

# Monoclonal gammopathy (Waldenström's macroglobulinaemia) producing specific red cell antibody

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**SYNOPSIS** Two cases of Waldenström's macroglobulinaemia have been seen at University College Hospital, Ibadan in the last four years. Case 1 was a 30-year-old soldier who presented with splenomegaly and anaemia, was treated with chlorambucil, and had a complete remission sustained for over two years. Case 2 was a 58-year-old retired civil servant who presented with very severe anaemia and also splenomegaly, and died within three weeks of admission. Both patients had most of the typical features of Waldenström's disease, including retinal changes and serum IgM levels of 4200 and 5500 mg/dl respectively. In both cases an atypical cold antibody was detected in the course of blood cross-matching procedures. In case 1, the antibody agglutinated all adult and cord red cells tested, including the patient's own cells, to a titre of 8000 and above at 4°C. Surprisingly enough, when the patient went into remission and the serum IgM level had fallen to 400 mg/dl, this antibody was no longer detectable and has not reappeared two years later. In case 2, the antibody agglutinated all adult red cells tested to a titre of 2000 at 20°C but not the patient's own red cells. Since cord cells were agglutinated only to a titre of 4 to 20°C it was concluded that the patient had an alloantibody with I-specificity. Therefore in both these patients the monoclonal immunoglobulin produced by the neoplastic lymphoid cell clone had specific activity against red cell antigens.

Since Waldenström's original description of three cases of macroglobulinaemia in 1944, various facets of these groups of monoclonal gammopathies have been described and the literature has been extensively reviewed (Imhof, Baars, and Verloop, 1959; Waldenström, 1961; Cohen *et al*, 1964; McCallister *et al*, 1967; Waldenström, 1970). The scarcity of reports of primary Waldenström's macroglobulinaemia in Africa would tend to suggest that this condition does not occur. McFarlane and Nwokolo (1966) described a Nigerian woman with Waldenström-type macroglobulinaemia associated with rheumatoid arthritis. This report presents two cases of primary Waldenström's macroglobulinaemia seen in the University College Hospital, Ibadan over the last 10 years.

## Case Reports

### CASE 1 (table III)

An 18-year-old soldier was seen in the medical out-  
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patient department of the University College Hospital (UCH), Ibadan on 28 November 1969. His illness had started three months earlier with progressive weakness, tiredness, and backache. He had been found to be anaemic and had been treated initially with bephenium hydroxy naphthoate (Alcopar) and iron in another hospital. Since he showed no response to medication, he was transfused with 4 units of packed cells over five days. He was then referred to UCH, Ibadan for further evaluation and treatment.

On admission, abnormal physical signs were pallor, mild icterus, a soft, slightly tender liver palpable 6 cm below the right costal margin, and a non-tender spleen palpable 2 cm below the left costal margin. There was no significant lymphadenopathy.

He developed photophobia, and funduscopy showed distention of retinal veins and bilateral fundal haemorrhages.

Investigations performed included: packed cell volume (PCV) 21%, total white cell count 3900/mm<sup>3</sup>; platelet count 305000/mm<sup>3</sup>; reticulocyte count

14.0% (table I). Haemoglobin electrophoresis revealed haemoglobin A only. The blood group was A, Rh positive, glucose-6-phosphate dehydrogenase activity was normal. The total serum bilirubin was 35.0 mg/dl (conjugated 4.5 mg/dl), alkaline phosphatase 8 King-Armstrong units/dl, thymol turbidity 12 units, thymol flocculation ++, SGOT 105 cabaud units per ml, SGPT 76 cabaud units, total cholesterol 155 mg/dl. Total serum protein was 8.5 g/dl (albumin 1.5 g and globulin 7.0 g/dl). Cellulose acetate membrane electrophoresis showed an intense and homogeneous band in the gamma globulin region. The Sia test was positive. A repeat LFT four weeks after admission was normal except for the abnormality noticed in the proteins.

The urine did not contain any Bence Jones protein and urine electrophoresis revealed a small amount of albumin. Skeletal survey showed no bone lesions and a chest x-ray was normal. Bone marrow biopsy showed normoblastic erythropoiesis with obvious lymphocytosis. Phytohaemagglutinin (PHA) induced lymphocyte transformation score was 9% (normal values 60-80%).

A diagnosis of Waldenström's macroglobulinaemia was made.

Haematological Indices	Time after Admission (weeks)				
	0	1	14	22	90
PCV	21	17	28	37	38
Total WBC/mm <sup>3</sup> × 10 <sup>3</sup>	3.9	5.65	5.55	5.9	5.4
Neutrophils	—	62	55	35	—
Lymphocytes	—	34	42	55	—
Monocytes	—	—	3	4	—
Basophils	—	1	—	8	—
Eosinophils	—	—	—	1	—
Retic count	—	—	0.5%	—	—
Platelet count × 10 <sup>3</sup>	—	—	200	132	160
Nucleated RBCs	—	3	—	—	—

Table I Case 1: Selected blood results following admission

NB From 6th to 90th week, the patient was on no specific treatment.

### Serological Studies

Quantitation of the 'M' band on the electrophoretic strip yielded a value of 61% of the total serum proteins; from this, the concentration of the paraprotein was calculated as 52 mg/ml. Quantitation of the immunoglobulins by the modification of the Mancini method of Fahey and McKelvey (Mancini *et al.*, 1965; Fahey and McKelvey, 1965) also gave IgM of 50 mg/ml. This concentration of IgM is in agreement with the value obtained for the 'M' band on electrophoresis, indicating that the paraprotein consists of IgM. This was confirmed by immunoelectrophoretic analysis, by gel filtration on Sephadex G 200, and by ultracentrifugation. The eluted 'M' band had only kappa light chains.

In the course of crossmatching, it was observed that the patient has a strong cold autoantibody, which agglutinated the red cells of 65 donors tested as well as the patient's own cells. From its serological properties, including the very high titre (see table II), it was concluded that this antibody was of the type encountered in 'cold agglutinin disease'.

	Case 1	Case 2	
Blood group of patient	A, Rh +	O, Rh +	
Number of donors incompatible	64/64	82/82	
Thermal latitude	Up to 37°C	Up to 37°C	
Titre 22°C: against adult RBC	800	2000	
	against cord RBC	800	4
	against patient's RBC	256	0
Serological specificity	Undetermined	Anti-I	

Table II Characterization of antibodies in two cases of Waldenström's macroglobulinaemia

This antibody did not have the usual specificity of anti-I because cord blood cells were also agglutinated to similar titres. Unfortunately, it was not tested with enzyme-treated red cells, and its exact specificity remains undetermined (Dacie, 1965). When the patient's serum was subjected to cellogel block electrophoresis, and the 'M' band was eluted, most of the antibody activity was found to be associated with it. Conversely, when the serum was absorbed with one volume of human group A red cells, by incubation at 4°C overnight, most of the 'M' band as revealed by electrophoresis was removed. We concluded that most or all of the paraprotein present in the patient's serum was an IgM immunoglobulin with cold autoantibody activity.

### Treatment and Progress

The patient was treated with four transfusions of 500 ml packed cells each, over a period of two weeks, prednisolone 80 mg daily in divided doses, and chlorambucil 6 mg daily. Chlorambucil was withdrawn after six weeks because of leucopenia. During

	Case 1	Case 2
Age	18	58
Sex	M	M
General condition	Fair	Poor
Enlarged liver	6 cm	—
Enlarged spleen	2 cm	2 cm
Retinal haemorrhage	++	++
Haematocrit %	21	12
Serum proteins (g/ml)	8.5	9.6
Serum IgM/ml	50	65
Proteinuria	+	+
Clinical course	Complete remission after treatment with 6 weeks of chlorambucil and 10 weeks of prednisolone. Alive 2 years after presentation	Death after 3 weeks

Table III Summary of findings in two cases of Waldenström's macroglobulinaemia

his eight weeks in the hospital, the patient complained of blurring of vision, and petechiae were noticed on the face, lips, buccal mucosa, and trunk. Plasmapheresis was performed: the PCV after the procedure was 28%. Hepatosplenomegaly gradually decreased and the patient was discharged after three months in hospital. At the time of discharge, the fundal haemorrhages had resolved and vision was normal. The PCV was 37%. The patient returned to his duties as a soldier. Two years after discharge, his PCV was 38% and the macroglobulin level was 4.5 mg per ml.

#### CASE 2 (table III)

A 58-year-old farmer was admitted on 20 August 1973 with an 18-month history of chest pain and progressive lethargy. Between 1969 and 1970, he had been treated for anaemia but did not respond to treatment.

Abnormal physical signs were gross pallor and a tender spleen palpable 2 cm below the left costal margin. On fundoscopy he had retinal haemorrhages, with tortuosity and varicosities of retinal capillaries producing the so-called fundus paraproteinaemicus.

Investigations performed were as follows: PCV 12%, WBC 9600/mm<sup>3</sup>, platelets 128000/mm<sup>3</sup>. Sternal marrow biopsy showed erythroid hyperplasia with marked lymphocytosis. The total serum proteins were 7.7 g/dl, albumin 2.1 g/dl, and globulin 5.6 g/dl. Electrophoresis of the serum on cellulose acetate membrane showed an intense and homogenous band in the gamma globulin region which proved to be macroglobulin. Quantitation of the IgM gave 61 mg/ml (method of Fahey and McKelvey). This IgM had only kappa light chains.

Further tests showed that the patient had a strong cold antibody with a specificity of anti-I (table II). However, the antibody did not agglutinate the patient's own red cells at room temperature and no autoagglutination was seen in the blood film. It was assumed that this antibody was an alloantibody and the patient's phenotype was adult-i but the necessary antiserum to prove this assumption was not available.

Despite repeated blood transfusions, plasmapheresis (thrice on three consecutive days) and chlorambucil, the patient died three weeks after admission. Permission for necropsy was refused.

#### Discussion

Waldenström's macroglobulinaemia is characterized by a marked increase in IgM and bone marrow abnormalities characterized by lymphocytosis (Dameshek, 1966). The other features like haemolysis, haemorrhages, and the hyperviscosity syndrome

are secondary manifestations of this monoclonal gammopathy. The clinical features of our patients satisfy all the criteria necessary for the diagnosis of Waldenström's macroglobulinaemia.

Macroglobulinaemia is characteristically a disease of old people, and the youngest age of onset of 107 patients reviewed by Imhof *et al* (1959) was 32 years.

It is not quite clear from the available literature whether an early age of onset is more often associated with a worse prognosis as regards failure of response to treatment and rapid termination. The mild hepatitis noted on admission in case 1 was probably the result of serum hepatitis following initial blood transfusion. Post-hepatitis remission was dramatic, and the patient has remained in remission for two years—up to the time of writing. It is tempting to implicate the hepatitis as a cause of remission. Similarly, reported cases of complete clinical and haematological remission following urethane treatment and severe hepatitis in multiple myeloma (London, 1955) and remission of macroglobulinaemia following serum hepatitis in a 59-year-old woman (Wolf *et al*, 1972) have been documented. Osserman and Takatsuki (1965) also described the case of a 75-year-old man with a transient IgG plasma cell dyscrasia with type K Bence Jones proteinuria who experienced a remission of the plasmacytic dyscrasia following cessation of sulphafurazole diethanolamine (Gantrisin) treatment and an episode of viral hepatitis. The mechanism by which viral hepatitis could cause a remission in primary macroglobulinaemia is unknown. One might suggest a direct effect where the viral antigen has destroyed the immunocompetent cells or that the viral antigen increased the resistance of the patients to the abnormal clone of plasma cells producing the abnormal immunoglobulins. Also, in our case 1, there was no evidence of an active haemolytic process which may have responded to treatment with steroids and chlorambucil. He showed no evidence to incriminate chronic active hepatitis (Sherlock, 1966) or subacute hepatitis (Cohen *et al*, 1963) as being the cause of his macroglobulinaemia.

In many chronic infections which may cause secondary macroglobulinaemia, like the tropical splenomegaly syndrome (Sagoe, 1970), trypanosomiasis (Mattern and Lobez 1964), kala azar, collagen or neoplastic disease, the IgM seldom forms a distinct and homogeneous band (figure). Also, the absolute values of IgM seldom exceed 40-50 mg/ml.

Treatment aims at reducing the plasma concentration of the circulating macroglobulins which are responsible for some of the clinical manifestations (MacKay *et al*, 1956; Bayrd *et al*, 1965). Removal of the abnormal proteins by plasmapheresis (Schwab and Fahey, 1960; Lawson *et al*, 1968) is a useful

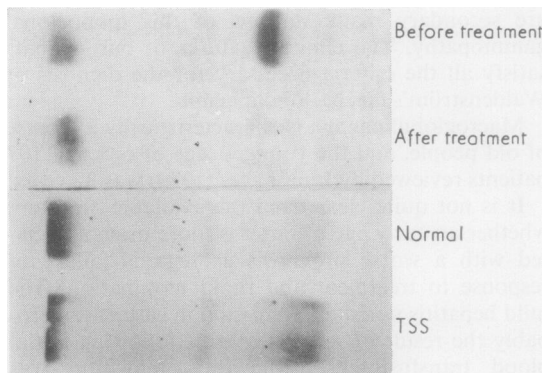


Figure Case 1 The electrophoretic pattern of the serum both before and after treatment compared with the pattern of the serum from a normal Nigerian donor and the pattern of the serum from a patient with a polyclonal increase in IgM suffering from tropical splenomegaly syndrome (TSS).

emergency measure. Blood transfusions for the correction of anaemia, steroids, and cytotoxic drugs like chlorambucil or cyclophosphamide are useful in reducing the rate of synthesis of the macroglobulins. Prolonged continuous treatment with chlorambucil has been advocated by several workers (Bayrd *et al.*, 1965; McCallister *et al.*, 1967). Our first patient is very unusual in that a complete remission, lasting just over two years, has followed a short course of chlorambucil.

The two patients presented are the only cases of Waldenström's macroglobulinaemia on record in the University College Hospital, Ibadan. The first patient's serum contained an autoantibody with properties similar to those causing 'cold agglutinin disease (CAD)', although the clinical manifestations of Raynaud phenomena were not observed, probably because of the relatively high environmental temperature. CAD and Waldenström's disease are both so rare that the possibility of their coexisting in this patient by chance alone need not be entertained. Rather, the evidence presented clearly indicates that they are causally related. Indeed, Waldenström's macroglobulinaemia can be defined as a lymphoma in which the monoclonal neoplastic cells secrete an immunoglobulin of the IgM class. It may happen that the IgM produced has specificity against a particular red cell antigen.

If the antigen concerned is present on the patient's red cells, the syndrome of CAD will result. Hence we conclude that CAD is a special variant of Waldenström's disease, which is a special variant of lymphoma. We may venture to make a prediction, by

analogy, regarding another type of immunoglobulin-producing neoplasm, namely multiple myeloma (MM). It is possible that eventually a case of MM will be found, secreting an IgG immunoglobulin also having red cell antibody specificity. In such a case, if the corresponding antigen were present on the patient's red cells, a syndrome of *warm-type* autoimmune haemolytic anaemia would complicate the disease.

In the second patient, the antigen against which the antibody was directed appeared to be absent from the patient's own red cells. However, the presence of this antibody made it impossible to obtain compatible blood for the patient because the corresponding antigen (I) was present on the red cells of all adult donors tested.

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