Macroglobulinemia: An Analysis for Forty Patients

By Malcolm R. MacKenzie and H. Hugh Fudenberg

Forty patients with Waldenström's macroglobulinemia were evaluated for criteria of diagnosis, clinical presentation and course, response to therapy, and appropriateness of the classification primary or secondary. A wide spectrum of presentations, course, and complications were present. Thus, the major criteria for diagnosis was a monoclonal IgM serum protein abnormality present in concentrations greater than 1 g/100 ml. Clinical manifestations included weight loss, mucous membrane bleeding, presence of abnormal masses, lymphadenopathy, hepatosplenomegaly, peripheral neuropathy, and central nervous system abnormalities. A high incidence (60%) of associated malignancy was noted. The hyperviscosity syndrome was a frequent complication (33%). Alkylation drugs were successful in inducing remission in approximately 40% of the patients. Plasmapheresis was uniformly successful in relieving hyperviscosity. It was found that attempts to classify patients as primary or secondary frequently proved in error with long-term observation and as such should be discarded. Hypotheses of etiology are discussed and include the IgM proteins as: markers of a malignant lymphoid line, antibodies to microscopic or submicroscopic organisms related (or not related) to tumor induction, and antibodies to tumor-specific antigens. Firm evidence for any of these possibilities is not available.

The disorder macroglobulinemia has attracted wide interest since its description by Professor Waldenström more than 25 yr ago. An enormous number of publications have appeared encompassing clinical manifestations and extensive laboratory investigation of the serum protein. Attempts at classification have not, however, yielded a clear picture of the clinical situation of these patients. An example is a recent classification of monoclonal protein disorders (i.e., an elevation of serum immunoglobulins of a single, light-chain type) that included the following categories: primary malignant—including the multiple myeloma, Waldenström’s macroglobulinemia, heavy chain disease, and malignancies of the blood forming organs; secondary—including neoplastic disorders of cell types not known to produce
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immunoglobulin, infectious “autoimmune” diseases, liver disease, etc.; and
primary benign. In examining our case material of 40 patients followed over
several years, we found that a given patient could fit into several categories
depending on the time selected during the course of his disease. As such, we
believe such classifications are arbitrary and prefer to consider these patients
as a whole, grouped together by the common abnormal finding of elevated
monoclonal IgM. In this discussion, we will present our criteria for diagnosis,
the range of clinical and laboratory manifestations, some of the physiologic
consequences of large quantities of circulating IgM, and our experience in
therapy.

MATERIALS AND METHODS

The patients were cared for primarily at the University of California, San Francisco
and the University of Cincinnati Medical Centers or were seen and followed in consulta-
tion with their referring physicians. Criteria for diagnosis were: an abnormal serum
electrophoretic pattern with a sharp peak in the beta or gamma globulin region that con-
sisted of at least 1 g/100 ml and represented a minimum of 15% of the total protein in
the serum. The level of 1 g/100 ml is a tenfold increase over the normal levels of serum
IgM. The nature of the abnormal electrophoretic peak was confirmed by immunoelcet-
rophoresis to be composed of immunoglobulin IgM. This IgM was composed of a single,
light-chain type, i.e., kappa or lambda. Confirmation of the macroglobulin nature was
obtained in studies of the analytical ultracentrifug. In addition, one or more of the
following clinical manifestations were present: significant weight loss, bleeding episodes,
abnormal lumps or masses, symptoms of peripheral neuropathy or central nervous system
manifestations such as loss of consciousness, and vertigo. Abnormalities present on physi-
cal examination included enlarged lymph nodes, enlarged liver or spleen, retinopathy
(dilated retinal veins, retinal hemorrhages), diffuse peripheral neuropathy, or signs of
cerebellar dysfunction. Laboratory findings included anemia, elevated estimated sedi-
mentation rate, cryoglobulins, and the presence of Bence Jones proteins in the urine.

Serum Protein Studies

Total protein concentration was determined by the biuret method or with a hand
refractometer. Serum electrophoresis was performed on paper or cellulose acetate at pH
8.6 by standard methods, and the patterns obtained were scanned in an analytical densitom-
eter in the usual fashion.

Serum proteins were isolated by euglobulin precipitation or starch block electrophoresis,
depending on their physical characteristics. The isolated proteins were further purified
by gel filtration chromatography on Sephadex G-200 columns.

Immunoelectrophoretic analysis of serum samples and isolated proteins was performed
by the method of Scheidegger using rabbit antisera to IgM, IgG, and IgA prepared by us.
All the Sephadex G-200 preparations gave a single line compatible with gamma macro-
globulins by immunoelectrophoresis with antisera to whole normal human serum proteins
and with antisera to IgM. Light chain typing was performed with antikappa and anti-
lambda antisera. Analytical ultracentrifugation was done in a Spinco model E ultracentri-
fuge equipped with Schlieren optics. The $S_{20W}$ was calculated by extrapolation to infinite
dilution.

Serum Viscosity

Viscosity measurements were done with an Ostwald capillary viscometer with a solvent
decent time of approximately 80 sec; distilled water was used as the reference solvent. The
normal range of serum viscosity relative to water is 1.4–1.8. Routine determinations were
performed at room temperature; determinations on extremely viscous serum (relative
viscosity above 20) or serum containing cryoglobulins were carried out at 37°C.
Blood Volume

Measurements with $^{51}$Cr-tagged cells, and T 1824 or $^{131}I$-labeled human albumin were performed as previously described.4

Immunofluorescence Studies

In four cases, tumor tissue was obtained by biopsy or at the time of autopsy, snap frozen in acetone dry ice and stored at $-20^\circ$C until sectioned. Sections 4 μm thick were cut on an International cryostat, mounted on glass slides coated with 0.5% gelatin, and incubated with the appropriate isolated IgM or with isothiocyanate-conjugated rabbit anti-IgM antisera prepared in our laboratory.5 The slides were examined with a Zeiss ultraviolet photomicroscope equipped with a HBO-200 mercury vapor bulb; a BG-12 excitor filter and 500 nm barrier filter were used.

CASE REPORTS

Case 2

A 73-yr-old man was first seen for evaluation of hearing loss and possible tympanoplasty in January 1963. Physical examination showed distended retinal veins. The liver was felt three fingerbreadths below the right costal margin, and the spleen tip was palpable. The hemoglobin level was 7.3 g/100 ml, hematocrit 26%, and white blood cell count 7,000/cu mm with a normal differential. Urinary excretion of Bence Jones protein was 1.2 g/24 hr. Serum electrophoresis showed a total protein level of 12.4 g/100 ml, with a slow gamma spike accounting for 41% of the total. The abnormal protein was identified as a macroglobulin by immunoelectrophoresis and analytical ultracentrifugation. A Sia test gave a positive result. Relative serum viscosity was 7. Red cell mass was 1.39 liters (−18%), and plasma volume was 4.54 liters (+81%).

The serum viscosity was controlled by plasmapheresis. Subsequent attempts at chemotherapy with alkylating agents (chlorambucil and melphalan) were unsuccessful. Overt diabetes mellitus developed requiring treatment with diet and oral hypoglycemic agents. In 1964 the patient had pulmonary edema on two occasions for which he was treated by plasmapheresis, and a maintenance regimen of digitalis and diuretic drugs was instituted. In June 1965 he had a severe episode of gram-negative septicemia (Escherichia coli) secondary to mild obstructive uropathy. For a 12-mo period beginning in September 1964, plasmapheresis was required at monthly intervals to control serum viscosity. Since September 1965, plasmapheresis has not been needed. In September 1967 the platelet count dropped to 50,000/cu mm. Bone marrow biopsy showed a heavy infiltration of lymphocytoid plasma cells and plasma cells. At present, serum viscosity is 2.8, and the serum total protein level is 9.8 g/100 ml, of which 40% is IgM. The patient is free of symptoms.

Comment: This case is a classical case of macroglobulinemia with hyperviscosity syndrome that failed to respond to attempts of chemotherapy with alkylating agents but the symptoms were controlled by chronic plasmapheresis over a period of 6 yr.

Case 5

A 69-yr-old man was first seen in September 1963. In October 1960 he had undergone a partial gastrectomy and Billroth I anastomosis elsewhere because of massive bleeding from a duodenal ulcer. Liver and lymph node biopsies were reported to show no abnormalities. Because of recurrent gastrointestinal bleeding, a laparotomy was performed in March 1962. Surgical specimens of liver tissue appeared normal. Six months later the patient was referred to the Medical Center because of severe malabsorption, continued gastrointestinal bleeding, and inability to maintain a hemoglobin level of 8.5 g/100 ml without frequent blood transfusions.

On admission, he had no ocular abnormalities and no adenopathy. The liver was palpable two fingerbreadths below the costal margin; the spleen could not be felt. The hemoglobin level was 7.3 g/100 ml, hematocrit 24%, white blood cell count 6,000/cu mm with a
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normal differential, and platelet count 297,000/cu mm. Sulfobromophthalein retention was 2% at 45 min, and a 2-hr postprandial blood glucose level was 186 g/100 ml. Serum viscosity was 11. A Sia test gave a positive result. The serum total protein concentration was 10.5 g/100 ml, with a slow gamma peak accounting for 65.5% of the total. The peak was identified as a gamma macroglobulin of the kappa chain type by immunoelectrophoresis and ultracentrifugal analysis.

The patient was treated by plasmapheresis followed by chlorambucil, 8 mg daily. He was seen on an outpatient basis until January 1964, when he was readmitted because of guaiac-positive stools and a hematocrit of 16%. Serum viscosity was 6. The serum total protein level was 12.4 g/100 ml, of which 54% was IgM. A bone marrow aspirate showed selective depression of red cell precursors, and chlorambucil was discontinued. Subsequent treatment consisted of plasmapheresis alone, which was only moderately effective since the patient lived too far from the Medical Center to be treated regularly. In November 1964 he was again admitted because of pneumonia. Until September 1965 he was symptomatically well, and serum viscosity was maintained at 4–6 by plasmapheresis (2 U) every 3 mo. In September 1965, however, he was readmitted because of symptoms of the hyperviscosity syndrome (severe headaches and moderately severe epistaxis). The serum total protein level was 11.3 g/100 ml, and serum viscosity was 8.3. Periodic treatment with plasmapheresis was again instituted but was required with increasing frequency. Another trial of chlorambucil was ineffective. The patient was hospitalized on four occasions between January 1966 and July 1966 because of hyperviscosity symptoms. Plasmapheresis became increasingly difficult because of the poor condition of his veins. In August 1966 the liver was palpable ten fingerbreadths below the right costal margin, and treatment with large doses of prednisone, 200 mg every other day, was begun. Subsequently, he had recurrent episodes of pneumonia that cleared after vigorous treatment; roentgenograms of the chest, however, suggested the presence of a mass in the left lower lung. The patient was discharged but was readmitted 3 wk later because of guaiac-positive stools. Roentgenograms of the chest showed a mass in the left lung, as well as a pleural effusion on the left. The patient showed no improvement and symptoms of intrabdominal complications became apparent. Laparotomy revealed a greatly enlarged liver studded with metastases. Massive tumor invasion, with necrosis and extensive bleeding, had occurred posterior to the liver. The bleeding could not be stopped, and the patient died.

At postmortem examination, a small nodule was found at the base of the left lung that proved to be a mucocarminic-positive adenocarcinoma. Massive metastases were present in the liver and kidney. Infiltrates of lymphocytoid cells were seen in the kidneys, liver, heart, lungs, and spleen, and moderate infiltration in the testes, skin, subcutaneous tissue, muscle, and bone marrow. Amyloid involvement of the renal glomeruli was also present.

Comment: This patient was followed over a period of 5 yr principally because of bleeding secondary to hyperviscosity syndrome. He failed to respond to alkylating agents but was carried satisfactorily with plasmapheresis. At the end of this period, he then manifested signs and symptoms of an additional malignancy that resulted in his demise.

Case 20

A 42-yr-old man was first seen in December 1959. Two months previously he had complained of fatigue and was found to be anemic. The hemoglobin level was 10 g/100 ml, and the white blood cell count was 15,000/cu mm with a relative lymphocytosis. Severe hemolytic anemia developed during the ensuing weeks. He then became semicomatose and was referred to the Medical Center.

On admission, the hematocrit was 8%. Jaundice was present. The liver and spleen were palpable 10 cm and 12 cm, respectively, below the right costal margin. Specimens of aspirated bone marrow showed infiltration by atypical lymphocytes. A Sia test gave a negative result. Serum electrophoresis demonstrated a total protein level of 10.4 g/100 ml, with a sharp peak in the fast gamma region. The ultracentrifugal pattern showed a marked increase in 195 globulin. Treatment with glucocorticoids was ineffective in controlling the
hemolytic anemia, and in March 1960 a splenectomy was performed. Histologically, the spleen showed extramedullary hematopoiesis but no other abnormalities. Biopsy specimens of liver and portal lymph nodes appeared normal. During the next 6 mo, the serum protein concentration showed a progressive decrease, and the patient became symptomatically well (Fig. 1). In January 1961 the blood count and serum electrophoretic pattern were normal. The liver was still enlarged. In July 1962, the leukocyte count had risen to 45,000 cu mm with 60–70% atypical lymphocytes. In July 1963, serum electrophoresis showed a small fast gamma globulin elevation, which on ultracentrifugation proved to be 19S globulin. The patient continued to be free of symptoms until August 1965, when massive and generalized lymphadenopathy developed. A lymph node biopsy showed changes compatible with Hodgkin's sarcoma. Treatment with cyclophosphamide produced a moderate response. During the fall of 1965, the serum electrophoretic pattern showed no abnormalities; the disease, however, was progressive. In December 1965 the patient had pleural effusions and pneumonitis. Treatment with vincristine resulted in rapid improvement with total hematologic remission and disappearance of adenopathy. The patient was comparatively well until April 1966, when lymph node enlargement was again noted. His condition deteriorated steadily, and death occurred. At no time during the terminal phase, however, was there a return of abnormal lymphocytes or the serum protein abnormality.

Comment: This patient is the best illustration of the difficulty of arbitrary classification. His initial disease began with a hemolytic anemia with associated immunoglobulin abnormality, which remitted totally after a splenectomy. Then, over the next 4 yr, he had the following course. A period of time when he manifested all the signs and symptoms of chronic lymphocytic leukemia with associated immunoglobulin abnormality. He then developed massive lymphadenopathy that proved by biopsy to be Hodgkin's sarcoma, and at the time of his demise no serum abnormality was present. He could have been called at any one period of time during his course: a classic Waldenström macroglobulinemia without evidence of any associated disease, a chronic lymphocytic leukemia with evidence of associated immunoglobulin, Hodgkin's sarcoma with associated immunoglobulin abnormality, and Hodgkin's sarcoma without immunoglobulin abnormality.

Case 22

A 53-yr-old woman was well until May 1965, when she first experienced increasing weakness and fatigue. Her physician found that she was anemic (hemoglobin level, 10 g/100 ml) and had Bence-Jones proteinuria. Serum electrophoresis showed a beta globulin elevation. No osteolytic lesions were found by skeletal survey. In June 1965 the patient was referred to the Medical Center for evaluation because of possible multiple myeloma.
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On admission no physical abnormalities were found. The hemoglobin level was 10.0 g/100 ml, and hematocrit was 30%. A bone marrow smear showed infiltration of lymphocytoid plasma cells. A Sia test gave a negative result, but serum protein studies demonstrated a cryomacroglobulin containing lambda light chains. Urinary excretion of Bence-Jones protein (lambda type) was 2 g/24 hr. Liver biopsy revealed lymphoid cell infiltration of the portal tracts. The patient was treated with chlorambucil, 6 mg daily, and felt well until December 1965 when bilateral pleural effusions developed. Multiple thoracocenteses were required for relief of dyspnea. No pleural lesion was found, although suspicious cells were found repeatedly in the pleural fluid. At that time the patient also complained of a severe nonspecific pain in the left arm. In June 1966 roentgenograms of the left humerus and clavicle showed osteolytic lesions. Biopsy of the clavicular lesion revealed histologic changes compatible with lymphosarcoma. X-irradiation of the left arm and clavicle gave some symptomatic relief. The disease progressed, however, and the patient died of gastrointestinal hemorrhage in March 1967. No autopsy was performed.

Comment: This lady illustrates the usefulness of examining the serum electrophoretic abnormality by immunologic methods. Because of her serum electrophoretic abnormality and the presence of Bence-Jones protein, her referring physician had felt that this was a case of multiple myeloma. This impression could have been strengthened when she developed a lytic lesion after approximately a course of 1 yr. However, on biopsy this proved to be a lymphosarcoma without any evidence of plasma cell abnormality.

Case 29

A 61-yr-old white female first seen in November 1957 because of symptoms of heaviness in her abdomen. On physical examination there was a mass in the right pelvis but no lymphadenopathy, palpable liver, or spleen. On laparotomy a retroperitoneal tumor was found. On biopsy this was interpreted as a lymphoblastic lymphosarcoma. She was treated with radiation (2700 R to the area of the mass). She did well between 1958 and 1961. In April of 1961, she returned to the hospital with complaints of fatigue and weakness. At that time she had marked lymphadenopathy, and her spleen was palpable 10 cm below the left costal margin. Her liver was not palpable. Her hemoglobin was 11 g, white count was 2500/cu mm with a normal differential count; platelets were 198,000/cu mm. Her total serum protein was 6.7 g/100 ml with a normal serum electrophoretic pattern. She was treated with intravenous cyclophosphamide followed by oral drug with a remission of her symptoms and physical findings. On follow-up examination in 1963, a serum electrophoretic pattern was obtained that showed a total serum protein of 6.4 g/100 ml, but a peak was present in her gamma globulin region consisting of 17.6% of her total protein. Because of leukopenia, prednisone therapy was instituted. On follow-up examination her serum abnormality continued to be present and increased, such that by January 1966 her total serum protein was 9.6 g/100 ml, 28% of which was gamma globulin. Her serum viscosity was 2.36, and immunoelectrophoresis demonstrated an IgM lambda peak. Her hemoglobin during this period ranged between 11.8 and 12 g/100 ml but with a continued mild leukopenia. In December 1966 the patient expired at an outside institution. Unfortunately no autopsy was performed.

Table 1. Summary of Physical Findings on 40 Patients With Macroglobulinemia

<table>
<thead>
<tr>
<th>Physical Finding</th>
<th>No. Cases</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Ocular changes</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Neurologic abnormalities</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Purpura</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>
Table 2. Summary of Abnormal Laboratory Findings at Time of Diagnosis on 40 Patients

<table>
<thead>
<tr>
<th>Test</th>
<th>No. Patients with Abnormal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin &lt; 12 g/100 ml</td>
<td>33</td>
</tr>
<tr>
<td>Leukocyte count &lt; 5,000/cu mm</td>
<td>9</td>
</tr>
<tr>
<td>Leukocyte count &gt; 12,000/cu mm</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count &lt; 100,000/cu mm</td>
<td>2</td>
</tr>
<tr>
<td>Excretion of Bence Jones proteins</td>
<td>4</td>
</tr>
<tr>
<td>Osteolytic bone lesions by x-ray</td>
<td>3</td>
</tr>
</tbody>
</table>

Comment: This patient illustrates a well-documented malignancy of the hemopoietic organs that over a period of years developed an abnormal immunoglobulin peak.

RESULTS

This group of patients' clinical manifestations of disease appears to be indistinguishable from other large series of macroglobulinemic patients reported in the literature. They were generally elderly, ranging in age from 40 to 80 yr with an emphasis on the sixth and seventh decade. A slight predominance of males occurred, 21 of the 40. Prominent physical findings are listed in Table 1 and include evidence of bleeding, enlargement of the liver, spleen or lymph nodes, and neurological abnormalities including diffuse peripheral neuropathy and signs of cerebellar dysfunction. A prominent finding was that of retinopathy, which consisted of dilated retinal veins (sausage veins) usually with associated punctate hemorrhages and, rarely, exudates. This finding correlated with the laboratory finding of hyperviscous serum and was present in approximately 36% of our patients.

Table 3. Red Cell Mass in 19 Patients With Macroglobulinemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Predicted Cell Mass* (liters)</th>
<th>Determined Cell Mass* (liters)</th>
<th>Deviation Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-C.Au</td>
<td>1.69</td>
<td>1.39</td>
<td>-18</td>
</tr>
<tr>
<td>3-A.Bl</td>
<td>1.78</td>
<td>1.56</td>
<td>-12</td>
</tr>
<tr>
<td>4-A.Bo</td>
<td>1.73</td>
<td>1.79</td>
<td>+3</td>
</tr>
<tr>
<td>5-F.Ca</td>
<td>1.62</td>
<td>1.27</td>
<td>-22</td>
</tr>
<tr>
<td>6-E.Cl</td>
<td>1.39</td>
<td>1.75</td>
<td>+26</td>
</tr>
<tr>
<td>7-A.Eu</td>
<td>1.56</td>
<td>1.24</td>
<td>-19</td>
</tr>
<tr>
<td>9-J.Fl</td>
<td>1.85</td>
<td>1.56</td>
<td>-16</td>
</tr>
<tr>
<td>11-C.Ga</td>
<td>1.37</td>
<td>0.77</td>
<td>-44</td>
</tr>
<tr>
<td>12-M.Gi</td>
<td>1.50</td>
<td>1.26</td>
<td>-16</td>
</tr>
<tr>
<td>13-L.Gr</td>
<td>2.72</td>
<td>2.30</td>
<td>-18</td>
</tr>
<tr>
<td>15-R.Ho</td>
<td>1.88</td>
<td>1.50</td>
<td>-20</td>
</tr>
<tr>
<td>16-O.Ka</td>
<td>1.69</td>
<td>0.86</td>
<td>-49</td>
</tr>
<tr>
<td>17-C.Lo</td>
<td>1.74</td>
<td>1.22</td>
<td>-30</td>
</tr>
<tr>
<td>19-C.Pi</td>
<td>1.66</td>
<td>1.37</td>
<td>-18</td>
</tr>
<tr>
<td>22-D.Qu</td>
<td>1.20</td>
<td>1.03</td>
<td>-14</td>
</tr>
<tr>
<td>25-P.St</td>
<td>1.71</td>
<td>1.14</td>
<td>-36</td>
</tr>
<tr>
<td>26-A.Va</td>
<td>1.58</td>
<td>0.84</td>
<td>-47</td>
</tr>
<tr>
<td>27-E.Vi</td>
<td>2.14</td>
<td>1.40</td>
<td>-35</td>
</tr>
<tr>
<td>30-R.Ko</td>
<td>1.80</td>
<td>1.80</td>
<td>0</td>
</tr>
</tbody>
</table>

*51Cr.
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Laboratory Findings

The initial abnormal, routine laboratory findings in our cases are summarized in Table 2.

Hematologic Findings

Anemia, defined here as a hemoglobin level of less than 12 g/100 ml, was found in 33 of the 40 cases. It was of normochromic-normocytic type, except where blood loss from bleeding abnormalities had led to iron-deficiency anemia. The determinations of red cell mass by $^{51}$Cr labeling demonstrated decreased values ranging from 12 to 49% in 16 of the 19 patients studied (Table 3). Two patients had concomitant hemolytic anemia (cases 20 and 26). The latter was associated with a high titer of cold agglutinin. White counts were usually within the normal range. In two cases, including case 20, differential counts showed lymphocytosis with abnormal cells. Only two of our patients had platelet counts of less than 100,000 cu mm upon admission. Coagulation defects were common. These are reviewed in a previous publication.13

Urinary Proteins

Significant proteinuria proved to be uncommon in this group of patients. Bence-Jones proteins, defined as free light chains of a single antigenic type, were found in the urine in four cases. All four patients gave classical heat tests for Bence Jones proteinuria.

Roentgenologic Findings

Bone surveys, in general, showed only mild or moderate osteoporosis. There were three exceptions: one patient who showed multiple osteolytic lesions throughout the skeleton (case 11) and two patients (cases 8 and 22) in whom osteolytic lesions developed during the course of the disease (Fig. 2). In all three of these cases the lesions were shown by surgical biopsy to consist of infiltrates of lymphosarcoma cells.

Bone Marrow Abnormalities

Bone marrow specimens were usually obtained by aspiration, although in some cases bone marrow biopsy was required to provide an adequate picture of marrow cellularity. The usual findings were a mixed population of plasma cells, lymphocytes, and the intermediate lymphocytoid plasma cell. In some cases, however, plasma cells predominated comparable to the bone marrow infiltrate seen in the multiple myeloma; in other extensive infiltration by lymphocytes was seen. A helpful differentiating point between myeloma and macroglobulinemia in these cases is often provided by the presence of increased numbers of tissue mass cells in the macroglobulinemic patient. Red cell precursors were usually present in normal numbers, megakaryocytes were plentiful, and granulocytes maturation was adequate. In some cases, extensive filtration of marrow by lymphoid plasma cell elements in association with peripheral thrombocytopenia and increasing anemia was seen as the disease progressed (case 5).
Serum Proteins and Viscosity

The results of serum protein studies at the time of diagnosis are shown in Table 4. Total protein concentrations ranged from 5.6 to 16.8 g/100 ml, and IgM levels from 1.2 to 11.9 g/100 ml or 16.9-70% of the total protein. In all cases, serum electrophoresis showed marked symmetrical peaks in the beta-gamma region. The peaks were usually seen in the fast gamma region, although in a few instances they appeared in the slow gamma region. The abnormal proteins of all patients were characterized as IgM by immunoelectrophoresis, confirming the diagnosis of macroglobulinemia. In 11 cases ultracentrifugal analysis of the isolated proteins showed sedimentation coefficients ranging from 16.8 to 20.0.

Light chain typing in 33 cases showed that the macroglobulin molecule contained kappa chains only (25 cases) or lambda chains only (8 cases). Serum samples were adequate for light chain typing in the majority of cases. In nine cases, isolation of the protein was required, and in two of the nine cases reduction to the monomer form or isolation of the light chains was necessary before typing could be accomplished.
The Sia water dilution test provided positive results in 45% of our patients. Thus, the presence of a negative test should not influence one in considering this diagnosis.

Some increase in relative serum viscosity was found initially in 26 of the 34 patients tested (Table 4). Of the 26 patients, 13 had clinical manifestations of the hyperviscosity syndrome at some time during the period of observation.

### Table 4. Results of Serum Protein Studies at Time of Diagnosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Relative Serum Viscosity</th>
<th>Total Proteins (g/100 ml)</th>
<th>Serum Concentration (g/100 ml)</th>
<th>°% of Total Protein</th>
<th>Mobility</th>
<th>Light Chain Type</th>
<th>Sedimentation Constant (S20W)</th>
<th>Sia Test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-A.El</td>
<td>1.8</td>
<td>8.0</td>
<td>1.5</td>
<td>18.6</td>
<td>Slow γ</td>
<td>K</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-C.Au</td>
<td>7.0</td>
<td>12.4</td>
<td>4.2</td>
<td>41.0</td>
<td>Slow γ</td>
<td>K</td>
<td>19.2</td>
<td>+</td>
</tr>
<tr>
<td>3-A.Bi</td>
<td>13.0</td>
<td>12.0</td>
<td>7.6</td>
<td>63.5</td>
<td>Slow γ</td>
<td>K</td>
<td>18.8</td>
<td>+</td>
</tr>
<tr>
<td>4-A.Bo</td>
<td>36.0</td>
<td>12.0</td>
<td>5.0</td>
<td>41.0</td>
<td>Slow γ</td>
<td>K</td>
<td>20.0</td>
<td>+</td>
</tr>
<tr>
<td>5-F.Ca</td>
<td>11.0</td>
<td>10.5</td>
<td>6.9</td>
<td>65.5</td>
<td>γ</td>
<td>K</td>
<td>17.5</td>
<td>+</td>
</tr>
<tr>
<td>6-E.CI</td>
<td>33.0</td>
<td>8.0</td>
<td>3.1</td>
<td>46.0</td>
<td>γ</td>
<td>K</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7-A.Eu</td>
<td>3.0</td>
<td>8.0</td>
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<td>70.0</td>
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*+, positive results; —, negative results.
The symptoms (epistaxis, headache, tinnitus, weakness) usually appeared when relative serum viscosity was 6–8. The symptomatic threshold, however, varied considerably from patient to patient. In the patients with the hyperviscosity syndrome, the symptoms were relieved by therapy with the consequent decrease in serum viscosity and serum macroglobulin levels.

A high serum concentration of IgM was a consistent finding in the patients with increased serum viscosity. In the patients with moderately increased macroglobulin levels, however, the occurrence of serum hyperviscosity was variable (Table 4). Ultracentrifugal analysis showed no correlation between the amount of 26S and 30S polymers in the serum of these patients and the presence or absence of hyperviscosity. Determinations of plasma volume in 19 of the 40 patients demonstrated a significant increase in the plasma volume in these patients with hyperviscosity syndrome. This increase showed a linear correlation with relative serum viscosity. Details of these studies were reported in a separate communication.4

Histopathologic Findings

Biopsy or autopsy material was available in 12 cases and showed the pathologic features characteristic of Waldenström’s macroglobulinemia.14,15 Extensive infiltrates of lymphocytoid cells, lymphocytes, and plasma cells were present in the liver, spleen, and lymph nodes, as well as in the kidney. With rare exceptions, the hepatic infiltration was limited to the portal areas and appeared to be correlated in degree with the severity of the disease. In one patient (case 22), parenchymal infiltration was associated with a lymphomatous process. In the patient in whom loss of consciousness was the initial symptom (case 28), localizing neurologic signs developed, and he became comatose and died. Postmortem examination showed diffuse cellular infiltration of the cerebral cortex and Virchow-Robin’s spaces but no localized tumor. Periodic acid Schiff staining inclusion bodies were searched for in all tissue sections but were not a prominent finding.

Infiltration by amyloid was found in two cases. In one patient (case 10), extensive deposits of amyloid were seen in the lymph nodes and spleen and in most of the blood vessels to parenchymal organs. The second patient (case 5) had amyloid deposits in the kidney but no significant loss of renal function.

Association With Additional Neoplasms

Twenty-two of our patients had either primary or associated malignancies or a history of a previous neoplasia successfully treated by surgical removal. More than half of these were malignancies of the lymphoid series. Eight patients had unrelated tumors including carcinoma of the lung (three cases), carcinoma of the vulva, cervix, colon, kidney, and epithelioma of the bladder, (one patient each). Three additional patients had well-localized basal cell carcinomas. The malignancies were a direct cause of death in three patients. The manifestations of lymphoma or carcinoma frequently appeared months to years after the onset of plasma protein abnormality. Two patients had nonmalignant tumors, a chromophobe adenoma and a parathyroid adenoma.

Studies were undertaken to explore a possible relationship between the
MACROGLOBULINEMIA

associated neoplasm and the IgM protein (see discussion). Tumors from four
patients (cases 5, 19, 20, and 22) were studied by immunofluorescent tech-
niques for antigens reactive with the respective patient macroglobulin. The
tumors were adenocarcinoma of the lung, adenocarcinoma of the kidney,
Hodgkin's disease, and lymphosarcoma. Sections were incubated first with
the isolated, purified macroglobulin of the donor patient, then isothiocyanate-
labeled rabbit antiserum to IgM. Binding of homologous or heterologous
macroglobulins to tumor could not be demonstrated. To determine if the
tumors were producing IgM, sections were incubated directly with isothio-
cyanate-conjugated rabbit anti-IgM antibody, none of the tumors was pro-
ducing detectable amounts of IgM. This is despite IgM production by
lymphocytoid plasma cells in the bone marrow, as demonstrated by immuno-
fluorescence.

Mode of Therapy

Therapy was based on the clinical status of the individual patient and the
presence or absence of clinical manifestations of the hyperviscosity syndrome.
In general, plasmapheresis or alkylating drugs, or both, were used in treat-
ment. Patients with symptoms of hyperviscosity received the first treatment
by plasmapheresis in the hospital after evaluation of blood volume and plate-
let status. In patients with demonstrable lymphomas, therapy with alkylating
agents was begun simultaneously. Patients without systemic complaints or
evidence of such malignancies were seen on an outpatient basis as soon as
plasmapheresis had reduced the serum viscosity to 3 or less. Thereafter,
plasmapheresis was individualized. If plasmapheresis was required at burden-
some, frequent intervals, alkylating agents were added. Chlorambucil, given
in moderate doses of 6–8 mg daily for 1–3 mo, followed by maintenance
doses of 2–4 mg daily, was used primarily. Cyclophosphamide (50–150 mg
daily) or melphalan (2–4 mg daily) were used in some cases. All patients re-
sponded to much lower doses of alkylating agents than are usually recom-
ended. High-dose chlorambucil therapy, 10–12 mg, carries a serious risk
of inducing aplastic anemias. We have seen two patients in whom drug-
duced aplasia was irreversible. In addition, one patient who received low
doses, 2–4 mg, of chlorambucil for 3 mo developed marrow aplasia that
lasted 3 mo.

Evaluation of Therapy

The variability of the natural course of Waldenström's macroglobulinemia
makes evaluation of therapy difficult. The insidious onset of the disease and
the frequent lack of symptoms at the time of diagnosis compound the diffi-
culty. We chose the time of diagnosis as our starting point for gross survival
information. This is arbitrary but affords an objective beginning. Twenty-
eight patients were followed closely enough to provide information.

Our criteria of therapeutic response was a 50% reduction in the size of the
lymph nodes, liver, and spleen, a 50% decrease in the serum IgM level, and
a reduction in serum viscosity (if increased) to asymptomatic levels (less than
4 U). Changes in hemoglobin or hematocrit levels proved unreliable in evalu-
ating the effects of therapy. Because of the variable physical findings, the criteria were applied as appropriate to the individual patient. A decrease in serum IgM level occurring during treatment and associated appropriately with the clinical course was considered a therapeutic response. Caution must be used in interpreting the significance of decreases in such levels as reductions not related to treatment did occur.

Results of Therapy

Nineteen patients, including ten with the hyperviscosity syndrome, were treated with alkylating agents for at least 3 mo. Eight of the group (40%) showed an objective response, as indicated by a decrease in serum IgM concentrations and serum viscosity. In two of the patients (cases 8 and 22), however, osteolytic lesions developed subsequently; in both it was found to be a lymphosarcoma by biopsy. In the 11 patients classified as nonresponsive, chlorambucil was continued until some objective indication of drug toxicity, usually leukopenia (less than 2,500 cells/cu mm) or thrombocytopenia (75,000 platelets/cu mm), was noted. In several patients, increasing anemia and enlargement of lymph nodes and liver or spleen occurred despite chemotherapy. In the patients with the hyperviscosity syndrome, plasmapheresis was effective therapy, since it prevented and reversed complications such as bleeding, congestive heart failure, and coma and reversed the retinopathy.

In the patients who responded to drug therapy, the average duration of survival from the time of diagnosis was 49.2 mo, whereas in the 11 nonresponsive patients it was 24.1 mo. This difference is highly significant ($p < 0.001$). There was no difference in the survival of either the responsive or nonresponsive patients treated by plasmapheresis, and chemotherapy compared with those treated by chemotherapy alone, or in the survival of the patients with the hyperviscosity syndrome compared with those with normal serum viscosity. The mean survival of patients with and without lymphoid tumors was equal (37 mo) if they were in the responding group.

In four patients in the series, the serum IgM levels showed a striking decrease that could not be attributed to therapy and was not associated with clinical remission. In three of the four, subsequent course was rapidly downhill, with the development of lymphomatous tumors in two (cases 20 and 22) and a widely and rapidly spreading adenocarcinoma of the lung in the third (case 3). Two of these patients were on maintenance chemotherapy, and their IgM levels had remained stable for 6 mo. The fourth patient, who received no chemotherapy for 2 yr, prior to the IgM drop remained free of symptoms, although marked thrombocytopenia developed (case 2). One other patient (case 4), described in detail elsewhere, failed to respond to a variety of alkylating agents but did have a clinical remission after treatment with prednisone.

DISCUSSION

Macroglobulinemia appears to be an abnormal transformation of an immunoglobulin-producing cell presumably of bone marrow origin. Patients may
present a wide variation of physical, laboratory findings, and clinical course. Some manifest malignant disease of organs other than the bone marrow and present a variable response in terms of quantity of serum IgM and its physiologic consequences, i.e., the presence or absence of hyperviscosity syndrome. In attempts to encompass this diversity, the concept of primary and secondary macroglobulinemia has been proposed. The latter group usually includes patients with lymphoma or other primary malignancies. This division, however, is necessarily arbitrary. As illustrated by our case material, patients can present with a serum abnormality some years prior to the manifestation of their lymphoma or other epithelial tumor. In case 5, 3 yr passed without visible manifestations of the carcinoma, during which frequent examinations were carried out. In case 20, 6 yr lapsed between the manifestation of macroglobulinemia and the presentation of tumor.

Thus, we feel that the arbitrarily delineation of primary and secondary monoclonal disease is untenable. We propose that macroglobulinemia be considered as a spectrum of disorders varying from benign monoclonal disease to rapidly advancing lymphoma or carcinoma, identified as separate from other malignant disease by the presence of the IgM protein. In view of the increasing evidence of the presence of antibody activity in such proteins, several hypotheses are possible: the IgM proteins are antibodies to some tumor specific antigen; the IgM proteins are antibodies to microscopic or submicroscopic organism related (or not related) to tumor induction; the proteins are merely markers of lymphoid cells that have undergone a malignant transformation and produce an appropriate or inappropriate (in the sense of no known antibody specificity) IgM protein; none of these factors are operable. Currently there is insufficient evidence to choose between these possibilities. Grey et al. have shown that monoclonal IgM proteins are present on the surface of the lymphocytes in nearly all patients with chronic lymphocytic leukemia, whereas normal lymphocytes have IgG, IgA, or IgM of both kappa and lambda types. Klein et al. have demonstrated IgM on the surface of Burkitt lymphoma cells. Thus, potential for production of specific monoclonal antibody appears to be present in malignant lymphoid disorders.

The physical characteristics of IgM protein are frequently responsible for a great majority of the patients' clinical manifestations, i.e., the hyperviscosity syndrome. Thus, it appears reasonable to us to address therapeutic efforts in this direction. Plasmapheresis, although cumbersome and frequently time consuming, is often rewarding in relieving the patients' symptomatology. This may be accomplished even in the patient who is not responsive to chemotherapy agents. In view of the variable course of this disorder, a patient should be observed for sufficient time to assess the severity of his disease. If the hyperviscosity syndrome is present, plasmapheresis and concomitant periodic measurements of IgM levels are indicated. This treatment alone may be adequate for the management of patients with IgM synthetic rates, such that their serum IgM return to symptomatic levels only 2–3 mo after therapy. In patients with active lymphomatous disease or rapidly recurring symptoms, chemotherapy is indicated. Success rate with chlorambucil in our patients was
much lower than that reported in the literature. Objective response was obtained in only 42% of the patients giving a trial of the drug. The reason for this difference in therapeutic results is not clear, but it is not related to the presence or absence of lymphoma, that is, there are an equal number of patients with lymphoma in the responding and nonresponding group. It may, however, reflect the referred nature of our patient population. As would be expected, those patients who do respond to chemotherapy have a significantly better prognosis than those who do not. Such therapy, however, has two significant risks: aplastic anemia that may be irreversible, and the development of an additional malignancy that may be drug related. There appears to be an increased incidence of acute myeloblastic leukemia in patients with multiple myeloma treated with alkylating agents. One patient (case 33) who developed aplastic anemia after intensive chlorambucil therapy expired from acute myeloblastic leukemia. Patients who have received renal allografts and are on long-term immunosuppressives have a higher incidence of malignancies, particularly of lymphatic origin, than the normal population. In all patients, the hyperviscosity syndrome and its associated complications of bleeding and congestive failure and coma can largely be prevented by plasmapheresis. It is suggested that such long-term plasmapheresis without chemotherapy may be applicable to the management of many patients with macroglobulinemia without hyperviscosity syndrome. The numerical survival values in our series are very arbitrary and should not be taken as prognostic values; as an example, at least two of our patients have survived for 10 yr since their diagnosis. One has been treated with plasmapheresis and low-dose chlorambucil. The second has been treated with plasmapheresis alone, except for a short 3-mo trial of chlorambucil that resulted in an episode of hypoplastic marrow.

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