a useful finding in distinguishing this condition from myeloma in some cases.13 Intranuclear and intracytoplasmic inclusions of PAS positive material are commonly seen, but are not specific for macroglobulinemia of Waldenström.29 Problems in diagnosis arise when (1) the infiltrate is pure plasma cells or well differentiated lymphocytes, (2) bone lesions are not present as in myeloma or (3) the patient is not leukemic as in chronic lymphocytic leukemia28; however, these conditions are of rare occurrence.

Other clinicopathologic states that may have associated monoclonal IgM protein in the serum include IgM myeloma, chronic lymphocytic leukemia, malignant lymphoma lymphocytic type or histiocytic type, and a variety of autoimmune (rheumatoid arthritis, autoimmune hemolytic anemia, chronic cold agglutinin disease), non-B cell neoplastic disorders, and chronic diseases.19,26 Other than in IgM myeloma,13 and Waldenström's...
macroglobulinemia, the IgM level in these disorders is seldom greater than 2,500 mg per dl, and more commonly 250 to 1,000 mg per dl (normal IgM 45 to 150 mg per dl).26 There have been reports of a number of examples of benign monoclonal gammopathy of the IgM type, which were asymptomatic and had no evidence of an infiltrative process of the bone marrow, lymph nodes or spleen.26 Many will remain this way for years, but some will manifest an underlying neoplasm on subsequent examination.

A recent report28 describes seven cases of B cell neoplasm having the same histologic features as classical macroglobulinemia of Waldenström, but each was secreting monoclonal IgG or IgA instead of IgM. It is conceivable that examples will be found where only heavy chains or no immunoglobulin is secreted. During this period, the same laboratory saw 190 cases of the IgM variety of Waldenström’s macroglobulinemia, for an incidence of about 3 percent having non-IgM paraprotein.

Materials and Methods

Investigation of the whole blood, plasma and serum viscosities were carried out on a microviscometer* utilizing various shear rates (figure 1). The routine relative serum viscosities were measured in a red blood cell pipet.31 The whole blood viscosities were performed on heparinized whole blood (heparin 10 units per ml).

Serum immunoglobulin assays were performed utilizing commercial immunodiffusion plates. Immunelectrophoresis on the serum and urine was performed with commercial materials and antisera.

Plastic double bag plasmapheresis† sets or a blood cell separator and blood processor‡ (figure 2), were used for plasmapheresis. ACD-adenine was the anticoagulant used. Precisely 1,500 ml of plasma were exchanged every two weeks and replaced by 1,500 ml of fresh frozen plasma. Standard 51Cr RBC tagging methods were employed for blood volume measurements.

Case Studies

CASE 1. Severe Epistaxis Managed by Plasmapheresis

A.R. is an 82 year old white man with recurrent severe epistaxis. He had complaints of headaches, dizziness and hearing loss which had been present for several months. Physical examination revealed moderate pallor and bilateral nasal crusting and bleeding. Bilateral one cm cervical lymph nodes were felt. The liver edge was felt three cm below the right costal margin with a total span of 14 cm. The spleen tip was palpated four cm below the left costal margin. There were no skeletal defects or purpura. Deep tendon reflexes were diminished. His eye grounds could not be visualized because of cataracts.

Laboratory Data

Data included hemoglobin 10.2 g per dl, hematocrit 29.7 percent, MCV 90 µ, MCHC 33.4, reticulocyte count 0.5 percent, WBC 4,900 with 75 percent segmented neutrophiles, 20 percent lymphocytes, 4 percent monocytes and 1 percent basophiles. The platelet count was 132,000 per µl. Sedimentation rate was 152 mm per hr. Marked rouleaux and a rare plasma cell were seen on the blood smear. The direct Coomb’s test was negative.

* Wells-Brookfield Microviscometer, Brookfield Engineering Laboratories, Inc., Stoughton, MA.
† Fenwall®.
‡ Hemonetic 30, Hemonetics Corp., Natich, MA.
Prothrombin time was 11.5 sec (control 11.0 sec), partial thromboplastin time 55 sec (N = 24 to 38 sec), fibrinogen 140 mg per dl (normal 200 to 400 mg per dl). Bleeding time 12 minutes (normal 3 to 6 minutes). Platelet aggregations with ADP, epinephrine, collagen and ristocetin were normal. Prothrombin consumption was 11.8 sec, control more than 15 sec. Thrombin time (5 μ thrombin per ml) was 20 sec (N = 16 to 28 sec).

Serum Protein and Viscosity

Initial studies on the serum proteins revealed a total protein 11.2 g per dl, IgM 5,600, IgG 400 and IgA 35 mg per dl. Serum immunoelectrophoresis showed IgM Kappa monoclonal gammopathy. The urine was negative for Bence Jones protein. Urine specific gravity was 1.014, pH 5.0, no RBC or WBC. The relative serum viscosity was 6.6; normal 1.4 to 1.8. The relative whole blood viscosity was 11.7; normal 5 to 7.

Biochemical Data

The serum calcium, phosphorus, glucose, bilirubin, alkaline phosphatase and SGOT were normal on an SMA-12 analysis. The BUN was slightly elevated at 22 to 26 mg per dl and creatinine was 0.9 mg per dl. The cholesterol was below 150 mg per dl on two occasions. The uric acid was 7.0 mg per dl, Na 136, K 4.6, Cl 100 mEq per l, CO₂ 24 mEq per l and pH 7.45.

Radiographic Studies

A bone survey was negative for osteoporosis and lytic lesions.

Bone Marrow Examination

A bone marrow aspiration and biopsy from the iliac crest revealed a moderately hypercellular bone marrow. Megakaryocytes were normal. The erythroid-myeloid ratio was 1:3. Erythropoiesis and granulopoiesis were normal. The marrow contained 10 to 15 percent plasma cells; some were atypical and lymphocytoid. The PAS stain was negative, but the MGP (methyl-green-pryonine) was positive indicating very active protein synthesis in these cells. The iron stores were normal.

Treatment

Plasmapheresis of 13 units was performed in two days, with replacement with nine units of fresh frozen plasma. After this the bleeding stopped, the partial thromboplastin time fell from 55 to 34 seconds (N = 24 to 38) and the platelet count decreased from 132,000 to 117,000 per μl. The bleeding time was shortened from 12 to 9 minutes. The whole blood viscosity changed to 5.2 (relative) and the serum viscosity to 3.0 (relative). The total protein was reduced to 7.6 g per dl, IgM 3,500 mg per dl, IgG 580 mg per dl and IgA 48 mg per dl. The nasal packing was removed on the third day with no further significant bleeding.

An attempt was made to treat him with chlorambucil, 4 mg per day, but this was stopped after six weeks because of neutropenia (WBC 1,800 to 60 percent segmented neutrophiles) and thrombocytopenia (platelets 70,000 per μl).

There was no apparent benefit from chlorambucil and repeated plasmapheresis was necessary to maintain a serum IgM below 5,000 mg per dl and serum viscosity below 5 (relative). The patient tolerated the procedure well and a stable state has been maintained for one year by removing 1,200 ml to 1,500 ml of plasma and replacing it with 900 ml of normal plasma every two weeks. When a three week schedule was tried, bleeding recurred.

During this time there have been no detectable complications of a serious nature related to plasmapheresis. The patient's blood count (RBC, WBC, platelets) remain stable without transfusions, the spleen and liver remain about the same size. His coagulation studies have returned to normal or near normal. His serum viscosity has remained in a range of 4.5 to 5.0 relative to water.

CASE 2. Pyelonephritis Managed by I.V. Fluids and Antibiotics

H.B. was diagnosed as having macroglobulinemia of Waldenström in 1973 when he presented with acute pyelonephritis, a rapidly rising BUN and creatinine and a serum protein of 12 g per dl. He responded rapidly to i.v. fluids and antibiotics and has had no urinary problems since that time.

Physical Examination (1973)

The patient was well oriented and alert. Blood pressure was 130/74. The eye grounds were normal and there was no lymphadenopathy or hepatosplenomegaly. No bruising or petechiae were present.

Laboratory Data

Data included hemoglobin 10.4 g per dl, hematocrit 32 percent, WBC 4,700 with 64 percent segmented neutrophiles, 26 percent lymphocytes, 5 percent monocytes and 5 percent eosinophiles. Sedimentation rate was 66 mm per hour. The Coomb's test was negative.

Coagulation Data

Platelet count was 203,000 per μl. Bleeding time was 13 minutes, prothrombin time 12.3 sec, partial thromboplastin time was 37 sec, fibrinogen 170 mg per dl and thrombin time 15.3 sec (5 μ per ml thrombin N = 16 to 27 sec).

Platelet adhesiveness was 12.1 percent (N = 25 percent), prothrombin consumption time 20 sec (N = 15 sec). Platelet aggregations with ADP, epinephrine, collagen and ristocetin were normal.

Serum Protein Data and Serum Viscosity

Total serum protein was 11 g per dl, IgM 8,000 mg per dl, IgA 23 mg per dl and IgG 270 mg per dl. Albumin was 2.7 g per dl. Serum viscosity (relative)
was 5.2. The urine contained 700 mg of protein, IgM Kappa type of Bence Jones protein. The serum IgM was monoclonal, Kappa type. A test for rheumatoid factor was negative. Cryoglobulins were negative.

**Blood Volume**

A whole blood volume of 8,345 ml (estimated 6,000) with a red cell mass of 2,382 ml (estimated 2,700) and a plasma volume of 5,963 (estimated 3,300) were found. A rectal biopsy was negative for amyloid.

Bone marrow aspiration and biopsy revealed moderate hypercellularity with adequate megakaryocytes and normal erythroid and granulocytic proliferation. There was an infiltration by atypical plasma cells which contained intranuclear inclusions interpreted as “Dutcher” bodies. The marrow contained 20 to 40 percent plasmacytoid cells.

**Radiographic Studies**

A bone survey was negative for osteolytic or osteoporotic lesions. Colon x-rays were normal. Chest x-ray was normal.

**Clinical Course and Treatment**

The patient was treated with chlorambucil, 4 mg daily, for two years with no significant change in his symptoms or laboratory data except for a slight decrease in gamma globulin. The bleeding time had reverted to normal when the BUN and creatinine returned to normal. He was then treated with chlorambucil in gradually decreasing dosages to 2 mg every other day with no significant difference in any clinical or laboratory parameter except for decrease in total IgM from 8,000 in 1973 to 5,200 in 1977, and a decrease in serum viscosity from 5.2 to 3.9 (relative). The urine continued to show small amounts of Bence Jones proteins. The BUN was 17 mg per dl and creatinine 1.5 mg per dl. His hemoglobin and hematocrit are unchanged.

**Summary of Viscosity and Coagulation Studies**

The results of viscosity studies on Case #2, H.B., are shown in figure 1. The cone plate viscometer at various shear rates demonstrated an abrupt change in viscosity at low shear rates and demonstrated the contribution of the red blood cells to the whole blood viscosity.

The profound effect of plasmapheresis on whole blood and serum viscosity of A.R. is shown in figure 2, demonstrating the optimal amount of plasmapheresis required to achieve a significant lowering of viscosity. The purpose of performing plasmapheresis, however, was to restore the patient’s coagulation defect to normal to prevent bleeding. His symptoms, owing to hyperviscosity per se, were modest.

The changes observed in his coagulation parameters pre and post plasmapheresis are shown in table II. These data show conclusively that his bleeding has been controlled by numerous plasmaphereses over a one year period.

**Discussion**

Two patients are presented and discussed as typical examples of the “syndrome” of macroglobulinemia of Waldenström. While some clinicians and

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**TABLE II**

Coagulation Profile for Case 1

<table>
<thead>
<tr>
<th>Preplasmapheresis</th>
<th>Postplasmapheresis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>91,000</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>9 minutes</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>13.1 seconds</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>36.8 seconds</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>135 mg per dl</td>
</tr>
<tr>
<td>Thrombin time (5 u per ml)</td>
<td>14.3 seconds</td>
</tr>
<tr>
<td>Reptilase time</td>
<td>13.3 seconds</td>
</tr>
<tr>
<td>Platelet factor 3</td>
<td>1 minute 15 seconds</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>88 percent</td>
</tr>
<tr>
<td>Whole blood viscosity</td>
<td>8.3 centipoise†</td>
</tr>
</tbody>
</table>

*1,500 ml of plasma removed and replaced by plasma (FFP).
†Normal for W.B. is 5.1-6.1 at a shear rate of 90 seconds⁻¹ in the Wells-Brookfield Viscometer.
pathologists include all patients having more than 1,000 mg per dl of IgM paraprotein (monoclonal) in their serum within the definition of "Waldenström's" macroglobulinemia. Others feel that there is clinical need of restricting the term "Waldenström's" macroglobulinemia to those patients having monoclonal IgM paraprotein and the histopathology of plasmacytoid lymphocytic infiltrates. The reason in keeping those entities separate at this time is primarily to avoid giving a highly toxic chemotherapeutic regimen to patients who may have prolonged survival with little or no therapy and to give more aggressive and toxic therapy to those having the clinicopathologic features of a malignant lymphoma, lymphocytic type, poorly differentiated, histiocytic lymphoma or of a multiple myeloma.

The symptoms of hyperviscosity or bleeding tendency should be treated by plasmapheresis if chemotherapy is not effective enough when used alone. The effectiveness of plasmapheresis in IgM paraproteinemia is due to the fact that 80 percent of the 19s globulin is intravascular, related to its high molecular weight; 7s globulins (IgG, IgA) are much more difficult to remove by this method. A recent report cites seven cases of a lymphoproliferative disorder having the same clinical course and the same histopathology of the bone marrow and other tissues as macroglobulinemia of Waldenström, but IgA or IgC monoclonal serum protein instead of IgM.

This suggests that clinicopathologic features, clinical course and response to various forms of treatment may correlate better with the histopathology than with the type of protein secreted by the cells. Further observations may clarify this. The classification of this type of histopathology as plasmacytic lymphoma has been proposed by Lukes. Subcategories of IgM, IgG, IgA, etc. might then be found to be essentially the same or perhaps different in their clinical behavior and response to therapy when sufficient numbers have been studied.

Our experience in studying the whole blood and serum viscosity in these patients and in reviewing the literature reveals that more meaningful information is likely to be obtained by measuring the whole blood viscosity at low shear rates, than by measuring serum viscosity. At the present time, too little information is available on the correlation of the symptoms of the hyperviscosity syndrome, with whole blood viscosity at low shear rates. Further studies will be needed to confirm the preliminary data of MacKenzie, showing that symptoms are unlikely to be due to hyperviscosity if the whole blood viscosity is less than eight centipoises as calculated utilizing Mannik's formula.

In general, it can be stated that treatment of the symptomatic patient should be with plasmapheresis if there is a significant hyperviscosity syndrome or overt bleeding disorder, until the symptoms are controlled by chemotherapy. If chlorambucil is not effective at a tolerable dosage, then a decision for long term plasmapheresis versus a different chemotherapeutic approach must be made. Some reports suggest that chlorambucil is not as effective as earlier reports have indicated.

Combination chemotherapeutic regimens consisting of melphalan cyclophosphamide, vincristine, prednisone and BCNU have been tried and found to be effective in a small number of cases refractory to other treatment.

Plasmapheresis on a biweekly to monthly basis is expensive and requires several units of plasma, albumin or plasma protein product each month, with a small risk of hepatitis to be considered, at least with the use of plasma. It is not completely free of complications or hazards but is reasonably safe. Some of the problems include depletion of blood
Acknowledgments

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References