Macroglobulinemia: Report Of Ten Cases

Dale R. Hines
MACROGLOBULINEMIA: REPORT OF TEN CASES

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INTRODUCTION

In 1944, Waldenström described two patients with a chronic illness characterized by fatigue, weight loss, bleeding from mucosal surfaces and lymphadenopathy. These patients were found to be hyperglobulinemic and macroglobulinemic (globulins with a Svedberg coefficient of 15 or greater by ultracentrifugation). The disease process eventually was called Waldenström's macroglobulinemia.

Since then, other disease states have been found to be associated with macroglobulins: systemic lupus erythematosus, kala-azar, multiple myeloma, carcinoma, leukemia, nephrosis, cirrhosis, congenital lues, and Sjögren's syndrome. Usually, macroglobulinemia secondary to these other diseases does not occupy as large a percentage of the total proteins as in Waldenström's macroglobulinemia.

The purpose of this article is to report ten cases of macroglobulinemia which were discovered from August, 1956 through December, 1961, and then to discuss macroglobulins and their clinical aspects. The first seven cases are classified as Waldenström's macroglobulinemia; the last three cases are secondary to other diseases.

The macroglobulins in the sera of the patients were determined by sedimentation velocity performed in the Spinco model E ultracentrifuge. Unfortunately, with the earlier calculations of macroglobulins as performed in our laboratory, it was not always possible to specify the percentage of the total protein, but it is included in the chart when possible. Figure 2 shows a photograph of ultracentrifugation done in case 2.

CASE 1 (G. H.) — A 57 year old white male was originally seen at this hospital in October, 1955 because of recurrent anemia. His history had been quite complex. The difficulty began in 1938 when he developed some symptoms suggestive of a peripheral neuropathy and he was told that he had a "possible early Ewing's tumor" of the femur and radiation was used. Tissue diagnosis was never established. He was later told that he had Hodgkin's disease and axillary lymph node biopsies revealed lymphadenitis.

During the early 1940's he continued to have intermittent anemia, diarrhea and neuritis. Diagnostic attempts were thorough but unrevealing. We do know that there was an elevated sedimentation rate (37 mm. in 1944) and that there was AG reversal at that time. The patient consulted a hematologist in 1947; bone marrow aspirations and lymph node biopsies again did not give a diagnosis. The sedimentation rate was 111 mm. per hour at this time.

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In 1950 anemia recurred and he was treated for recurrent urinary tract infections, possibly secondary to instrumentation and resulting urethral stricture from cystoscopy in 1943. He was also started on steroids in 1950. He stated that in 1952 he had an "eye hemorrhage" which occurred four times in the next three years. The patient had an attack of herpes zoster in 1953. In 1954 he had rectal bleeding, hematuria and occasional epistaxis. A diagnosis of multiple myeloma had been considered.

Physical examination on admission at this hospital revealed a cachectic white male, obviously pale, with punctate hemorrhages seen in both fundi and congestive retinal veins, moderate peripheral lymphadenopathy and the spleen tip was palpable 3 to 4 cm. below the left costal margin.

Admission laboratory work revealed a white blood count of 11,200 with 30 per cent lymphocytes on smear; rouleaux formation was also observed. The hemoglobin was 6 Gm., hematocrit 22, serum protein showed 2.14 Gm. per cent of albumin and 7.43 Gm. per cent of gamma globulin; the total proteins were 11.8 Gm. Bone marrow examination showed intense hyperplasia, predominately small monotonously patterned lymphocytes (75.3 per cent) which had replaced normal marrow elements. In addition plasmacytosis of 5.5 per cent was noted.

The patient was discharged to the Outpatient Department after one week with a diagnosis of probable diffuse lymphosarcoma and was treated with steroids.

He was readmitted in December, 1955 with a recent history of severe epistaxis requiring transfusions. Hepatomegaly was noted on this admission and treatment consisted of nitrogen mustard; a total of 27 mg. was given in three days. The Rumpel-Leede's was 3 plus bleeding time greater than 12 minutes and a coagulation time of 15 to 18 minutes was noted with a normal clot retraction.

The patient was discharged and required weekly transfusions by his local physician from January to May, 1956.

The patient was again admitted in May, 1956 and ultracentrifugation of the serum was done and revealed macroglobulinemia. The Sia test was positive. The rate of disappearance of tagged red blood cells was 100 to 68 per cent in five days. The patient developed a deep incapacitating hemorrhage in the left thigh in August, 1956 and an ecchymosis measuring 20 cm. in diameter over the left chest. Surprisingly, the two sedimentation rates done at this hospital were recorded as 1 mm. per hour and 14 mm. per hour in 1956 and 1958 respectively.

In February, 1957 he was admitted for weakness, anemia, hearing loss, neuropathy, and had consistently been receiving transfusions (15 in January, 1957 alone). He received four microcuries of P32 in February 1957 without clinical or laboratory change.

In July, 1958 he was hospitalized for consideration of splenectomy to decrease the hemolytic component of his anemia; this was decided to be unwise. During this time he developed a large hematoma of the left buttock and gluteal area and had melena also.

In October, 1959 he became febrile, increasingly icteric and died after a seven day downhill course.

Post mortem examination revealed diffuse involvement of the liver, spleen, kidney, lymph nodes, bone marrow, adrenal and soft tissue. The prominent symptom of peripheral neuritis throughout the long 21 year history of this illness could be explained by perineural cuffing by mature lymphocytes. The tumor tissue itself was composed of mature lymphocytes with a 10 to 20 per cent differentiation to a plasma cell type. The terminal episode appeared to be due to severe confluent bronchopneumonia.

Comment:
This patient clinically was a classic case of Waldenström's macroglobulinemia, yet post mortem findings were classified as lymphosarcoma. The latter is a pathologic diagnosis which the former designation is given to a combination of symptoms, signs, and laboratory findings. Mackay et al. reported four similar cases and hypothesized that malignant lymphosarcoma may acquire a functional capacity to synthesize paraprotein following occurrence of a somatic mutation.

CASE 2 (J. B.) — A 57 year old Syrian male was seen in the Emergency Room in July, 1961, with complaints of back pain with left sciatic radiation since a fall two and one-half months previously. Lumbosacral spine x-rays appeared normal. The pain persisted and
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Figure 1

Photograph of the serum protein electrophoretic pattern from Case 2. The characteristic gamma "spike" is seen on the left.

he was found to have an elevated sedimentation rate in September, 1961. He was admitted to the hospital in October, 1961 because of back pain, anemia, anorexia and a 20 pound weight loss.

Physical examination showed him to be in moderate distress due to pain. There was slight AV nicking on funduscopic examination; no lymphadenopathy, a grade II ejection murmur over the precordium and the abdominal examination showed no organomegaly. Lasègue's sign was positive on the left side.

Laboratory work showed a white blood count of 4,700 and a hemoglobin of 9.8 Gm., a corrected sedimentation rate of 32 mm. per hour, total proteins were 10.1 Gm. per cent with a gamma "spike" of 4.41 Gm. per cent (Figure 1), cryoglobulins were negative, Sia
test was positive. Bone marrow aspiration revealed a left shift of the granulocytic series, increased normoblasts and a smattering of giant neutrophils. There were 13.2 per cent lymphocytes and .6 per cent plasma cells. Ultracentrifugation of the serum showed approximately 22 per cent macroglobulins at S17 and 4 per cent at S26 with cryoglobulins being present (Figure 2). Bone marrow biopsy of the lumbar spine revealed particle smears showing solid cellularity, half of the cells being adult lymphocytes "suggestive of early chronic lymphatic leukemia".

During this admission fresh blood in the stool was noted, occasional mild epistaxis occurred, and the liver was palpable 3 cm. below the right costal margin.

The patient left the hospital voluntarily and without permission even though exact diagnosis was uncertain and the Radiation Therapy Department had recommended treatment.

He was readmitted a few days later and was given radiation therapy to the back with a total dose of 2,000 R in two weeks without much relief of the back pain. Nitrogen mustard was administered (0.1 mg. per kg.) and the back pain decreased somewhat but chest pain started, relieved partially by nitroglycerin. A peripheral smear revealed much rouleaux formation and repeat bone marrow examination showed 30 per cent small adult lymphocytes and 1 per cent plasma cells with intense rouleaux formation. He was discharged on Prednisone five mg. three times a day, to be tapered gradually.

He had epistaxis again in December 1961, and was readmitted in January 1962 for low back and chest pain. Physical examination at this time revealed the liver to be 2 cm. below the right costal margin without splenomegaly. Tenderness was again noted over the back area and he also had chest pain with some tenderness over the anterior rib cage. The macroglobulins had changed with 17 per cent of the macroglobulins being at S22 and 24 per cent at S26. Bone marrow examination again showed lymphocytosis with 25.7 per cent of the bone marrow cells being in the lymphocytic series and most of these were adult-looking cells.

He was given another course of nitrogen mustard with some symptomatic improvement but the serum protein pattern showed no change. He was last seen in February, 1962. The hemoglobin was 9.8 Gm.; chest pain was gone but the back pain still persisted.

Comment:
This patient presents symptoms and signs of Waldenström's macroglobulinemia, except for bone pain. Dutcher and Fahey\textsuperscript{1} found in their review three of 60 patients with Waldenström's disease who had bone pain.

CASE 3 (C. R.) — A 63 year old white female presented herself in March, 1957 for a complete check-up because of an elevated sedimentation rate for five years. Her symptoms included multiple aches and pains in the extremities and the back which were somewhat vague. There had been no weight loss.

Physical examination was essentially unremarkable with multiple PVC's being noted on cardiac examination and senile vaginitis on pelvic examination. Abdominal examination was negative. The white blood count was 5,500, hemoglobin 10.8 Gm. and a peripheral blood smear showed rouleaux formation. The AG ratio was 4.2/4.2 and the sedimentation rate 40 mm. per hour.

She was not seen again until November, 1957 at which time she was admitted for evaluation of the anemia, high sedimentation rate and the elevated globulins. Her chief complaint at that time was "burrowing pains" of the extremities and the chest. Physical examination was unchanged. The hemoglobin was 10.2 Gm., sedimentation rate 38, serum electrophoresis showed gamma globulins with an anomalous peak of 3.34 Gm. per cent. Bone marrow aspiration did not give good smears. Waldenström's macroglobulinemia was suspected after the serum electrophoresis despite the negativity of the clinical signs and symptoms. Ultracentrifugation was not done at this time.

The patient was discharged with a diagnosis of dysglobulinemia, cause undetermined, arteriosclerotic heart disease and normocytic normochromic anemia.

In May, 1958 a basal cell carcinoma was removed from the lip. In December, 1958 bruises over the pretibial area (spontaneous) were noted. In November, 1959 epistaxis occurred. Gamma globulins at this time were 3.34 Gm. per cent and the electrophoretic pattern was more "peaked" in the gamma globulin area. In October, 1959 a basal cell carcinoma was removed from the side of the nose. In May, 1960 ultracentrifugation was performed on the serum and large amounts of macroglobulins were found; the Sia test was negative. In October, 1960 venous engorgement was noted in the left eye. There
Figure 2

Photograph of the ultracentrifugation pattern from Case 2. The largest peak on the left is a mixture of albumin and globulin; the two smaller peaks are the macroglobulins.

were several attacks of bronchitis noted in the history and there were symptoms suggestive of a peripheral neuritis in the right shoulder. In December, 1960 adenopathy of the right anterior cervical nodes was noted.

The patient was followed in the Outpatient Department at intervals until February, 1962 and did fairly well. At the latter time she had onset of severe epistaxis after blowing her nose which required transfusion. The cervical nodes were quite enlarged at this time. The bleeding was stopped by packing the nose after some difficulty. The hemoglobin, during this admission, ranged between 7.7 Gm. and 8.5 Gm. Bleeding studies, including prothrombin consumption time, were normal. Fibrinogen level of the blood was 418 mg. per cent. Bone marrow examination showed 36.4 per cent cells of the lymphocytic series, no plasmacytes and otherwise not remarkable.

The patient was last seen in March, 1962 and was doing fairly well.

CASE 4 (J. S.) — A 47 year old white woman was initially seen at this hospital in April, 1959 because of epigastric and right upper quadrant pain for one year which radiated through to the back occasionally.

She gave an interesting past history and the main points are as follows: In 1928 she contracted syphilis from her husband and subsequently had two full term babies that died at three months and seven weeks respectively. She had had pneumonia six times since 1935 and pleurisy in 1958 and 1959. Bronchograms in 1958 were normal and a sedimentation rate was 22 mm. per hour in 1948. In 1955 she had radiation for profuse vaginal bleeding. A D & C was done and showed polypoid hyperplasia. She was told that she had an “abnormal bleeding time”. Also in 1955 all her teeth were extracted.
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and vitamin K was necessary to stop the bleeding. From 1945 to 1948 she had been a heavy drinker. She lost 26 pounds in two years prior to being seen here and three months prior (January, 1959) was found to have gallbladder stones, a peptic ulcer and splenomegaly.

Physical examination revealed a healthy appearing woman with positive physical findings consisting of palmar erythema and tender epigastrium. The liver was palpated 7 cm. below the right costal margin and the spleen 6 cm. below the left costal margin.

Laboratory work revealed a white blood count of 5,550 with a hemoglobin of 12.4 Gm. per cent. Rouleaux formation was noted on blood smear. Serum protein electrophoresis showed gamma globulins of 2.05 Gr. per cent and a gamma "spike". Ultracentrifugation revealed approximately 40 per cent of the total serum proteins to be macroglobulins with sedimentation coefficients of 34, 26 and 18. Bleeding studies were normal except for a prothrombin consumption time of 22 seconds. Slit lamp examination of the conjunctival vessels of the sclera revealed dilated venules, marked segmentation and granularity in the terminal vascular bed. Clumping was quite marked (Figure 4). Bone marrow examination revealed 3 per cent cells in the plasmacytic series, 14 per cent in the lymphocytic series—"The chief abnormality 8.4 per cent giant developing neutrophils".

The patient was discharged early May, 1959 and continued to work as manager of a motel, though she had frequent pulmonary infections and fever. She was seen at intervals in the Ophthalmology Clinic for a granulomatous conjunctivitis with a large whitish mound of presumptive lymphoid tissue on the conjunctival surface of each lower lid, probably related to her disease.

In April, 1961 the spleen tip was at the umbilicus — two years after the patient was seen initially. Her last appointment here was in the Ophthalmology Clinic for treatment of chronic conjunctivitis and dacryocystitis in November, 1961.

Comment:

In reviewing many cases in the literature, there is frequent reference to fundoscopic changes in the eyes of patients, but no mention was made of conjunctivitis or lymphoid hyperplasia of the conjunctive. Perhaps this is a rare manifestation or has been overlooked.

CASE 5 (J. T.) — A 57 year old white male was admitted for hernia repair in July, 1956. A review of systems revealed decreased appetite, fatigue and mild dyspnea on exertion in the previous few months.

Physical examination revealed slight narrowing of the retinal arterioles, palpable left anterior cervical lymph nodes, bilateral indirect inguinal hernia and prostatic hypertrophy.

Admission laboratory work revealed a white blood count of 5,100 with 56 per cent lymphocytes, 6.4 Gm. hemoglobin, rouleaux formation was noted on peripheral smear, and the red cells were normocytic and macrocytic. A sternal bone marrow aspiration was attempted with difficulty. A repeat bone marrow (iliac) aspiration showed 70.2 per cent lymphocytes, mostly mature and typical. AG ratio was 3.6/4.8. A bone biopsy was obtained which revealed a marked infiltration with cells of the lymphatic series. Roentgenographic metastatic survey revealed localized Paget's disease of the right femur.

The patient was given prednisone 2½ mg. daily. He was discharged in August, 1956, after ten transfusions with the diagnoses of anemia, erythrocytic hypoplasia, etiology unknown. He was readmitted in late September, 1956 with a diagnosis of serum hepatitis, manifested by scleral icterus, anorexia, nausea, vomiting and hepatomegaly with the liver edge 2 cm. below the right costal margin. The spleen was palpable in the right lateral decubitus. The Sia test was positive and macroglobulinemia was discovered. The serum electrophoresis at this time showed 10.2 Gm. per cent total protein with 2.3 Gm. per cent of albumin and 5.2 Gm. per cent gamma globulin.

The discharge diagnoses were a) homologous serum hepatitis, b) chronic lymphatic leukemia, and c) macroglobulinemia. On December 2, 1956 the patient awoke with numbness and tingling of both hands which cleared in 24 hours; however, the next day he was irritable, restless and uncooperative. He was admitted on December 4, 1956. Physical findings at this time revealed dehydration, shotty axillary nodes. The liver and spleen were 2 cm. below the costal margin. His condition deteriorated steadily and he expired on December 6, 1956.

Pertinent post-mortem findings were generalized lymphadenopathy, splenomegaly with large infarction, replacement of bone marrow by small lymphocyte-type cells and Paget's disease of the right femur.
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Comment:

Macroglobulins, the lymphocytic bone marrow and the normal peripheral WBC better fit Waldenström's macroglobulinemia than chronic lymphatic leukemia. The differentiation is often a problem, however.

CASE 6 (A. G.) — This 60 year old white male was seen at this hospital initially in February, 1958 with the chief complaint of cough and “congested lungs”. Physical examination revealed moderate pulmonary emphysema and the left lobe of the prostate was “stony hard”. He was seen in the Urology Clinic and a clinical diagnosis of carcinoma of the prostate was made and the patient was started on estrogen therapy. Follow-up revealed the right lobe to be more indurated than the left lobe and the left lobe now felt normal. He was advised to come into the hospital for biopsy but for some reason did not elect to. Bone films and serum acid phosphatase values were normal.

He was not seen here from May, 1958 to January, 1961, and at that time was referred because of coldness, numbness, weakness of the legs, and a 30 pound weight loss. The patient had been a moderately heavy drinker for 25 years.

Physical examination showed minimal lymphadenopathy (cervical, inguinal and one epitrochlear node) and frequent PVC's. The liver and spleen were 3 cm. below the costal margin. The skin of the distal extremities was cool with dependent mottled cyanosis. A 1 cm. indurated node was palpated within the right lobe of the prostate gland. Neurologic examination revealed generalized hypotonia, muscle atrophy, bilateral foot drop, decreased position and vibratory sensation of the lower extremities, patchy hyperesthesia, and a positive Romberg test.

Laboratory values included a white blood count of 10,650 and rouleaux formation was noted on blood smear. The hemoglobin was 13.6 Grm. and the sedimentation was 38 mm. per hour. Serum proteins revealed an albumin of 2.85 Grm. per cent, a gamma globulin of 3.09 Grm. per cent. The gamma globulin on electrophoretic pattern showed a sharp gamma “spike”. Bone marrow examination showed no particles in marrow smears; the myeloid erythroid ratio was high (10-1), and there were 26 per cent lymphocytes and .6 per cent plasma cells. Ultracentrifugation was done and 33 per cent of the total proteins were macroglobulins with the majority at S18 and smaller fractions at S26 and S33.

Therapy consisted of vitamins and Chloromycetin for a urinary tract infection. He was discharged with a diagnosis of macroglobulinemia, polyradiculoneuropathy secondary to macroglobulinemia, pyelonephritis and suspected carcinoma of the prostate.

He was then followed in the Outpatient Department until March, 1961, when he was admitted for penicillamine treatment which has been reported elsewhere to be of value in macroglobulinemia. There was symptomatic improvement and the Sia test became negative but the serum proteins were essentially unchanged.

The patient was again admitted in May, 1961. He now presented a pseudotabes-type neurologic picture. He was again given a course of penicillamine without even subjective improvement. He was seen in the Outpatient Department in June, 1961 and has been hospitalized elsewhere since then.

Comment:

The neurologic manifestations of macroglobulinemia predominated in this case. Logothetis and others reported that 25 per cent of the patients they reviewed with macroglobulinemia had neurologic signs. The rare combination of macroglobulinemia, neurologic and psychiatric manifestations in a febrile patient is termed the Bing-Neel syndrome. Treatment with penicillamine will be commented on later.

CASE 7 (J. M.) — This 69 year old colored male was admitted in August, 1956 with a 24 hour history of twitching and weakness of the right arm and leg. Physical examination revealed an elderly male unable to walk, with right sided hemiparesis, no organomegaly, and a positive Babinski sign on the right. Admission diagnosis was left middle cerebral artery thrombosis. The patient gradually developed other neurologic signs (central facial paralysis, receptive and expressive aphasia).

Routine laboratory work revealed a white blood count of 10,850 with 15.1 Gr. per cent of hemoglobin. Admission VDRL was positive; further serologic tests showed the Kahn to be positive and the quantitative Kolmer was found to be “markedly anticomplementary”; spinal fluid Kahn was negative. The anticomplementary substance was found to be a protein and serum electrophoresis revealed 2.18 Gr. per cent of albumin and 2.04 Gr. per cent of globulin with a “globulin spike”. A bone marrow examination

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showed an increase in plasma cells (3.6 per cent), increase in eosinophils 4.4 per cent and lymphocytes 16.2 per cent. Macroglobulins were found with a sedimentation coefficient of 23 and 24.5 and cryoglobulins were present.

The hemiparesis persisted with slight clinical improvement until September 27, 1956 when he suddenly expired quietly.

Post mortem examination revealed no significant lymph node enlargement but the nodes were hyperplastic microscopically. The bone marrow showed increased numbers of plasma cells (not in sheets) and "a few more lymphocytes" than normal. The brain showed left middle artery thrombosis and encephalomalacia.

Comment:

Logothetis and others,2 in their review of world literature on macroglobulinemia, found four of 182 cases with hemiplegia. The anticomplementary effect of serum from hyper-gammaglobulinemic patients has been demonstrated in lymphogranuloma inguinale, liver cirrhosis, disseminated LE, and myelomatosis.22 The anticomplementary effect is demonstrated by incubation of a mixture of complement plus globulin (in suitable proportion) which inhibits the hemolytic action of the complement on sensitized sheep RBC's. Normal gamma globulin is prevented from doing this by the inhibitory effect of the other serum proteins in the complement fixation reaction. As mentioned above, a large excess of gamma globulin may be expected to make a serum more anticomplementary,8 but this is by no means predictable.

CASE 8 (J. W.) — A 59 year old white male was admitted to this hospital on July 9, 1959, with the chief complaint of numbness and tiredness in both feet. The patient had noticed onset of general malaise in December, 1958, had a vocal cord polyp removed elsewhere in February, 1959, and was told that he had "leukemia" at that time, after blood studies. A bone marrow done elsewhere in May, 1959 was reported: "72 per cent of the cells are lymphocytes of which about 10 per cent are atypical or show some immature features". There was a moderate alcoholic history and a 35 pound weight loss which the patient ascribed to dieting.

Physical examination revealed a ruddy face, hepatomegaly 8 cm. below the right costal margin, a few wheezes on auscultation of both lung fields, varicose veins and obesity.

Laboratory work revealed a white blood count of 13,700, hemoglobin 13.8 Gm. The blood smear showed 20 per cent lymphocytes, 35 per cent leucocytoid lymphocytes, total proteins were 7.8 Gm. with an albumin of 3.51 Gm. per cent and a gamma of 2.67 Gm. per cent. The gamma fraction on electrophoresis was in the shape of a "hump" rather than a "spike". Chest x-ray showed a widened mediastinum. Bone marrow examination revealed numerous giant neutrophils although megaloblasts were rare; there were increased normoblasts and a moderate increase in lymphocytes (19.6 per cent) and 1.2 per cent plasmacytosis.

The patient was discharged with a probable diagnosis of chronic lymphatic leukemia and was readmitted four months later (November, 1959) because of dermatitis and cellulitis of both legs. He also had a peripheral neuropathy and radiculopathy of the lower extremities. At this time borderline macroglobulinemia was discovered.

In March, 1960 the patient was again admitted for increasing somnolence and the "Pickwickian syndrome" was added to the diagnoses. Increased evidence of superior vena caval obstruction was noted. Radiation therapy to the mediastinum gave improvement. The patient was again admitted in September, 1960 because of recurring symptoms of superior vena caval obstruction, drowsiness and a 16 pound weight gain. He again improved after radiation treatment. The serum protein at this time showed 9.9 Gm. per cent total with 4.37 Gm. per cent of albumin and 3.80 Gm. per cent of gamma globulin with a tendency towards a "spike" on electrophoresis.

He was last seen in the Outpatient Department in October, 1960, at which time a large node was noted in the left supraclavicular area. He has been lost to follow-up since then.

Comment:

This patient's clinical and laboratory findings suggest macroglobulinemia secondary to chronic lymphatic leukemia.

CASE 9 (J. S.) — This 63 year old retired cook has been seen intermittently at this hospital since 1937 for various minor difficulties. In 1946 he was admitted for evaluation of a confusing neurologic picture — hysteria, multiple sclerosis and platybasia were considered, with the latter plus functional elements the discharge diagnosis.
He was next seen in 1955. Vague symptoms (staggering, blurred vision with changes in the weather, nocturnal leg cramps, gaseousness) involving different organ systems were mentioned. Mild lymphadenopathy (generalized) was noted and the liver edge was 7 cm. below the right costal margin. Neurologic examination was abnormal but unchanged from that ten years previously (ataxia, positive Romberg, nystagmus, large irregular left pupil and positive Hoffmann’s sign bilaterally).

Laboratory work showed a white count of 5,600, hemoglobin of 14.8 Gm., corrected sedimentation rate of 36 mm. per hour. Liver function tests were obtained to evaluate hepatomegaly; cephalin cholesterol was 4 plus, thymol turbidity was 12 units and the thymol flocculation was 4 plus. An AG ratio at that time was 5/2.4.
A few days after admission the patient demanded to be discharged, although the hepatomegaly and positive liver flocculations had not been evaluated.

He was next seen here in September, 1958 with a history of albuminuria and ankle edema for one year. He appeared chronically ill. The liver was palpated 6 cm. below the right costal margin. There was moderate lymphadenopathy of the cervical, axillary and inguinal areas and 3 plus pitting edema of the ankles. The white blood count was 5,500, the hemoglobin was 11.3 Gm., corrected sedimentation 32 mm. per hour, and 4 plus albuminuria. The liver flocculations were still abnormal. Serum protein electrophoresis showed an albumin of 1.18 Gm. per cent and globulins of 1.04 Gm. per cent. There was a tendency toward a "spike" in the gamma region. A liver biopsy revealed amyloidosis; bronchiectasis was also diagnosed with the aid of bronchograms.

He was again admitted in July, 1960 for enlarging lymphadenopathy. The white blood count and hemoglobin were normal at this time but rouleaux was noted on peripheral smear. There was 3 plus albuminuria and 6.5 Gm. of albumin in the urine for 24 hours. Abnormal coagulation studies at this time showed a bleeding time of 7 1/2 minutes and a Rumpel-Leede's was 3 to 4 plus positive. Serum proteins revealed an albumin of 2.24 Gm. per cent and gamma globulins of 1.70 Gm. per cent. The gamma globulins were noted this time to spike sharply on electrophoretic pattern and macroglobulins were found by ultracentrifugation. A trial of steroids for the nephrotic syndrome was without much effect.

He was seen again one year later (1961) for severe itching of several months duration. A variety of medications were tried with partial relief. Interestingly, the gamma globulins returned to normal range and the gamma spike had disappeared.

The patient was last seen in December, 1961 with mild symptoms of uremia.

Comment:

Macroglobulinemia, when secondary to another disease (amyloidosis in this patient), does not usually occupy as large a percentage of the total protein and may be transient. The latter phenomenon probably occurred, as the characteristic gamma "spike" was not present on the last electrophoretic pattern.

Case 10 (R. D.) — This 53 year old Hungarian female was admitted to this hospital in September, 1957, because of a weight loss of 20 pounds and fatigue in the previous two months. She had painful interphalangeal joints for one and one-half years and was on small doses of cortisone. There was also a history suggestive of Raynaud's phenomenon.

Physical examination revealed vitiligo, hepatomegaly 8 cm. below the right costal margin, symmetrical fusiform swelling of the interphalangeal joints and ankles, and minimal adenopathy in the cervical, epitrochlear and inguinal areas.

Initial laboratory work showed a white blood count of 12,850 with a shift to the left, hemoglobin 10.8 Gm., sedimentation rate 36 mm. per hour, total proteins 5 Gm. per cent with 0.6 Gm. per cent albumin and 2.8 Gm. per cent gamma globulin. Abnormal liver flocculation tests were found. The serum cholesterol was 72 mg. per cent, total serum lipids were 311 mg. per cent and BSP 5 per cent. A liver biopsy revealed fatty metamorphosis. Bone marrow examination revealed only 3.2 per cent cells of the lymphocytic series and 1.6 per cent cells of the plasmacytic series; severe rouleaux formation was noted. Lymph node biopsy in the cervical region revealed adenocarcinoma, primary unknown. A mild degree of macroglobulinemia was found by ultracentrifugation of the serum.

The patient was started on treatment with steroids and a course of nitrogen mustard without much benefit.

In December, 1957 she was admitted for acute pulmonary edema and was noted to have Cushing's syndrome secondary to treatment. She improved and was followed in the Outpatient Department and posterior cervical lymphadenopathy was again palpated which gradually increased in size to 4 cm. in June, 1958. At the same time she complained, for the first time, about deafness in the right ear and nasal stuffiness and obstruction. The right nasal cavity revealed obstruction and biopsy of this area revealed carcinoma of the nasopharynx. She was given cobalt therapy to this area with some improvement.

She was readmitted in February, 1961 with pulmonary metastases. The serum proteins at this time showed a quantitatively normal amount of gamma globulins (1.13 Gm. per cent) but there was a gamma "spike" noted on the electrophoretic curve. She was given courses of Uracil-mustard in the early months of 1959 without any benefit.

The last admission, for terminal care, was in July, 1959 and she died shortly after admission.
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Figure 4
Photograph of conjunctival vessels of the sclera of a patient with macroglobulinemia (Case 4). Notice the segmentation and clumping of the erythrocytes in the dilated venules. The periphery of the iris is seen along the lower margin. (Magnified 80X).

The post mortem findings were chiefly that of epidermoid carcinoma of the pharynx, carcinomatosis of the lungs, bone, liver and bronchopneumonia.

Comment:
This case illustrates macroglobulinemia secondary to carcinoma. The “spike” in the gamma range on electrophoresis persisted despite quantitatively normal gamma globulins.
Normal and Abnormal Macroglobulins

Macroglobulins are glycolipoproteins which have a molecular weight of 1,000,000 or higher, and have a sedimentation constant greater than 15 Svedberg units in an ultracentrifugal field. The normal sedimentation constant of albumin is 4.5; that of normal gamma globulin is seven. The sedimentation constant is designated as Svedberg units (S) and represents a certain speed in a specific field of gravity. It is not to be confused with Svedberg's flotation unit (Sf) which is applied to fractions of lipoproteins studied by means of flotation following ultracentrifugation. In normal sera, 2 to 5 per cent of the total proteins are macroglobulins. An arbitrary criterion of 10 per cent macroglobulins (or greater) of the total serum proteins is recognized as macroglobulinemia.

The macroglobulins of normal sera contain the rheumatoid factor, properdin, cold agglutinins, Wasserman and heterophile antibodies, blood group AB, typhoid "O" agglutinins, penicillin antibodies, and isohemagglutinins. Normal macroglobulins are present in the alpha fractions, but pathologic macroglobulins are found in the beta or gamma fraction.

Two terms should be clarified before discussing abnormal macroglobulins. DYSPROTEINEMIA refers to quantitative alterations in normal serum components, while PARAPROTEINEMIA refers to gamma globulin normally absent, or present in minimal amount, which is greatly increased in certain pathologic states. The latter includes macroglobulinemia, multiple myeloma, and cryoglobulinemia. The macroglobulins in Waldenström's macroglobulinemia usually are 20 to 30 per cent or more of the total serum proteins, while in secondary macroglobulinemia the amount present is usually less, and may be found only transiently (e.g. case 9). The macroglobulins probably represent polymers of normal-sized globulins.

Macroglobulins are produced in the reticulo-endothelial system, and in Waldenström's macroglobulinemia, evidence suggests that their source is in the lymphocytoid cells of the bone marrow. This has been shown by immunofluorescent and cytochemical techniques. PAS positive material has been demonstrated in both the nucleus and the cytoplasm of the abnormal cell.

Macroglobulins from different patients are not antigenically similar as shown by precipitin testing and passive transfer of anaphylaxis.

What causes the formation of these abnormal macroglobulins? Waldenström first hypothesized that these giant protein molecules may be produced in response to a viral infection and that they might be "virus proteins" with simultaneous decrease in formation of albumin and fibrinogen. Mackay et al theorize that malignant lymphosarcoma may acquire the capacity to synthesize paraproteins following somatic mutation. Ritzmann et al, in their comprehensive review of macroglobulinemia, believe it is a response to an enzymatic defect in the course of protein synthesis. The answer awaits further investigation.

Clinical Manifestations.

Waldenström's macroglobulinemia occurs most commonly in males over 50 years of age. Common presenting symptoms are fatigue, weight loss, dyspnea, mucosal
MACROGLOBULINEMIA

(usually nasal or oral) bleeding, disturbed vision, neurological disturbances, vasomotor phenomena, and recurrent infections. The latter may be due to inability to produce new humoral antibodies.\textsuperscript{18}

Physical findings may include hepatosplenomegaly, lymphadenopathy, fundoscopic changes (consisting of congested retinal veins, "sausage-shaped" kinking of the veins, and hemorrhages), pallor, neurologic abnormalities, and muscle wasting. Fifty-two of 60 cases in one series\textsuperscript{3} showed hepatosplenomegaly and/or lymphadenopathy.

Laboratory Findings

Abnormal laboratory findings are frequent and diverse. The typical findings are: 1) an increased sedimentation rate, sometimes over 100 mm/hr., 2) hypergammaglobulinemia with a gamma "spike" on serum electrophoresis (Figure 1), 3) a relative preponderance of lymphocytoid cells in the bone marrow (which is often difficult to aspirate), and 4) the sine qua non, demonstration of macroglobulins by ultracentrifugation.

Other findings include the blood smear which usually shows a normocytic normochronic anemia with rouleaux formation and sometimes a relative lymphocytosis. A red blood cell count may be impossible because of agglutination of cells in the counting chamber. The Sia test is a nonspecific test for euglobulins (the latter meaning a globulin that is insoluble in water but soluble in saline). In this series it was positive in five of seven cases tested, but it may give false negatives or false positives (e.g., one may have a positive Sia test in multiple myeloma without macroglobulins).\textsuperscript{22} Bence-Jones proteinuria is not a rare finding though none of our patients demonstrated it (seven were tested). X-rays of the bones may show osteoporosis occasionally, but never the punched-out lesions typical of multiple myeloma.

Bleeding disorders often play a prominent part in this disease and almost all known clotting factors have been found to be deficient in one or another case.\textsuperscript{19} In the present series three of five tested showed abnormal coagulation studies. Waldenström\textsuperscript{4} thought fibrinogenopenia was the chief difficulty but this has not been a consistent finding. Pachter and coauthors, in studies from this hospital, believed the bleeding diathesis to be caused by a coating of the platelets by the macroglobulins,\textsuperscript{19} and further, that the molecular size of the macroglobulin prevented platelet factor\textsuperscript{3} release.\textsuperscript{20} Others believe the macroglobulin may mechanically interfere with fibrin formation.\textsuperscript{21}

Interestingly, liver flocculation tests are almost always abnormal in this disease, but seldom in multiple myeloma;\textsuperscript{10} five patients tested in the present series revealed abnormal liver function tests (Table I).

Differential Diagnosis

The differential diagnosis of Waldenström's macroglobulinemia includes many of the conditions which present as a chronic disease of the reticuloendothelial system. However, once the serum protein electrophoresis is obtained, the characteristic tall gamma "spike", which is almost always present, rapidly narrows the choices to
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multiple myeloma, macroglobulinemia and some types of cryoglobulinemias. Other hyperglobulinemic disease states show a wider, broad-based "hump" in the gamma fraction.

Some cases of "aleukemic lymphatic leukemia" in the past may well fit the criteria of Waldenström's macroglobulinemia. An example of a difficult patient to classify would be one with a WBC from 10-15,000/cu. mm., 40 per cent lymphocytes on peripheral smear, 5 to 10 per cent macroglobulins on ultracentrifugation, and a bone marrow showing 30-60 per cent lymphocytes. Some would classify this as Waldenström's macroglobulinemia, others as chronic lymphatic leukemia with secondary macroglobulinemia. As always, each case must be diagnosed individually.

Different authors have cast doubt on the advisability of classifying Waldenström's macroglobulinemia as a separate disease entity because of the diversified histopathologic findings in these patients. Despite this, it appears to becoming recognized as a disease entity, and Quattrin et al believe it to be such. Probably it is included in a spectrum of diseases with multiple myeloma at one end, lymphosarcoma and chronic lymphatic leukemia at the other end and Waldenström's macroglobulinemia somewhere between.

Treatment

At present, a good practical mode of therapy has not been discovered for this disease. Results of therapy are difficult to evaluate; the average life span in one series was 38-40 months from the onset of symptoms but this may vary from a few months to many years. Case 1 of our series survived 22 years from the onset of symptoms. Steroids and nitrogen mustard have been tried in several of the patients described in the report, and in many others without impressive results; the same may be said for urethane, radiation, and splenectomy. The latter seemed to help a progressive, severe anemia in one patient but did not effect the macroglobulins. Three other methods bear more mention and will be described briefly.

Plasmapharesis has been found to be of value, both subjectively and objectively in two patients described by Schwab and Fahey. The method essentially involves venesection, centrifuging the blood, and reinfusing the red blood cells only. They have done this at periodic intervals. Skoog et al performed metabolic balance studies on one patient during plasmapharesis, and though there was a definite objective improvement with decrease of the paraproteins, pre-plasmapharesis levels soon returned after stopping the procedure. This method may be promising if it can be proven to help prevent the vascular complications (bleeding diathesis, anemia, retinal vascular changes) and still be economically feasible.

Penicillamine has been tried, as it ruptures the bonds of the polymers of the abnormally large gamma globulins. This was used with beneficial results in one case in the literature, but the duration of improvement was not given. Bloch et al used oral penicillamine in 2 patients and found a decrease in the total protein and gamma globulin, but there was no symptomatic effect. In case #6 described here the results were not impressive.
<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>Case 10</th>
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<tr>
<td>WBC</td>
<td>11,200</td>
<td>4,700</td>
<td>5,500</td>
<td>5,550</td>
<td>5,100</td>
<td>10,650</td>
<td>10,850</td>
<td>10,850</td>
<td>13,700</td>
<td>5,600</td>
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<tr>
<td>Hgb (gms. %)</td>
<td>6.6</td>
<td>9.8</td>
<td>10.8</td>
<td>12.4</td>
<td>6.4</td>
<td>13.6</td>
<td>15.1</td>
<td>13.8</td>
<td>14.8</td>
<td>10.8</td>
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<tr>
<td>Sed. Rate (mm/hr.)</td>
<td>1-14</td>
<td>32</td>
<td>40</td>
<td>22 (1948)</td>
<td>21</td>
<td>38</td>
<td>21</td>
<td>38</td>
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<td>36</td>
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<td>% Lymphocytes Peripheral Smear</td>
<td>30</td>
<td>29</td>
<td>29</td>
<td>36</td>
<td>56</td>
<td>37</td>
<td>32</td>
<td>55-75</td>
<td>29</td>
<td>23</td>
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<tr>
<td>Rouleaux</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Serum Proteins (gms. %)</td>
<td>11.8</td>
<td>10.1</td>
<td>8.7</td>
<td>7.7</td>
<td>10.2</td>
<td>7.5</td>
<td>6.8</td>
<td>7.8</td>
<td>5.9</td>
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<tr>
<td>Alb. (gms. %)</td>
<td>2.14</td>
<td>3.95</td>
<td>3.45</td>
<td>3.23</td>
<td>2.35</td>
<td>2.85</td>
<td>2.18</td>
<td>3.51</td>
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<td>Alpha 1 (gms. %)</td>
<td>.47</td>
<td>.24</td>
<td>.52</td>
<td>.28</td>
<td>.51</td>
<td>.30</td>
<td>.41</td>
<td>.67</td>
<td>.32</td>
<td>.45</td>
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<td>Alpha 2 (gms. %)</td>
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<td>.67</td>
<td>.66</td>
<td>.86</td>
<td>.71</td>
<td>.53</td>
<td>.95</td>
<td>.65</td>
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<td>.69</td>
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<tr>
<td>Beta gms. %</td>
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<td>.82</td>
<td>.73</td>
<td>.68</td>
<td>1.53</td>
<td>.70</td>
<td>1.22</td>
<td>.70</td>
<td>.64</td>
<td>.73</td>
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<tr>
<td>Gamma (gms. %)</td>
<td>7.43</td>
<td>4.41</td>
<td>3.34</td>
<td>2.95</td>
<td>3.10</td>
<td>3.09</td>
<td>2.04</td>
<td>2.67</td>
<td>1.70</td>
<td>1.13</td>
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<td>Bone Marrow Abnormalities</td>
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<tr>
<td>Macroglobulins</td>
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<td></td>
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<tr>
<td>Sia Test</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Cryoglobulins</td>
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<td>Neg.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Pro time (cont.=15 sec.)</td>
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<td>19 sec.</td>
<td>17 sec.</td>
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<tr>
<td>Rumple-Leede's</td>
<td>Neg. – 3+</td>
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<td>Neg.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Bleeding Time</td>
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<td>4.5 min.</td>
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<tr>
<td>Clotting Time (Lee-White)</td>
<td>15 min.</td>
<td>6.5-9 min.</td>
<td>12.5 min.</td>
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<tr>
<td>Prothrombin Consumption</td>
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<td>22 sec.</td>
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<td>Ceph. Chol.</td>
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<td>Thymol Turb.</td>
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<tr>
<td>Thymol Floc.</td>
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</tr>
<tr>
<td>Miscellaneous</td>
<td>RBC fall out 100% to 68% in 5 days</td>
<td>Bone marrow biopsy; 50% adult lymphocytes</td>
<td>Fibrinogen 418 mg %</td>
<td>RBC fall out 12.8 gms. to 7.9 gms. (62%)</td>
<td>Bone marrow biopsy: lymphocytic infiltration</td>
<td>Spinal fluid Pandy ; Spinal fluid protein; 176 mgm. %</td>
<td>VDRL + Kahn + Quant. Kolmer anti-complementary spinal fluid Kahn neg.</td>
<td>Chest x-ray: widened mediastinum</td>
<td>3-4+ albuminuria liver &amp; lymph node biopsy: Amyloidosis</td>
<td>Cerv. node biopsy: Metast. carcinoma Liver biopsy; fatty metamorphosis</td>
</tr>
</tbody>
</table>
Chlorambucil has been mentioned in other reports only incidentally as not being of much benefit, but both subjective and objective improvement was observed in a series of 4 patients with Waldenström's macroglobulinemia by Bayrd.21

SUMMARY

Ten cases of macroglobulinemia discovered from 1956 to 1961 at Henry Ford Hospital are described; seven are probably examples of macroglobulinemia of Waldenström, and three are secondary to other diseases.

The characteristics of macroglobulins are discussed, as well as the clinical and laboratory manifestations of macroglobulinemia.

Treatment of this rare condition has not been of much benefit in the past, but two newer methods, plasmapharesis and chlorambucil, deserve more investigation.

ACKNOWLEDGEMENT

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REFERENCES
