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Medical Memoranda**Macroglobulinaemia Treated with Prednisone, Azathioprine, and Folic Acid***British Medical Journal*, 1970, **3**, 750

Primary macroglobulinaemia is a condition within the spectrum of the malignant immunoproliferative disorders and is generally treated with cytotoxic drugs in an attempt to suppress growth of the abnormal cells. This report describes the case of a patient in whom severe anaemia responded to treatment with prednisone, folic acid, and azathioprine when other cytotoxic drugs had failed and the patient appeared to be in a terminal stage of the illness.

Case Report

A woman aged 39 came to hospital in 1960 with gingivitis, palatal ulcers, and fever and was found to have a neutropenia. Some enlarged lymph nodes were present, but the spleen was not palpable. Bone marrow examination suggested chronic lymphatic leukaemia, and plasma protein electrophoresis showed a band within the gammaglobulin (total gammaglobulin 2.4 g./100 ml.). The patient responded to betamethasone after chlorambucil treatment had been unsuccessful. She remained well for eight years, with normal peripheral blood counts, while taking a small maintenance dose, and then relapsed in 1969 with similar clinical and haematological features though no lymph node enlargement was now found.

The bone marrow again showed a pronounced excess of lymphoid cells, some of which had numerous microsomes and a poorly formed endoplasmic reticulum. Erythropoiesis was normoblastic and the serum folate concentration was normal. Plasma protein electrophoresis showed an M band, subsequently found to be a 19S (IgM) globulin, and immunofluorescent studies with an antiglobulin prepared from the patient's own abnormal serum protein suggested that it was derived from large marrow cells, thought to be reticulum or blast cells. The serum immunoglobulin concentrations were abnormal (IgG 760 mg./100 ml., IgA 40 mg./100 ml., and IgM 1,500 mg./100 ml.). Other findings were: Hb 12.4 g./100 ml.; W.B.C. 1,600/mm³ (neutrophils 1%, lymphocytes 90%, monocytes 9%); reticulocytes <1%; platelets 356,000/mm³; urinary urobilinogen not detected at 1 in 20 dilution; Bence Jones protein absent; skeletal x-ray picture normal; Coombs test negative; cryoglobulin absent; total gammaglobulin 1.9 g./100 ml.

In spite of treatment first with chlorambucil in addition to a small dose of betamethasone and then with a combination of cyclophosphamide and prednisone, the haemoglobin fell steadily over 10 weeks to 1.6 g./100 ml. and the total white cell count to 350/mm³, without any change in the marrow appearances. Throughout this period there was no reticulocytosis or increase of urobilinogen in the urine. Blood transfusion was accompanied on three occasions by clinical evidence of a severe reaction, including jaundice, and was abandoned. The patient was then treated with azathioprine 150 mg. and prednisone 40 mg. daily. Though the marrow was normoblastic, folic acid was also given in a dosage of 5 mg. twice daily in case there might be an unexpected haemopoietic response. A pronounced reticulocytosis resulted almost immediately and was followed by clinical and further haematological improvement. The marrow seven weeks later showed a decrease in abnormal cells and an increase in

granulocytes and normoblasts. Normal peripheral blood counts were obtained after four months, when the chemotherapy was reduced to azathioprine 100 mg. and prednisone 20 mg. daily together with the folic acid and have so far persisted for more than a year. The serum immunoglobulin concentrations have not been significantly altered by the therapy.

Discussion

Macroglobulinaemia, like myeloma, is predominantly a disease of the older age groups. In this patient, who was only 39 at the time of her first hospital attendance, the diagnosis has been based on the demonstration of an abnormal quantity of 19S (IgM) globulin in her plasma together with the results of light microscope, electron microscope, and immunofluorescent studies of the bone marrow. These are consistent with macroglobulinaemia (Maldonado *et al.*, 1966; Marmont and Damasio, 1968). The severity of the anaemia, together with the low concentration of circulating macroglobulin and the unchanged level of total gammaglobulin eight years after the appearance of symptoms, is not the usual pattern in primary macroglobulinaemia (Waldenström, 1965) and for this reason the patient is thought to have the condition in an atypical form.

The main feature that we wish to stress is the response to a combination of azathioprine, prednisone, and folic acid when other methods of therapy had failed. The pronounced reticulocytosis which followed soon after the introduction of this regimen might suggest that the abnormal process was a depression of haemopoiesis, perhaps immunological, which has been corrected by the treatment. The improvement in the marrow appearances, however, indicates clearly that therapy reduced the number of abnormal cells. Our reasons for giving folic acid were not very good, particularly as the serum folate level had been normal. Nevertheless, it is still possible that the folic acid helped the regeneration of erythropoietic tissue.

The way in which these drugs acted in this patient is uncertain. Perhaps this combination of drugs has a mode of therapeutic action differing from that of other cytotoxic agents, and it should be tried, possibly without folic acid, in other such patients who are deteriorating.

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