MACROGLOBULINAEMIA OF WALDENSTRÖM

BY

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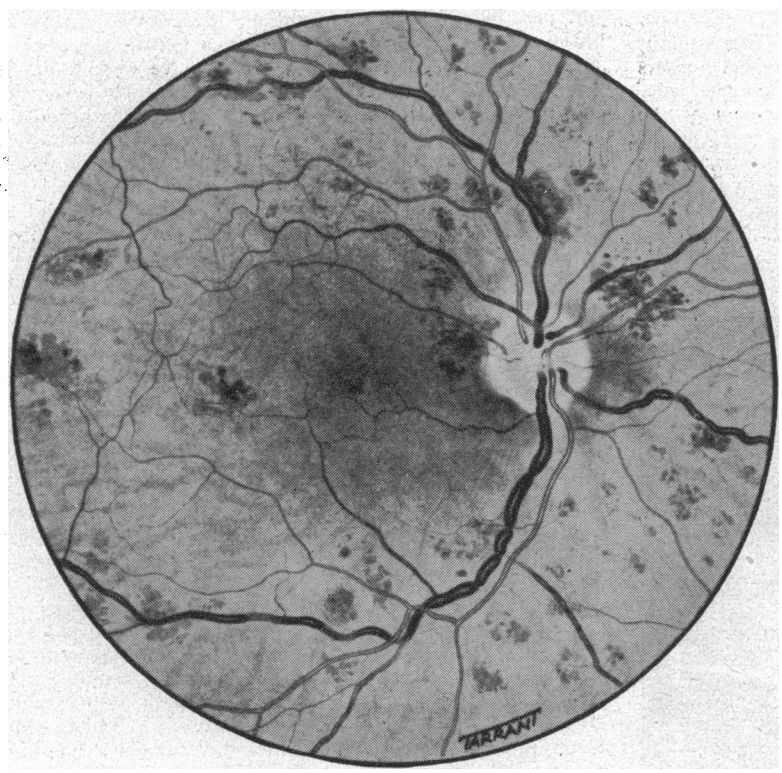
In 1944 Waldenström described two cases of macroglobulinaemia. A similar case is here presented, with a brief review of the literature.

Case Report

A man aged 60 was referred to one of us in November, 1954, by Dr. D. R. Daniel, with a history of deteriorating vision for the previous two years. Apart from this he had little in the way of symptoms, but occasional mild epistaxes followed admission.

The only physical sign of note was a retinitis, but this presented striking and unusual features, the retinal veins being visibly distended and somewhat tortuous, and the fundi showing many scattered haemorrhages (see Fig.). Vision was reduced to 6/60 in both eyes. Slightly enlarged glands were present in both axillae. Anaemia was not apparent. There was no purpura, no enlargement of the liver or spleen, and no fever. Slight albuminuria appeared on occasion.



Case of macroglobulinaemia: retinal drawing.

Investigation revealed a hypochromic microcytic anaemia with a haemoglobin of 31%. White counts varied between 4,000 and 6,400 per c.mm., with lymphocytes ranging from 22 to 54%, and an occasional lymphoblast. Rouleaux formation was marked. The E.S.R. was greatly elevated, ranging from 130 to 170 mm. in the first hour (Westergren). Marrow smears showed a lymphocyte preponderance, with lymphoblasts more in evidence than in the peripheral blood (Dr. A. H. T. Robb-Smith). Liver biopsy (followed by bleeding) revealed minimal lymphocytic periportal infiltration (Dr. J. F. Heggie).

The serum was remarkably viscous, but did not gel in the cold. Total plasma proteins were 9.9 g.% (albumin 2.5 g.; globulin 7.4 g.). Paper electrophoresis showed an abnormal globulin with a mobility lying between the β and γ fractions, proportions of the various constituents being albumin 2.3 g.%, $\alpha 1$ globulin 0.46 g.%, $\alpha 2$ globulin 1.01 g.%, abnormal globulin 3.26 g.%, γ globulin 1.47 g.% ; the figure for the abnormal globulin includes β globulin, as there was no clear line of demarcation. A paper electrophoresis after treatment showed only slight changes in pattern, but a clear demarcation appeared between the abnormal and the β globulins (abnormal globulin 2.82 g.%, β globulin 0.61 g.%). The main abnormal features of this protein pattern are the decreased amount of albumin and the very large amount of abnormal globulin present. The formol-gel test was strongly positive. Ultracentrifugation produced a sedimentation constant for the abnormal globulin of 18, indicating a molecular weight of over one million (Dr. A. S. McFarlane).

Bleeding, clotting, and prothrombin times, platelet count, and serum fibrinogen were within normal limits. *X*-ray pictures of the lumbar spine, pelvis, and skull showed no abnormality. Blood W.R. and Kahn were negative.

He was treated with blood transfusions initially, iron, cortisone, and tri-(2-chloroethyl)-amine. A slow but steady improvement took place. Vision recovered to 6/9 in both eyes, and retinal haemorrhages largely disappeared. The haemoglobin rose to 100%. A significant part of the recovery seemed to follow use of the nitrogen mustard. The man was well and at work 18 months after first being seen.

Discussion

Some important features of 16 similar cases studied, and of our own case, are shown in the Table.

Clinical Features.—The condition has been reported more often in men than in women, and usually in the older age groups. It seems to be only slowly progressive, the illnesses having lasted up to 14 years. Anaemia has been usual. A slight-to-moderate lymphadenopathy and enlargement of the liver and spleen have been reported. A haemorrhagic tendency has been usual, epistaxes and bleeding from the gums being the common manifestations. A haemorrhagic retinitis has been reported in five cases besides our own. Bone pains are not a feature, and *x*-ray films have been normal or have shown diffuse osteoporosis, contrasting with the findings in classical multiple myelomatosis.

Clinical Pathology.—The blood has been strikingly viscous, and the E.S.R. unusually high (in the region of 150 mm. in the first hour—Westergren). An absolute or relative lymphocytosis in the peripheral blood has been usual. Various disturbances of the bleeding mechanism have been reported, but as often as not the cause of bleeding has not been explained. Hyperglobulinaemia due to the presence of a macroglobulin has been present. Bence Jones proteinuria has been observed in five cases.

Macroglobulinaemia.—The distinguishing characteristic of a macroglobulin is, as the name suggests, the large size of the molecule. The molecular weights are all in the region of 1,000,000, while that of normal serum albumin is 65,000 and of the α, β, and γ globulins 150,000 to 300,000. Other abnormal proteins may be found in the serum or elsewhere,

Macroglobulinaemia: Case Features

Author	Sex and Age	Duration (Years)	Lymphocytosis		Macroglobulin	
			Blood	Bone Marrow	Mobility	Sedimentation Constant
Waldenström (1944)	M 62	8	Yes	Yes		19·2
	M 65	2	,,	,,	Between β and γ	19·7, 25, 29·3
Bichel *et al.* (1950)	M 76	14	,,	,,	β	20
Tischendorf and Hartmann (1950)	M 66	2	,,	,,	β	Mol. wt. 1,800,000
McFarlane *et al.* (1952)	M 52	14	,,	,,	Between β and γ	18, 28
Schaub (1952) ..	F 32	3	,,	,,	Between β and γ	19–20
Pernis *et al.* (1954)	M 68	2	,,		γ	17·5, 24
	M 64	1½	,,	Yes	β	20
	M 72	2	,,	,,	γ	26
Wilde and Hitzelberger (1954)	M 72	8	,,	,,		16·6
	F 51	6	No	,,		19
	F 71	3	Yes	,,		16
Mandema *et al.* (1955)	M 69	1		,,	γ	15·8
	M 71	8 12		,,	γ	19·2, 30·9
Mackay *et al.* (1956)	M 67	14	Yes	,,	γ	15, 20
Jim and Steinkamp (1956)	F 79	4	,,	,,	γ	17, 24
Present case ..	M 60	2	,,	,,	Between β and γ	18

such as the Bence Jones proteins, which have molecular weights of the order of 25,000 to 75,000. Cryoglobulins—that is, globulins which coagulate or precipitate in the cold—vary greatly in molecular weight and in other ways. The macroglobulins found in the cases mentioned appear to be a group of proteins rather than a single entity. The Table shows that the sedimentation constants are not identical, and that the electrophoretic mobilities have lain in the β or γ globulin ranges or sometimes in between. Six have been described as cryoglobulins; such cryoglobulin could not be detected in the blood of our patient. Some macroglobulins give a positive "water" test—that is, copious precipitates are formed when the serum is dropped into large volumes of distilled water—but this property is not invariably present, and was absent in our case. A feature of this group of cases is the large amount of macroglobulins found in the blood. In our case as much as 2 to 3 g. per 100 ml. was present. Small quantities of macroglobulin may be present in normal serum (Pedersen, 1945), and therefore pathological macroglobulinaemia may be due to a derangement of normal mechanisms.

Pathogenesis.—The presence of an excess of globulin and of abnormal globulins is characteristic of various disorders involving the reticulo-endothelial system. The similarity of the 17 cases here discussed suggests that a clinical entity is being described, but its nature remains uncertain. The lymphocytosis in the peripheral blood is paralleled by lymphoid hyperplasia in bone-marrow smears, but an excess of plasma cells has also been found in the latter on occasion. Lymphoid or plasma-cell hyperplasia, or both, have been observed in sections from lymph nodes, spleen, bone marrow, and other organs obtained on biopsy or at necropsy. The condition therefore has affinities with both lymphatic leukaemia and multiple myelomatosis, but final elucidation of its nature must await further evidence. In any event, it is unlikely that macroglobulinaemia will be found confined to any one disease, any more than Bence Jones proteinuria is exclusively associated with multiple myelomatosis. The second case reported by Schaub (1952) may be a case in point.

Treatment.—Cortisone, amidines, urethane, and nitrogen mustard have been used by others without seeming effect on the underlying process, though the last-mentioned drug appeared to be of value in our case.

Summary

A case of macroglobulinaemia is described. The rather characteristic features of this and similar cases from the literature are reviewed.

We wish to thank Dr. J. F. Heggie for laboratory facilities; Dr. A. H. T. Robb-Smith for a report on the bone-marrow smears and for advice on pathological aspects of these cases; Dr. A. S. McFarlane for the ultracentrifuge study; Mr. J. H. Dobree for ophthalmological reports; Mr. T. R. Tarrant, of the Institute of Ophthalmology, for the retinal drawing; and Dr. R. G. Macfarlane and Professor N. H. Martin for assistance.

REFERENCES

Bichel, J., Bing, J., and Harbo, N. (1950). *Acta med. scand.*, **138**, 1.
Jim, R. T. S., and Steinkamp, R. C. (1956). *J. Lab. clin. Med.*, **47**, 540.
McFarlane, A. S., Dovey, A. Slack, H. G. B., and Papastamatis, S. C. (1952). *J. Path. Bact.*, **64**, 335.
Mackay, I. R., Eriksen, N., Motulsky, A. G., and Volwiler, W. (1956). *Amer. J. Med.*, **20**, 564.
Mandema, E., Schaaf, P. C. van der, and Huisman, T. H. J. (1955). *J. Lab. clin. Med.*, **45**, 261.
Pedersen, K. O. (1945). *Ultracentrifugal Studies on Serum and Serum Fractions*. Almqvist and Wiksells, Uppsala.
Pernis, B., Wuhrmann, F., and Wunderly, C. (1954). *Acta haemat. (Basel)*, **11**, 309.
Schaub, F. (1952). *Schweiz. med. Wschr.*, **82**, 890.
Tischendorf, W., and Hartmann, F. (1950). *Acta haemat. (Basel)*, **4**, 374.
Waldenström, J. (1944). *Acta med. scand.*, **117**, 216.
Wilde, H., and Hitzelberger, A. L. (1954). *Blood*, **9**, 875.

Medical Memoranda

Anterior Tibial Syndrome after Acute Arterial Occlusion, Treated by Decompression

In his report of instances of an anterior tibial syndrome following arterial embolism, Watson (1955) suggests that surgical decompression of the ischaemic muscles should be attempted. The present communication reports the successful use of this treatment in a case of acute arterial occlusion which was probably due to arterial thrombosis rather than embolism (Jepson, 1955).

CASE REPORT

A man aged 68 was admitted as an emergency case at 11.15 p.m. on July 20, 1955. Five hours previously he had experienced a sudden severe pain in his right leg, which rapidly became cold, numb, and paralysed. For several months before admission he had suffered from angina of effort and intermittent claudication.

On examination his general condition was good and his temperature normal. A loud blowing systolic murmur was heard all over the praecordium, maximal at the aortic area, but there was no other evidence of cardiac disease. The left lower limb appeared healthy and the usual pulses could be felt in it. The right was pale, and felt cold from a level just above the knee. No pulsation could be felt distal to the femoral artery. Voluntary movements of the ankle were absent and there was complete sensory loss distal to the knee.

Medical treatment for arterial embolism was instituted with tolazoline, papaverine, heparin, and phenindione. Within 24 hours the whole limb, except the outer side of the foot, felt as warm as the left. No pulses had returned, but motor and sensory functions had greatly improved.

On the next morning the patient complained of pain down the front of the right leg. The pain increased during the day, and could be controlled only by morphine. By the evening the antero-lateral part of the leg was swollen and the skin over it reddened. Dilated veins could be seen here, and the maximum calf circumference was ½ in. (1.3 cm.) more than on the left side. Sensory loss was demonstrable in this area and in that corresponding with the cutaneous distribution of the anterior tibial nerve. In view of the patient's good general state and severe pain, the anterior tibial compartment was explored.

Under general anaesthesia, a linear incision some 8 in. (20 cm.) long was made over the reddened skin area. When the deep fascia was incised the anterior tibial muscles bulged outwards and were seen to have a well-marked patchy yellowish discoloration. This faded during the next five minutes, and the muscles by that time appeared normal.