Macroglobulinemia
Clinical Features and Differential Diagnosis

By Henry Wilde and Anton L. Hitzelberger

WALDENSTRÖM was the first to describe a disease which he termed "macroglobulinemia." This showed the following main characteristics: (1) a greatly increased blood sedimentation rate (BSR), (2) an increase in serum globulins, and (3) the presence of serum globulins having an abnormally high molecular weight, so-called "macroglobulins."

In addition to these constant findings, a variety of other manifestations may include: (1) a history of weakness and dyspnea often of several years duration; (2) an inclination toward hemorrhages in the naso-pharynx, in the retina, and in the central nervous system without an increased coagulation time or thrombocytopenia; (3) a generalized swelling of lymphatic tissue, including hepatosplenomegaly; (4) vascular disturbances of the extremities; (5) a normochromic anemia with changes in the bone marrow; and (6) spontaneous jellification of blood serum at room temperature with a slight increase in total serum protein.

Several laboratory tests are of value in establishing this diagnosis. Of a number of tests which have been designed to show abnormalities in serum proteins, the euglobulin test is technically the simplest. A drop of serum is added to a test tube of distilled water; if turbidity develops, which is soluble in a sodium chloride solution, the test is termed positive and a change in the serum protein system is suspected. The peripheral blood picture of a patient with macroglobulinemia may show normal values, but a slight leukocytosis with lymphocytosis and monocytosis has been observed. Prothrombin, thrombocytes, and coagulation time are normal even though there is a bleeding tendency in some cases. An examination of the sternal marrow often reveals fairly large numbers of cells which seem to be a "cross" between lymphocytes and plasma cells. Blood sera show positive euglobulin tests, and the Takata-Ara, Cadmium, thymol turbidity, and Weltmann tests are usually positive. There is an increase in one of the globulin fractions, and a determination of serum protein molecular weights always shows the presence of macromolecular proteins with weights of about one million.

With the relatively small number of cases described, there is no agreement regarding the etiology of this disease. It has been classed as one of the reticuloendothelioses, a primary disturbance in protein synthesis, or an atypical type of lymphocytic leukemia. The disease pursues a chronic course over a period of several years, is not amenable to any known form of therapy, but appears to have a considerably better prognosis than chronic lymphocytic leukemia or myeloma, both of which it may resemble.

From the University Medical Clinic, Freiburg, Germany.
Submitted January 13, 1953; accepted for publication February 10, 1954.
We wish to thank Dr. H. Begemann for examining the sternal puncture samples. The determination of serum protein molecular weights was performed at the Hoffmann-La Roche laboratories at Basel.
MACROGLOBULINEMIA

REPORT OF CASES

Case 1—E. E., 72 Year Old Male

Under clinical observation since 1946 for Ascariasis, tuberculosis and persistent normochronic anemia with BSR of 120 to 125 mm. per hour, constant weakness, no bone lesions, hepatosplenomegaly, or purpura. First diagnosed as chronic lymphocytic leukemia. Sternal marrow: hypocellular, predominance of lymphocytic elements and reduction of erythropoietic elements. Peripheral blood: hemoglobin 10.4 Gm. per cent, erythrocytes 3.2 million, leukocytes 10,000 per cu. mm. with differential count showing: metamyelocytes 5 per cent, polymorphonuclears 43 per cent, eosinophils 8 per cent, monocytes 5 per cent, lymphocytes 39 per cent. Thrombocytes 200,000 per cu. mm. Serum protein fractionations: albumins 31 per cent, alpha-globulin 8 per cent, beta-globulin 12 per cent, gamma-globulin 49 per cent. Two serum protein molecular weight determinations showed: 1949: 8 to 10 per cent macro-globulins, 9 per cent total serum protein; 1952: 26 per cent macroglobulins at 16.6 S.U., 9 per cent total serum protein.

Urethane therapy had no beneficial effect, but Ciba amidin derivative 2834-37 resulted in a reduction of the lymphocytic bone marrow infiltration and a negative euglobulin test. No change was observed in the BSR, and the euglobulin test became positive after therapy was discontinued.

Case 2—M. K., 51 Year Old Female

Under clinical observation since 1948 for myomatosis uteri with subsequent hysterectomy and old pyometra. Weakness, moderate bleeding tendency. BSR 85 to 108 mm. per hour. No bone lesions. Marked hepatosplenomegaly. Lower extremity edema. Normal bleeding and coagulation times. Sternal marrow: hypocellular, predominance of lymphoid and plasmoid reticulum cells and marked reduction in erythropoietic system. A splenic puncture yielded material in which the more mature forms of granulopoiesis predominated. Peripheral blood: hemoglobin 14.2 Gm. per cent, erythrocytes 5.3 million, leukocytes 16,000 per cu. mm. with differential showing: myelocytes 8 per cent, metamyelocytes 1 per cent, polymorphonuclears 27 per cent, eosinophils 5 per cent, monocytes 8 per cent, lymphocytes 6 per cent. Thrombocytes 140,000 per cu. mm. Normal Price-Jones distribution of erythrocytes. Blood counts varied a great deal. There were increased beta- and gammaglobulin fractions. A serum protein molecular weight determination showed 13.5 per cent macroglobulins in the 19.0 Svedberg unit region. During the patient’s prolonged stay, she was subjected to therapeutic attempts with nitrogen mustard, P₃₂, and Amidin (Geigy) without any indication of general improvement.

Case 3—E. H., 71 Year Old Female

Under clinical observation since 1951 for frequent grippe-like infections, pneumonia, weakness, a persistent BSR of 149 to 153, no purpura, no bone lesions, marked hepatosplenomegaly, marked icterus. Peripheral blood: hemoglobin 4.0 Gm. per cent, erythrocytes 1.2 million, leukocytes 3700 per cu. mm. Further testing substantiated the preliminary diagnosis of acquired hemolytic anemia (positive Coombs’ test, autoagglutinins). The patient received blood transfusions and 100 mg. cortisone daily for three weeks. BSR on discharge: 63 to 85; hemoglobin 15.5 Gm. per cent; erythrocytes 4.3 million, leukocytes 4200 per cu. mm. On second admission one year later: BSR 132 to 142, osteoporosis but no bone lesions, marked hepatosplenomegaly, no icterus, hemoglobin 11.5 Gm. per cent, erythrocytes 3.1 million, leukocytes 4400 per cu. mm., polymorphonuclears 58 per cent, eosinophils 9 per cent, monocytes 12 per cent, lymphocytes 39 per cent. Bone marrow: predominance of lymphocytic and plasma cells. Serum protein fractionations: albumins 37.5 per cent, alpha globulins 17.5 per cent, beta globulins 33.7 per cent, gamma globulins 11.3 per cent. A serum protein molecular weight determination showed 22.8 per cent macroglobulins at 16 S.U. Since the patient left the hospital shortly after completion of these tests, we were not able to subject her to a second therapeutic attempt with cortisone.
Discussion

Since marked increase in the blood sedimentation rate is the earliest abnormality which all the known cases of macroglobulinemia have in common, some discussion of the diagnostic value of this test seems indicated. Esser and Schmengler showed, by reading the BSR every fifteen minutes, that the BSR of their patients with proven macroglobulinemia reached values close to the maximum at the end of the first hour. Although this is also our observation, we are of the opinion that such a steep BSR curve is of no diagnostic value since we have observed similar curves in patients with subacute bacterial endocarditis, cancer without anemia, myeloma, and tuberculosis. It is noteworthy that anemia may lead to an increased BSR, and such an increased BSR may be superimposed upon an increased BSR due to abnormal serum protein conditions. This may explain an increase in the BSR which we have noted to occur with the appearance of anemia in the aforesaid cases of macroglobulinemia. Blood transfusions have resulted in change of the BSR toward normal. We think that polycythemia may also have the effect of producing a falsely normal BSR in the presence of actual serum protein pathology. This can be shown in the history of case M. K. As the hemoglobin levels of the patient increased progressively to a maximum of 19 Gm. per 100 cc, there was a corresponding decrease in the BSR to a minimum of 1 to 2 mm. After the hemoglobin had been reduced to normal values by P32 therapy, a rapid increase was observed in the BSR until it had reached values near 100 at the end of the first hour. A marked increase in gamma globulins was observed, corresponding to the experience of other authors (Waldenström, Esser, Schmengler, Schaub, Heilmeyer and Begemann, Wuhrmann and Wunderly). Changes in the globulin:globulin and globulin:albumin ratios are atypical.

The bone marrow in macroglobulinemia offers a rather atypical picture. A relatively cell-poor marrow was found in both our cases and has been described by other authors as well. An increase in lymphoid types with curious transition forms to plasma cells has often been observed. It is the opinion of Schaub that cases which have a preponderance of the plasmoid types should be given a poorer prognosis. Bianchi, et al. reported one patient with clinical macroglobulinemia who showed at autopsy a bone marrow with plasmoid infiltrations which appeared malignant, suggesting the possibility that macroglobulinemia can be simulated by, or possibly evolve into, a multiple myeloma. The only characteristic factor in the bone marrow seems to us to be an increase in reticulum cells, and it is interesting that these cells have been reported by Leitner to be involved in serum protein synthesis.

In the peripheral blood, we observed a monocytosis in all of our cases. The reduction in marrow elements manifested itself in patient E. E. as a normochromic anemia, while the patient M. K., who also had a marked reduction of marrow hemopoietic elements, had a peripheral erythrocytosis which prevented a final conclusion as to the true state of hemopoiesis. The increase in mature neutrophils in case M. K. was not observed in patient E. E. With the possible exception of a slight monocytosis and lymphocytosis, the white blood count and differential seem to offer little which may be called characteristic in this disease.
We observed spontaneous jellification of serum at room temperature and a positive euglobulin test in all of our cases. Each of these findings indicates an increase in the serum euglobulin fraction and may be observed in sera from several tropical diseases as well as in subacute bacterial endocarditis. We have also observed spontaneous serum jellification and a positive euglobulin test in connection with a number of vague disturbances of serum protein synthesis (patients K. S. and F. K.—vide infra).

The purpura in macroglobulinemia is of great interest and is not associated with thrombocytopenia or demonstrable abnormality of the coagulation factors. Although it is said to be uncommon, it has been well documented (Tischendorf and Hartmann and our case M. K.). It has been theorized that this purpura is due to "endotoxic" or hyperergic damage to capillary endothelium; in this regard the noncardiac edema and increase in the vascular fluid:cell ratio in case M. K. also suggest a loss of fluid due to a damaged endothelium.

It is important to differentiate the purpura of macroglobulinemia from the disease called purpura hyperglobulinemica. This condition, also described by Waldenström, is, like macroglobulinemia, characterized by purpura in the presence of apparent normalcy of the blood coagulation factors, and an increase in gamma globulins. It differs, however, in the absence of macromolecules. Waldenström has reported that an additional point of differentiation lies in electrophoretic analysis of serum: typical purpura hyperglobulinemica is said to be characterized by a flat "virus type" gamma globulin peak, while sera of macroglobulinemia patients show a sharp gamma globulin peak. However, our case M. K., a proven instance of macroglobulinemia, showed the purpura hyperglobulinemica-type electrophoretic pattern. Determination of molecular weights of serum proteins may therefore offer the only means of positive differentiation between these two conditions. In this regard it seems likely that there are possible transition forms between these two types of purpura.

The differential diagnosis from multiple myeloma lies primarily in the absence of typical myeloma plasma cells, the lack of Bence Jones proteinuria (with the exception of two cases reported by Wuhrmann and Riva), and the lack of radiologic bone lesions. The chronic course of a macroglobulinemia also speaks against the usual malignant course of multiple myeloma.

To differentiate clinically from chronic lymphocytic leukemia is much more difficult. Course and prognosis often have great similarities in these two conditions, and the appearance of hepatosplenomegaly in some cases of macroglobulinemia may make a differential diagnosis on clinical grounds alone impossible. As in the early differentiation from multiple myeloma and purpura hyperglobulinemica, the ultracentrifuge is the final authority.

The following two cases emphasize the necessity of ultracentrifuge studies in establishing the diagnosis of macroglobulinemia, since both resembled the disease clinically, but neither showed macromolecules upon ultracentrifugation of serum.

K. S., 21 Year Old Male

Under clinical observation since 1944 for unexplained anemia, BSR 105 to 120 mm., and weakness. No bone lesions, hepatosplenomegaly, or purpura. First diagnosed as chronic lymphocytic leukemia. Recent sternal marrow: cell poor, predominance of plasmoid
reticulum cells. Hemoglobin 9.7 Gm. per cent; erythrocytes 2.5 million; leukocytes 8000 with differential showing immature neutrophils 1 per cent, mature neutrophils 68 per cent, eosinophils 6 per cent; monocytes 5 per cent, lymphocytes 20 per cent. Thrombocytes 356,000. Serum Fe 218 gamma; serum Cu 129 gamma. There was an increase in the gamma globulin fraction at 9 per cent of total serum protein. The ultracentrifuge studies revealed only 3 per cent macromolecules in the 19 Svedberg unit range.

F. K., 61 Year Old Female
Under clinical observation since 1952 for ulcer of the stomach, BSR 70 to 102 mm., and weakness. No bone lesions, hepatosplenomegaly, or purpura. Sternal marrow: increase in plasmoid reticulum cells. Hemoglobin 15 Gm. per cent, erythrocytes 4.5 million, leukocytes 4000 per cu. mm. with differential showing immature neutrophils 12 per cent, mature neutrophils 46 per cent, eosinophils 2 per cent, lymphocytes 40 per cent. Thrombocytes 91,000. There was an increase in the gamma globulin fraction. Since, after attempts including surgical exploration, it was not possible to find the cause for the high BSR, a preliminary diagnosis of macroglobulinemia was made. A subsequent ultracentrifuge analysis of serum did not corroborate the clinical impression, there being only 2 per cent macroglobulins in the 14 S.U. range. We were forced to discharge the patient without a definitive diagnosis but are of the impression that a beginning plasmacytoma should be considered. (Since this article was written this has been proved to be the case.)

COMMENT
In regard to the aforementioned case K. S., it should be added that Schaub has shown that macroglobulinemia is not restricted to aged persons and that the youth of this patient is therefore no deterrent to consideration of this disease in a differential diagnosis. Unfortunately the ultracentrifugation was carried out after cortisone therapy, and we are inclined to believe that in a true case of macroglobulinemia, cortisone might cause a reduction in the BSR as well as in macroglobulin content of the serum. The clinical improvement which the proven case of macroglobulinemia, patient E. H., showed after cortisone therapy justifies such an assumption. As a result of our experience, we should like to agree with Wuhrmann and Wunderly in demanding proof for the presence of serum macromolecules before making a final diagnosis of macroglobulinemia. Dr. Hässig of the Swiss Red Cross at Bern, was able to develop a serologic test for the presence of macroglobulins, and through his courtesy we were able to have the reaction carried out in all of our cases. It corroborated the results obtained by ultracentrifugation.

Considering the histories of our patients, all of whom demonstrated prolonged chronic infections, we would like to suggest that we might not be dealing with a disease sui generis but only with a syndrome. The possibility should also be seriously considered that macroglobulinemia may be one of the allergic-hyperergic manifestations of prolonged infectious sensitizing insults on the reticuloendothelial system.

SUMMARIO IN INTERLINGUA
Es summarisate le tractos caracteristic de macroglobulinemia super le base del description original de Waldenström e de contributiones ulterior per altere autores. Sequo le presentation de tres casos typic con un discussion del problemas del diagnose differential. Le marcate acceleration del sedimentation sanguinee que es caracteristic de omne reportate casos de macroglobulinemia non es
MACROGLOBULINEMIA

acceptate per le autores como specific. Le purpura de macroglobulinemia es considerate como de grande interesse sed require un caute differentiation ab le si-appellate purpura hyperglobulinemic. Le differentiation diagnostic de macroglobulinemia ab multiple myeloma se estabbi principalmente per le absentia del typic cellulas myelomatic del plasma. Le differentiation ab chronic leukemia lymphocytic es difficilissime. In illo e generalmente le autoritate final es ultracentrifugation. In despecto del relativamente parve numero de casos in le litteratura le autores se senti justificate super le base del historias (Ie br patientes a postular que macrogbobulinemia es forsan solmente un syndrome e non un morbo sui generis. Illes etiam mentiona le possibilitate que macrogobulinemia es un del manifestationes allergico-hypergic de probongate infectiose attaccos sensibilisante super le sistema reticuloendothelial.

REFERENCES

Mactrogloubinemia: Clinical Features and Differential Diagnosis

HENRY WILDE and ANTON L. HITZELBERGER