The African Journal of Medicine and Medical Sciences

Volume 16
1987

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Palo Alto Melbourne

Methods

The splenic size was determined by measuring along its longest axis from its tip to the costal margin at the anterior axillary line. The liver was measured from its edge to the costal margin in the mid-clavicular line.

Routine haematological blood counts were performed by standard methods. Serum IgM for each patient was quantitated by the Mancini method (Fahey & McKelvey, 1965) using Hyland plates (from Hyland Laboratories, California, U.S.A.). Raised results were confirmed by repeating the tests. Lymphocytes were cultured in single strength TC 199 (obtainable from Burroughs Wellcome, Beckenham, Kent, U.K.) supplemented with 20% inactivated human AB serum and containing streptomycin (100 µg/ml), penicillin (100 units/ml) and mycostatin (50 units/ml). Setting up, and the assessment of, lymphocyte transformation tests (LTT) were as previously described (Ukaejiofo & David-West, 1979). Tests that showed depressed lymphocyte transformation were repeated to exclude false negatives

Protein electrophoresis was also performed routinely to determine the clonal pattern of the immunoglobulins. Treatment schedule of Leipman and Votaw (1978) was followed on patients as reported in Tables 1 and 2.

Case reports

(1) T.S., a 26-year-old female petty-trader presented with neck swelling and cough of 3 months' duration. On examination, she was pale and had generalized lymphadenopathy and peritonsillar masses. Her spleen and liver were each enlarged 10 cm. Her blood counts were as follows: haematocrit, 18%; total leucocytes (WBC), 46,800/mm^3 (77% of which were mature lymphocytes); platelets, 190,000/mm^3. LTT, 16%; serum IgM, 8600 mg/100 ml Lymph node biopsy was reported as non-Hodgkin's lymphoma, well differentiated type. A diagnosis of CLL was made and the patient was treated with COP (i.e. cyclophosphamide 400 mg/m^2 orally, days 1 to 5, vincristine 1.4 mg/m^2 day 1), and prednisolone 100 mg/m^2 orally, days 1 to 5 in a 21-day cycle, of which days 6–21 were free from cytotoxic drugs (Leipman & Votaw, 1978). She was also treated with paludrine. The masses disappeared after three courses of chemotherapy, and the patient defaulted.

(2) O.A., a 30-year-old female farmer presented with 3 months' history of fatigue, weight loss, breathlessness on mild exertion, and loss of appetite. On examination, she was pale, with a spleen size of 22 cm and liver of 11 cm. Haematocrit was 22%; WBC was 350,000/mm^3 (with differential lymphocytes count of 91%). A diagnosis of CLL was made. IgM was 4500 mg/100 ml and LTT, 0%. She was treated with cyclophosphamide tab. 100 mg daily, paludrin 100 mg daily and allopurinol 100 mg t.d.s. for 2 months. Her spleen shrank to 18 cm and liver to 8 cm. She defaulted.

(3) K.L., a 50-year-old female gave a history of general weakness and inability to carry on

Table 1. Haematological and immunological features

Patients' initials	Age	Sex	Total WBC (per mm^3)	Differential lymphocytes count (%)	PCV (%)	Platelets (×10^3/mm^3)	IgM (mg/100 ml)	PHA-LTT score (%)
T.S.	26	F	46,800	77	18	190	8600	16
O.A.	30	F	350,000	98	22	75	4500	0
K.L.	50	F	44,400	93	21	59	2300	11
S.A.	33	F	69,900	88	29	80	1320	8
F.E.	60	F	286,000	80	25	110	720	0
N.G.	68	M	65,200	87	20	80	1850	0
A.Ak.	75	M	36,200	87	30	ND	4000	2
A.Am.	45	M	65,400	94	33	150	1200	4

ND = Not done.

Afr. J. Med. med. Sci. (1987) 16, 113–118.

Chronic lymphocytic leukaemia with raised serum IgM levels

E. O. UKAEJIOFO, K. E. ONWUKEME*, A. S. SAGOE* AND G. J. F. ESAN
Department of Haematology, University College Hospital, Ibadan, Nigeria

Summary

Eight patients diagnosed as having chronic lymphocytic leukaemia (CLL) from clinical and haematological data were also observed to possess immunological characteristics similar to tropical splenomegaly syndrome (TSS). We suggest that the raised IgM level in these cases may be the effect of chronic exposure to malaria in patients who later developed CLL. Consequently, raised serum IgM, which is a feature of TSS, may also be found in some cases of CLL in Nigeria.

Résumé

Huit malades qui, après la diagnose, avaient été confirmés souffrant de la leucémie lymphocytique chronique (CLL) selon les données cliniques, ont été aussi identifiés comme possédant des caractéristiques immunologiques semblables au 'splenomegaly syndrome' (TSS). Nous suggérons que le niveau élevé de IgM dans ces cas pourrait être l'effet de l'exposition chronique à la malaria dans les malades qui ont développé, plus tard, le CLL. Par conséquent, le sérum IgM élevé qui est un trait de TSS pourrait être trouvé aussi dans certains cas de CLL au Nigéria.

Introduction

Chronic lymphocytic leukaemia (CLL) and tropical splenomegaly syndrome (TSS) are two disease entities that have been variously described. Some of the most common clinical diagnostic criteria for CLL in the tropics at presentation include: anaemia (100%), splenomegaly (92%), hepatomegaly (76%) and superficial lymph node enlargement (67%), while the laboratory findings include leucocytosis above 50,000/mm^3 in 62% (Essien, 1976). Also present is depressed response to stimulation by phytohaemagglutinin (PHA) (Sagoe, 1970; Ukaejiofo & David-West, 1979). The major clinical diagnostic criteria for TSS at presentation include massive splenomegaly, immunity to malaria, and clinical and immunological response to anti-malarials (Edington, 1967; Watson-Williams & Allan, 1968; Sagoe, 1970; Greenwood & Fakunle, 1979). The most important laboratory finding to aid differential diagnosis at presentation is said to be a raised serum IgM value above normal (Sagoe, 1970; David-West, 1974; Ukaejiofo & David-West, 1979; Greenwood & Fakunle, 1979; Fakunle, 1981).

Some patients diagnosed as CLL on clinical and laboratory findings may also have the classical immunological findings associated with TSS (Ukaejiofo, 1981; Ukaejiofo, Sagoe & Osunkoya, 1983); and those known to have TSS may also show features of CLL (Fakunle *et al.*, 1979). We produce further evidence to show that raised serum IgM may not be fool-proof in the diagnosis of TSS.

Patients and methods

Patients

Sera of eight out of twenty patients who presented at the Haematology Clinic of the University College Hospital, Ibadan, Nigeria, with splenomegaly during a 3-year longitudinal study were all tested routinely for IgM level. Their pretreatment sera were deep-frozen at −20°C and tested about 2 weeks after the diagnosis of CLL had been established.

Correspondence: E. O. Ukaejiofo: Department of Medical Laboratory Sciences, University of Nigeria, Enugu Campus, Nigeria.

*Present address: Department of Pathology & Haematology, University of Jos, Jos, Nigeria.

with her trade for 4 years, and an abdominal mass that had been present for 1 year. Examination revealed pallor. Her liver was enlarged 4 cm, and her spleen was 34 cm. She had a haematocrit of 21%; WBC of 44,400/mm^3 (93% of which were small lymphocytes); LTT was 11% and serum IgM was 2300 mg/100 ml. She was diagnosed as CLL. Treatment was to be started when she developed fever and died.

(4) S.A., a 33-year-old female presented with 4 months' history of abdominal swelling. She was pale with splenomegaly of 22 cm. Haematocrit was 29%, WBC was 69,000/mm^3 (with lymphocytes comprising 88% and blast cells 10%); platelets were 80,000/mm^3; LTT was 8%; IgM was 1320 g/100 ml. A diagnosis of CLL was made and she was placed on chlorambucil 5 mg daily and 60 mg of prednisolone. Her spleen regressed to 18 cm and the patient defaulted.

(5) F.E., a 60-year-old female trader presented with a history of cough, generalized pruritus, left abdominal mass and weight loss of [illegible] months' duration. Further examination revealed generalized lymphadenopathy involving [illegible] nodes. Her spleen was enlarged 20 cm and her liver was 6 cm. haematocrit was 25%; WBC was 28,000/mm^3 (80% of which were lymphocytes, 2% were blast cells). LTT was 0% and serum IgM was 720 mg/100 ml. Her diagnosis was CLL and she was placed on a daily dose of 5 mg chlorambucil. She absconded 12 months later with a spleen of 14 cm and WBC of 24,000/ml (96% of which were lymphocytes).

(6) N.G., a 68-year-old male farmer, presented with a history of abdominal swelling and weight loss, his spleen was 28 cm, liver was 12 cm, and he was pale. Blood counts showed: haematocrit, 20%, WBC, 65,200/mm^3 (of which 87% were lymphocytes), LTT, 0%; IgM, 1850 mg/100 ml. A diagnosis of CLL was made. He was placed on chlorambucil 5 mg daily for 2 months. His liver shrank to normal size and his spleen regressed from 28 to 19 cm. The patient absconded.

(7) A.Ak., a 75-year-old male farmer, presented with epigastric pain of 3 months' duration. He was pale, with liver enlarged 5 cm and spleen 29 cm; haematocrit of 30%, WBC of 36,200/mm^3 (87% of which were lymphocytes), LTT of 2% and IgM of 4000 mg/100 ml were recorded. A diagnosis of CLL was made and he was treated with two courses of COP. His liver reduced to normal size but his spleen shrank to 26 cm before he was lost to follow-up.

(8) A.Am., a 45-year-old male farmer, presented with neck swelling, abdominal swelling and easy fatiguability of 2 weeks' duration. His spleen was enlarged 26 cm and liver 12 cm haematocrit was 33%, WBC was 65,400/mm (with 94% lymphocytes some of which were atypical), LTT was 4%, and serum IgM was 1200 mg/100 ml. A diagnosis of CLL having been made, he was treated with daily dose of 150 mg of cyclophosphamide. His spleen and liver did not regress significantly after months. Instead there was a rather progressive generalized lymphadenopathy. He then commenced on treatment with COP. After five courses, the generalized lymphadenopathy reduced, hepatomegaly disappeared, but the liver was 8 cm when he was lost to follow-up.

Discussion

The normal level for serum IgM in the locality where this study was performed has been reported as 50–400 mg/100 ml with a mean of 189 mg/100 ml (Sagoe, 1970). A more recent report (Oyeyinka *et al.*, 1984) gives a mean of 117 mg/100 ml and a range of 2–233 mg/100 ml (mean ± 2 s.d.). The IgM level for these patients ranged from 720 to 8600 mg/100 ml which is in keeping with the expected values in TSS. These eight cases had gross splenomegaly and lymphocytosis, which are also features of TSS and, as well, had depressed responses to PHA, which is inconsistent with TSS. Gross lymphadenopathy was also a constant feature in all eight cases. A diagnosis of gross lymphoid hyperplasia (GLH) was not entertained because of the depressed PHA responses and raised serum IgM level. In GLH, immunoglobulin levels are normal although other features are similar to those of TSS (Bryceson Fleming & Edington, 1976).

In a 10-year retrospective study, Essien (1976) showed that of the eighty-five cases of CLL diagnosed in Ibadan, splenomegaly was a feature in 92%, lymphadenopathy in 67%, and leucocytosis exceeding 50,000/mm^3 in 62%. It is noteworthy that he observed that the long surviving patients in his study may have been those with features of TSS, although neither serum IgM estimation nor PHA stimulation was performed. All the eight patients in our study

Table 2. Clinical features

Patients' initials	Lymphnodes		Spleen size (cm)		Liver size (cm)		Period under treatment (weeks)	Drugs used
	At presentation	Post treatment	At presentation	Post treatment	At presentation	Post treatment		
T.S.	Generalized	None	10	0	10	0	8	COP paludrine
O.A.	NP	NP*	22	20	11	7	8	Cyclophosphamide allopurinol paludrine
K.L.	NP	NP	34	—	3	—	—	—
S.A.	Generalized	NP	22	9	NE	NE	12	Chlorambucil prednisolone paludrine
F.E.	Generalized	NP	20	10	6	NE	52	COP paludrine
N.G.	NP	NP	12	NE	28	19	8	Chlorambucil paludrine
A.Ak.	Generalized	NP	29	5	26	NE	4	COP paludrine
A.Am.	Generalized	Reduced	26	10	12	NE	32	Chlorambucil allopurinol paludrine

*NP = Not palpable, NE = not enlarged.

blood lymphocytes from patients with lymphoproliferative disorders in Nigeria. 2. Chronic lymphocytic leukaemia (C.L.L.). *Afr. J. Med. med. Sci.* **12**, 197–202.

Watson-Williams, E.J. & Allan, N.C. (1968) Idiopathic tropical splenomegaly syndrome in Ibadan *Br. Med. J.* **4**, 793–796.

(*Accepted* 15 *May* 1986)

fulfilled the laboratory and clinical criteria for the diagnosis of CLL, and in addition showed significantly depressed responses to PHA. Their serum proteins on electrophoresis were polyclonal. Preud'homme and Seligmann (1972) observed that 5% of patients with CLL have high IgM levels because of a monoclonal IgM paraproteinaemia. It is also known that CLL patients show secondary IgM deficiency (Fakunle *et al.*, 1977); and that lymphoma patients also show significantly low IgM levels (Ngu *et al.*, 1976).

Patient K.L., who died while preliminary investigations were going on, obviously had had the disease for a long period before presenting for treatment. In the two cases (A.Am. and F.E.) where it was possible to re-order IgM estimations, the levels fell to normal (240 mg/100 ml and 360 mg/100 ml, respectively) before they were lost to follow-up.

Two factors have been suggested as being responsible for raised IgM in TSS, namely: chronic exposure to malaria and genetic inheritance (Sagoe, 1970; Fakunle & Greenwood, 1976; Fakunle, 1981). It has been suggested by Fakunle and Greenwood (1976) that IgM is overproduced, representing an exaggeration of the hypergammaglobulinaemia normally seen in patients repeatedly exposed to malaria. It is possible that raised IgM levels seen in our eight cases of CLL are the effect of chronic exposure to malaria in patients who later developed CLL. Consequently, raised serum IgM, which is a feature of TSS, may also be found in some cases of CLL in Nigeria.

One major problem we faced was that the patients readily defaulted once there was a feeling of well-being. Otherwise a prolonged follow-up would have helped in arriving at a more definite diagnosis.

Acknowledgments

We thank Professor B. O. Osunkoya for useful comments on the manuscript; Late Professor E. A. Lewis and Dr C. K. O. Williams, for managing one patient each. Mr 'Tunji Oladepo gave excellent secretarial assistance.

References

Bryceson, A.D.M., Fleming, A.F. & Edington, G.M. (1976) Splenomegaly in Northern Nigeria. *Acta Trop.* **33**, 185–214.

David-West, A.S. (1974) Relapses after withdrawal of proguanil treatment in tropical splenomegaly syndrome. *Br. Med. J.* **3**, 499–501.

Edington, G.M. (1967) Pathology of malaria in West Africa. *Br. Med. J.* **1**, 715–718.

Essien, E.M. (1976) Leukaemia in Nigerians; 2. The chronic leukaemias. *East Afr. Med. J.* **53**, 96–103.

Fahey, J.L. & McKelvey, E.M. (1965) Quantitative determination of serum immunoglobulins in antibody-agar plates. *J. Immunol.* **94**, 84–90.

Fakunle, Y.M. & Greenwood, B.M. (1976) Metabolism of IgM in the tropical splenomegaly syndrome. *Trans. R. Soc. Trop. Med. Hyg.* **70**, 346–348.

Fakunle, Y.M., Damisah, M., Ajdukiewicz, A.B., Whittle, H.C. & Greenwood, B.M. (1977) IgM deficiency in Nigerians. *Trans. R. Soc. Trop. Med. Hyg.* **71**, 451–452.

Fakunle, Y.M., Greenwood, B.M., Flemming, A.F. & Danon, F. (1979) Tropical splenomegaly syndrome or chronic lymphatic leukaemia? *Trop. Geogr. Med.* **31**, 353–358.

Fakunle, Y.M. (1981) Tropical splenomegaly. In: *Clinics in Haematology*, vol. 10 (ed. by L. Luzzatto), pp. 963–975. Saunders, U.K.

Greenwood, B.M. & Fakunle, Y.M. (1979) The tropical splenomegaly syndrome — a review of its pathogenesis. In: *The Role of the Spleen in the Immunology of Parasitic Diseases*, pp. 229–244 Schwabe & Co. AG, Basel.

Leipman, M. & Votaw, M.L. (1978) The treatment of chronic lymphocytic leukaemia with COP chemotherapy. *Cancer* **41**, 1664–1669.

Oyeyinka, G.O., Salimonu, L.S., Williams, A.I.O., Johnson, A.O.K., Ladipo, A.O. & Osunkoya, B.O. (1984) Range of normal serum immunoglobulin (IgG, IgA & IgM) values in Nigerians. *Afr. J. Med. med. Sci.* **13**, 169–176.

Ngu, V.A., McFarlane, H., Osunkoya, B.O. & Udeozo, I.O.K. (1966) Immunoglobulins in Burkitt's lymphoma. *Lancet* **2**, 414–416.

Preud'homme, J.L. & Seligman, M. (1972) Surface-bound immunoglobulins as a cell marker in human lymphoproliferative diseases. *Blood* **40**, 777–794.

Sagoe, A.S. (1970) Tropical splenomegaly syndrome: long-term proguanil therapy correlated with spleen size, serum IgM, and lymphocyte transformation. *Br. Med. J.* **3**, 378–382.

Ukaejiofo, E.O. & David-West, A.S. (1979) The use of lymphocyte transformation and IgM estimation as diagnostic aids in leukaemoid reactions. *J. Trop. Med. Hyg.* **82**, 197–200.

Ukaejiofo, E.O. (1981) *Lymphocyte Sub-populations in Lymphoproliferative Disorders in Nigeria*. M.Sc. Dissertation, University of Ibadan, Nigeria.

Ukaejiofo, E.O., Sagoe, A.S. & Osunkoya, B.O. (1983) Immunologic identification of peripheral