Waldenström's macroglobulinaemia treated with cyclophosphamide and chlorambucil

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SYNOPSIS A case of primary macroglobulinaemia of Waldenström is described in which prolonged treatment with the alkylating agents of cyclophosphamide and chlorambucil led to a sustained reduction in the concentration of circulating macroglobulin together with a concurrent improvement in the patient's symptoms.

The term 'macroglobulinaemia' was first introduced by Waldenström (1944) to describe a syndrome characterized by the presence of large quantities of circulating globulins of high molecular weight. Small amounts of macroglobulin may be found in normal plasma, but for diagnosis of the pathological state, macroglobulins, with a sedimentation value of $S_{20\text{ w}}16$ or more, should constitute at least 10% of the total plasma proteins (Martin, 1960). Macroglobulins may sometimes occur as an associated feature of diseases such as chronic lymphatic leukaemia and lymphosarcoma. But in some patients no such disease can be found, and these constitute primary or essential macroglobulinaemia of Waldenström. Irrespective of its exact aetiological basis, the well-defined abnormality of the serum proteins and the generally recognizable clinical picture make it useful to accept macroglobulinaemia as a disease entity; for many of the clinical features, as for example, the abnormal bleeding tendency, the development of retinopathy, heart failure, and the neurological manifestations, would appear to be the consequence of the high concentration of circulating globulins (Kappeler, Krebs, and Riva, 1958; MacKay 1959; Ritzmann, Thurm, Truax, and Levin, 1960b).

Response to treatment of Waldenström's macroglobulinaemia is often disappointing. Steroids and A.C.T.H. produce transient benefit (Glenchur, Zinneman, and Briggs, 1958; MacKay, 1959; Ritzmann *et al.*, 1960b). Whereas experience with cytotoxic agents has been conflicting, early reports suggested that alkylating agents had little effect (Glenchur *et al.*, 1958; Kappeler *et al.*, 1958; Wintrobe, 1961), although recently, a response to chlorambucil has been recorded (Bayrd, 1961; Clatanoff and Meyer, 1963). This paper describes a

further case of Waldenström's macroglobulinaemia successfully treated with long-term cytotoxic therapy.

CLINICAL DETAILS

A 50-year-old married woman was admitted to hospital complaining of weakness, lassitude, and swollen glands. During the preceding six months she had noticed swelling of the glands in her neck and had become progressively more weak and tired. In the last three months she had noticed increasing shortness of breath and palpitations on exertion. Her appetite had become impaired and she had lost one stone in weight. In addition, she bruised more easily and had had four small haemoptyses in the last year.

On examination, she was anaemic and there were scattered bruises on the arms and legs. The cervical and supraclavicular lymph glands were slightly enlarged, but there was no lymphadenopathy elsewhere. The liver was palpable 2 cm. below the costal margin but the spleen could not be felt. The ocular fundi showed distension and tortuosity of the retinal veins, but no haemorrhages could be seen. Examination was otherwise normal.

INVESTIGATION The haemoglobin concentration was 50% (7.4 g./100 ml.), the red cells numbered 3.0 millions/c.mm. and the indices were normal, but marked rouleaux formation was present. The white cell count was 3,700/c.mm. (polymorphonuclear leucocytes 36%, lymphocytes 56%, and monocytes 7%); no immature cells were present. The platelet count was 200,000/c.mm. The erythrocyte sedimentation rate was 160 mm. in the first hour (Westergren). The direct antiglobulin (Coombs) test was negative, the prothrombin time was 50% of normal (15 sec.), and the bleeding and clotting times were within normal limits. The plasma protein concentration was 7.5 g./100 ml., albumin 3.1 and globulin 4.4 g./100 ml. Paper electrophoresis showed an intense, well-defined band in the gamma globulin region. Quantitation of this component showed it to comprise 30% of the total plasma protein and to amount to a concentration of

FIG. 1. Ultracentrifugation sedimentation patterns of sera. Ultracentrifugation was performed at 52,640 rev./min. for 30 min. at 26°; phase plate angle 50°. Migration is from left to right. In each case ▲ indicates the position of the macroglobulin peak. (a) before treatment; (b) during treatment with cyclophosphamide (150 mg./day); (c) at the end of maintenance treatment with cyclophosphamide; (d) during treatment with chlorambucil.

2.0 g./100 ml. The Sia test was positive. The urine did not contain any Bence Jones protein, but a small quantity of albumin was demonstrated on electrophoresis. Radiographs of the chest showed enlargement of the right hilum and tomography demonstrated this to be glandular in origin; the sputum did not contain any malignant cells. Radiographs of the skeleton were normal. Sternal marrow aspirate showed that 65% of the white cell series consisted of small lymphocytes, but no excess plasma cells were seen. Biopsy of a cervical gland showed some infiltration with lymphocytes and plasma cells. Ultra-centrifugation of the serum demonstrated the presence of macroglobulin of $S_{20} \text{ w} 17.1$ Svedberg units in a concentration of 1.8 g./100 ml. and comprising 26.8% of the total serum proteins (Fig. 1a).

TREATMENT AND PROGRESS The patient was transfused with 8 pints of blood. Treatment was started with penicillamine ($\beta\beta$ -dimethyl cysteine) 0.9 g. increasing to 1.8 g./day (as four divided doses) for three weeks. This had no effect on the clinical state. There was no appreciable change in the serum proteins (Fig. 2), nor in the electrophoretic pattern. The Sia test remained positive and ultracentrifugation showed no reduction in the quantity of circulating macroglobulin.

Cyclophosphamide was then given in a dosage of 50 mg. three times a day. A further transfusion was required during the first few weeks of treatment, but subsequently the haemoglobin was maintained at a value of 60% or more, and no further transfusions have been required. The patient's general conditions improved and bruising became less marked. Examination of the ocular fundi showed the calibre and the shape of the veins to have returned to normal. The superficial lymph glands

regressed in size and further chest radiographs showed the hilar mass to have disappeared. During this time, the serum globulin fell to 2.7 g./100 ml. and the Sia test became negative. Electrophoresis showed a progressive reduction in the quantity of the abnormal protein and ultracentrifugation showed the concentration of macroglobulin ($S_{20} \text{ w} 19.9$) to have fallen to 0.22 g./100 ml. (Fig. 1b).

Subsequently, a fall in the peripheral white cell count necessitated reduction in the dosage of cyclophosphamide to 100 mg./day. No change occurred in the total concentration of serum globulin, but ultracentrifugation showed a rise in the concentration of macroglobulin to 0.82 g./100 ml., a value which comprised 11.9% of the total serum protein (Fig. 1c).

After six months' treatment, the patient noticed that her hair was beginning to fall out; cyclophosphamide was therefore stopped and chlorambucil substituted, in dosage of 6 to 10 mg./day, later being reduced to maintenance level of 2 to 4 mg./day. During the last 18 months' of treatment with chlorambucil the serum globulin has remained between 2.2 and 1.5 g./100 ml. (Fig. 2). The Sia test has remained negative, and ultracentrifugation shows the concentration of circulating macroglobulin of $S_{20} \text{ w} 17.2$ to be reduced to a value of 0.39 g./100 ml. (6.2% of the total serum protein), an amount equal to one-sixth of the initial value (Fig. 1d). The patient's initial clinical improvement has been maintained; the fundi have remained normal, there has been no recurrence of lymphadenopathy and no abnormal bleeding. The haemoglobin has remained above 60% and no further transfusions have been required. During the whole course of treatment the patient's general health has been satisfactory and there has been complete relief

FIG. 2. Response of patient to penicillamine, cyclophosphamide and chlorambucil. ●—● serum albumin (g./100 ml.); ▲—▲ serum globulin (g./100 ml.); ○—○ serum macroglobulin (g./100 ml.). SIA test + strongly positive, (+) weakly positive, — negative. ■ penicillamine; ▨ cyclophosphamide; ▤ chlorambucil.

of symptoms. In addition to performing her normal household duties, she has continued to go out to work.

DISCUSSION

The high concentration of circulating macroglobulin is thought to be responsible for some of the clinical manifestations of the syndrome (MacKay, Eriksen, Motulsky, and Volwiler, 1956; Kappeler *et al.*, 1958; MacKay, 1959), for the disturbance of blood clotting and interference with normal capillary and platelet function may predispose to bleeding, whilst the

increased viscosity of the plasma may contribute to the development of heart failure and be responsible for the occurrence of retinal changes (Spalter, 1959). Cellular infiltration and deposition of abnormal protein in the perivascular spaces may account for the neurological disturbances that occur (Logothetis, Silverstein, and Coe, 1960). Treatment should therefore aim at reducing the concentration of circulating macroglobulins.

Removal of the abnormal proteins by plasmapheresis or exchange transfusion may be a useful emergency procedure (Schwab and Fahey, 1960;

Conway and Walker, 1962). But the practical value of such treatment is limited, for the improvement is only temporary and the concentration of circulating macroglobulins returns to its former level within two to three weeks (Skoog, Adams, and Coburn, 1962).

Depolymerization of the macroglobulins with a consequent reduction in the viscosity of the plasma can be achieved *in vitro* by the addition of thiols of low molecular weight such as mercaptoethanol or $\beta\beta$ -dimethyl cysteine (Deutsch and Morton, 1958; Glenchur *et al.*, 1958), whilst on occasion, reduction of circulating macroglobulin has also been achieved in patients given penicillamine ($\beta\beta$ -dimethyl cysteine) by mouth (Bloch, Prasad, Ananstasi, and Briggs, 1960; Ritzmann, Coleman, and Levin, 1960a). However, Conway and Walker (1962) were unable to detect any such effect, nor was any seen in the present case. The Sia test remained positive, the level of the serum proteins remained unaltered, and ultracentrifugation showed no appreciable change in the quantity of circulating macroglobulins.

Numerous therapeutic agents have been tried in an attempt to reduce the rate of synthesis of the abnormal macroglobulins. Steroids and A.C.T.H. usually have a transient if any effect (Glenchur *et al.*, 1958; MacKay, 1959; Ritzmann *et al.*, 1960b; Kok, Whitmore, and Ainsworth, 1963), although a more prolonged improvement has been recorded (Pitney, O'Sullivan, and Owen, 1958; Fairley, 1963). Likewise, x -irradiation and P_{32} therapy are of limited value (MacKay *et al.*, 1956). The results of treatment with cytotoxic agents have been conflicting. Early studies suggested that alkylating agents had little effect (Kappeler *et al.*, 1958; Glenchur *et al.*, 1958; Ritzmann, *et al.* 1960b; Wintrobe, 1961), but a reduction of macroglobulin following prolonged treatment with chlorambucil has been reported by Bayrd (1961) and more recently by Clatanoff and Meyer (1963). A similar response was found in the present patient with cyclophosphamide and later with chlorambucil given over a total period of 20 months. The concentration of serum globulin fell to normal and the Sia test became negative. Electrophoretic studies showed a marked fall in the concentration of the abnormal protein and this was confirmed by ultracentrifugation.

Concurrent with the sustained reduction of circulating macroglobulin there was a satisfactory symptomatic improvement in the patient's condition. The lymph glands regressed, bruising decreased in severity, no further haemoptyses occurred, and the appearance of the retinal veins returned to normal. Furthermore, the haemoglobin concentration has been maintained above 60%. When anaemia develops in Waldenström's macroglobulinaemia, repeated

transfusions are usually necessary, and our patient required 10 pints of blood during the two months before treatment was started, whereas during the last 20 months no transfusions have been necessary. A similar reduction of transfusion requirements following treatment with chlorambucil was also observed by Clatanoff and Meyer (1963).

Evidence suggests that macroglobulins arise from the abnormal synthetic activity of lymphocytoid cells (Zucker-Franklin, Franklin, and Cooper, 1962), and it is probable that macroglobulinaemia should be regarded as a syndrome rather than as a distinct disease entity (Martin, 1960). Macroglobulinaemia may occur as an incidental feature in established cases of chronic lymphatic leukaemia, lymphosarcoma, or Hodgkin's disease, and treatment of the primary disorder with alkylating agents may cause the concentration of macroglobulins to fall (MacKay *et al.* 1956; Fairley, 1963). On the other hand, in primary macroglobulinaemia of Waldenström the accumulation of macroglobulins in the blood is the dominant feature of the disease, although reticulo-endothelial tissue may show a characteristic proliferation of lymphocytoid and plasma-like cells (Zollinger, 1958; Kok *et al.*, 1963). Waldenström's macroglobulinaemia may therefore be classified amongst the lymphoproliferative states (Hayhoe, 1966; Wintrobe, 1961), and like them, long-term treatment with alkylating agents, such as cyclophosphamide and chlorambucil, may result in a satisfactory remission of the disease.

We wish to thank Dr. K. O. Black, under whose care this patient was admitted, for permission to publish details of the case, and Professor N. H. Martin for his help in establishing the diagnosis and for reviewing the histological sections. We should further like to thank Mr. P. Cull and Mr. D. Tredinnick of the Department of Medical Illustration, St. Bartholomew's Hospital, for preparing the charts and photographs.

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