A CASE OF IgA MULTIPLE MYELOMA: NUTRITIONAL PERSPECTIVE IN DIAGNOSTIC TESTING

***ANETOR J.I, +AJOSE F I and **AKINGBOLA T.S**

**Department of Chemical Pathology, College of Medicine, University of Ibadan, Ibadan, Nigeria.*

+Medical Centre International Institute of Tropical Agriculture (IITA) Ibadan, Nigeria.

***Department of Haematology, College of Medicine, University of Ibadan, Ibadan, Nigeria.*

ABSTRACT

A 64-year-old security guard and longstanding known hypertensive presented with hypertensive heart disease (HHD), weight loss, an enlarged prostate, and a spontaneously fractured rib. Malignancy of the prostate with possible metastases to the ribs was strongly suspected. Biochemical profiling revealed a paraprotein. Other biochemical and hematological correlates that were on hand before serum protein electrophoresis were rather atypical. Paraprotein studies by immunofixation revealed IgA myelomatosis. Unlike previous reports from Caucasians there was normocalcaemia, normal protein level, microcytic hypochromia, low MCHC, cholesterol level at the lower limit of the reference range and normal urea level (in the face of markedly raised creatinine level). Nutritional modulation of the classical laboratory features of this disease may account for the fairly atypical laboratory picture.

The need to appreciate the influence of nutritional status on the laboratory (especially biochemical) features of a disease and thus interpretation of diagnostic tests appears of exceptional current importance, given the widening gap in socioeconomic status and the level of poverty between the resource poor and developed countries from which the classical, clinical and laboratory features of most diseases were first described.

This case report reminds of the need not only to recognize theoretically the impact of nutritional status on the laboratory characteristics of a disease but of the practical application of the nutritional perspective in the interpretation of diagnostic investigations, especially in nutritionally disadvantaged communities.

KEY WORDS

Multiple Myeloma, Nutritional Status, Protein electrophoresis, Malignancy, Immunofixation, Resource Poor Communities.

INTRODUCTION

Multiple Myeloma (MM), which is a malignant proliferation of plasma cells, can be solitary or generalized. The bone and soft tissues are often involved. Lesions may be visible on x-rays. Anaemia is common owing to the infiltration of the bone marrow by abnormal plasma cells. The serum globulin level may be so high to the point of causing a number of problems including thrombosis because of the hyperviscosity of blood. Paradoxically, haemorrhage

and susceptibility to infection are relatively common.

Hypercalcaemia defined as serum calcium level above 2.75 mmol/L (11.0mg/dl)(1) is a frequent finding and renal failure may arise(2). This may indeed account for over 33% of deaths from this disorder, which for uncertain reasons is more common in blacks than in whites(3). Some of the clinical features of this condition include osteolytic lesions of the skull, rib fracture and weight loss as well as greater susceptibility to infection due to abnormal immunoglobulins and attendant immunoparesis.

In most biochemical investigations of multiple myeloma evidence is placed on hypercalcaemia, hyperproteinaemia, hyperuricaemia and uraemia especially azotaemia.

Apart from the role that nutritional status may play in higher risk to this malignancy(3), the possible variation

Author for Correspondence

Dr. J.I. Anetor

Department of Chemical Pathology,
College of Medicine, University College Hospital,
Ibadan.

E-mail: anetorji@yahoo.com

that may occur in these biochemical markers owing to different nutritional status, which may becloud the diagnosis, especially in the presence of multiple pathologies, is seldom considered. This may be important in nutritionally disadvantaged and resource poor communities.

We present here a case of an IgA multiple myeloma in a 64-year-old male security guard, with a long-standing hypertensive heart disease (HHD) and a recent enlargement of the prostate. This patient did not present with the complete classical biochemical features of multiple myeloma but was subsequently found by serendipic biochemical profiling including protein chemistry, especially immunofixation to suffer from IgA multiple myeloma.

Case Presentation

This 64-year old security guard who was first diagnosed hypertensive about 12 years earlier (1997) presented with imminent congestive cardiac failure (CCF), prostatic enlargement (a recent development) and a fractured 8th rib, thought by the radiologist to be from metastasis. His hypertension had been well controlled, first with propranolol, and later on with metoprolol and moduretic and had maintained relative good health until November 1997. After his CCF was stabilized he was referred to the medical out patient department (MOP) of the University College Hospital, (UCH) Ibadan, for the management of his HHD and later to the Urology unit for the prostatic enlargement. This was evaluated to be benign. He was then returned to the cardiology unit of the same hospital where he was admitted on 15/1/98 for the continuation of the

treatment of his HHD. The patient also presented about this time with troublesome cough. He was emaciated and complained of generalized body pain.

By this time the laboratory results had come out, remarkably the serum electrophoresis showed a paraprotein. This was the first indication that the patient might have multiple myeloma (MM). The first biochemical and haematological results were rather atypical. The patient at this point was referred to a haematologist and a further sample collected for paraprotein studies. A skull x-ray was also ordered. This revealed multiple luseries. The patient was managed during this period with the following, drugs Melphalan 10mg daily, Allopurinol 100mg t.d.s. Prednisolone 20mg t.ds. for two weeks. The patient became stable at this point.

On 27/2/98 he was discharged and placed on sick leave for a month and scheduled for re-admission at a later date for his next course of chemotherapy. There was clinical improvement with a weight gain of 7kg, temperature of 36.5°C and blood pressure of 100/60 mmHg.

However, the patient obtained redundancy from his employers and retired to his village, where he later died. No post mortem was done.

Clinical And Laboratory Data On Presentation

When this patient first presented to his physician on November 11th 1997 he complained of easy fatiguability. He had lost some weight having dropped from a baseline weight of 59.5kg to 54.4kg. He was quite pale. He also presented with enteritis at the same time, the significant haematological findings were haematocrit 29%, Hb 8.5g/dl and erythrocyte sedimentation rate (ESR) 150mm/hr. The red cell morphology showed microcytic hypochromia; this was accompanied by an MCHC of 29%. No rouleux formation was however observed in the film of this patient.

Tables I, II, and III showed the laboratory data obtained from the patient

TABLE II. Urinalysis and Complete Blood Count in this Case Urinalysis

Yellow clear urine
PH – 6.0
SG – 1.030
Protein 2+
Blood = 2+ (mainly Hb)
Leukocyte esterase test – Negative. Bence Jones protein (Bradshaw's test – positive; test was done after demonstration of paraproteinaemia).

TABLE 1. Some Biochemical Laboratory Data in this Case (11/11/97)

Patients Result	Reference Values	
Total Protein(g/l)	78	60 - 80
Albumin (g/l)	26	35 - 50
Total globulin	52	17 - 32
AST (I.U/L)	18	Up to 23
ALT (I.U/L)	6	Up to 12
ALP (I.U/L)	71	60 -170
LDH (I.U/L)	257	125 - 290
Urea (mmol/L)	5.3	2.5 - 7.5
Creatinine(mmol/L)	186	62 - 133
Uric acid (mmol/L)	429	208 - 417
K ⁺ (mmol/L)	4.7	3.5 - 5.0
Cl ⁻ (mmol/L)	103	98 - 108
Total Calcium (mmol/L)	2.60	2.18 -2.63
Total acid Phosphatase (I.U/L)	7.3	Up to 11.0
Prostatic acid Phosphatase (I.U/L)	0.81	Up to 4.0
Total Cholesterol (mmol/L)	2.9	2.6 – 5.2
Triglycerides (mmol/L)	0.65	0.34 – 1.54

Microscopy

Others – NAD

Haematological Data

Hb (g/L) 85

Haematocrit 29%(0.29L/L)

Total leukocyte count $3.74 \times 10^9/L$

ESR (mm/hr) >150

MCHC(g/dL) 29

RBC Morphology

Hypochromia -+

Microcytosis -2+

WBC Differential

Neutrophil (%) 40

Lymphocytes(%) 60

Eosinophils}

Basophils} Nil

Monocytes}

Bone marrow aspiration was not done for some uncontrollable reasons.

TABLE III. Paraprotein Studies Including Immunofixation Data (25/11/97)

Patient's	Result Values	Reference
TOTAL PROTEIN	(g/L) 88.0	60 – 80
Albumin	(g/L) 30.0	35 -50
IgG	(g/L) 11.20	6.5 -16.0
IgA	(g/L) 33.10	0.4 -3.5
IgM	(g/L) 2.41	0.5 -3.0

Increased alpha-I and gamma globulin bands were observed on electrophoresis (Figure I)

An intense band in the beta globulin region and a second faint band in the mid gamma region were also evident.

The principal band in the beta position was typed by immunofixation to be an IgA Lambda paraprotein.

Reference values are, those used at Unilabs; James town Road London NW1 7BX, U.K

FIGURE 1. CAM Electrophoretic strip of patient's serum performed on 11/11/97

DISCUSSION

The hypothesis that nutritional status may modulate the biochemical presentation of multiple myeloma is seldom considered in practice. The importance of nutrition to human health has gained renewed interest in the last few decades. Nutritional medicine concerns itself with the interaction of nutritional factors with human biochemistry, physiology and anatomy and the clinical application of knowledge of these interactions to the modulation of structure and function for the prevention, diagnosis and treatment of disease as well as improvement of health.

The major problem in this case is that this was a patient with CCF arising from long standing HHD and a recently enlarged prostate thought to have metastasized to the ribs. Thus the finding of a spontaneous rib fracture common in this condition was not pursued, probably because the associated biochemical data were not completely classical. The weight loss though remotely considered to be due to occult neoplasm was thought to be due to the putative malignant prostate.

It should however be always borne in mind that nutritional issues directly or indirectly impinge upon many investigations carried out in clinical laboratory medicine. Many parameters are altered by nutritional status. Indeed diagnostic tests may only be valid if certain nutritional requirements are satisfied.

In our patient, calcium was below the upper limit of the reference range 2.6 mmol/L (10.4 mg/dl) reference (2.13 – 2.63 mmol/L or 8.5 – 10.5mg/dl). Hypercalcaemia is common in multiple myeloma. This often refers to calcium level greater than or equal to 11mg/dl (2.75 mmol/L or 12 mg/dL) (1, 4).

The total calcium level below the upper limit of normal in this case of myelomatosis may probably reflect a degree of malnutrition. The patient belonged to a low socio- economic status (SES), a social class that is

also associated with a high incidence of multiple myeloma(5). Though, the hypercalcaemia of multiple myeloma is due to the release of lymphokines called osteoclast-activating factors (OAF) (6,7). It stands to reason that hypercalcaemia may be more readily achieved in individuals who are calcium replete thus attaining normocalcaemia in a previously hypocalcaemic state is not unlikely.

In individuals who in contrast previously harboured a low calcium level, (hypocalcaemia) when the osteoclast activating factors from lymphokines secreted by the tumour are mobilized may only succeed in raising the plasma level to the upper limit of the reference range. A situation probably operant in our patient.

Another evidence corroborating the probable existence of a compromised nutritional status in this patient is that the indices of abnormal renal function creatinine and urea (table 1) did not rise proportionately. Whereas creatinine markedly exceeded the upper limit of the reference range for this analyte in agreement with previous observations (6), urea was unlike creatinine below the upper limit of the reference range and like calcium close to the upper limit of the reference range. It is well recognized that creatinine is superior to urea as an index of significant renal impairment because of the heavy dependence of urea on adequate intake of protein of which it is the metabolic end point. This was probably why the very recent review of Kyle et al of 1027 patients with newly diagnosed multiple myeloma only considered creatinine as an index of renal function (1).

The presence of microcytic hypochromia and an MCHC of 29% suggest that iron deficiency the most common form of nutritional anaemia (8) also existed in this patient. Most previous reports from the affluent communities have all reported that the anaemia associated with multiple myeloma was normocytic normochromic (anaemia of chronic disease) (6,9). A tempting inference from the foregoing is that in nutritionally disadvantaged communities hypercalcaemia should be de-emphasised or that levels at the upper limit of normal or even less in the presence of other suggestive clinical evidence should be suspect.

The initial total protein level, again contrary to earlier reports (7,10) did not exceed the upper limit of normal, on fractionation however, it was found that total globulin fraction was well within the level compatible with myelomatosis.

It is again interesting, that the albumin fraction, which is commonly employed as an index of nutritional status, was lower than typical levels reported in Caucasians.

Though hypoalbuminaemia is common in many

neoplastic states owing mainly to hypercatabolic states and the disproportionate shift in the use of amino acids in the synthesis of protein in favour of one clone of immunoglobulin, a basal (pre existing) hypoalbuminaemia may not be excluded.

One clinically useful point is that the absence of hyperproteinaemia is not sufficient reason to exclude protein fractionation particularly serum protein electrophoresis to detect the probable existence of a monoclonal gammopathy. Uric acid level in this patient is consistent with earlier observations (11). This arises largely from breakdown of the products of hyperplasia (increased turnover of nucleoprotein) in the bone marrow leading to massive uric acid production, which clog the nephrons, and renal tubule, which in part accounts for death from renal failure in 33% of cases (6). Thus like reports from developed countries uric acid level may be a reliable index for the diagnosis of this disorder.

Other biochemical indices such as alkaline phosphatase activity were normal inspite of the very extensive osseous involvement in myelomatosis excluding the existence of osteoblastic activity. This is also consistent with earlier observations from other environments (9). Though low cholesterol level particularly in the affluent might be considered a metabolic effect of undetected disease it may also be another indication of some degree of malnutrition in this patient who in particular was a long-standing hypertensive on drugs, which may raise cholesterol level (12).

In addition to elucidating the type of myelomatosis, paraprotein studies (Table II) reveal that probably owing to intensified efforts to improve the patient's nutritional status (improved feeding) albumin rose from an initial level of 26g/L to 30g/L (CF table 1) though the continued myeloproliferative process also caused an increase in total protein. The lower albumin level observed two weeks earlier (11/11/97) might reflect, cancer cachexia. In the majority of cases cancer cachexia is probably multifactorial. Management is often a difficult problem and nutritional support though an apparent obvious solution could in theory accelerate tumourgenesis (13,14).

This probably largely explains the differential in total protein levels within two weeks. This probably again alludes to the nutritional perspective in the interpretation of diagnostic laboratory data which is most often forgotten.

Two symptoms of this patient, which may be relevant to IgA myelomatosis, are perhaps worthy of note. These were the troublesome cough (so called because it was refractory to treatment) and enteritis, which the patient later developed. These may infact be clinical

or symptomatic manifestations of IgA functional deficiency. Normal IgA functions in protecting the respiratory and gastrointestinal tracts being synthesized underneath the underlying mucosal linings of these tracts (15-19)

IgA multiple myeloma is the second most frequent hypergammaglobulinaemia (6,20), it may have clinical and biochemical correlates that may be obscured by the compromised nutritional status of the patient. This is perhaps of particular relevance to practitioners in nutritionally disadvantaged communities.

Some of the classical biochemical features of multiple myeloma such as hypercalcaemia hyperuricaemia, uraemia and hyperproteinaemia were not consistently present in this patient to help niche an early diagnosis of the disease by a fair degree of accuracy. This was because the possibility of compromised nutritional status is often not frequently considered in diagnostic testing. Though the early accurate diagnosis of this patient was beclouded by the multiple pathologies of HHD and an enlarge prostate it reminds us to bear in mind the nutritional perspective in diagnostic investigations.

ACKNOWLEDGEMENT

We wish to express our sincere appreciation to Dr. R. B. Rosalki, Consultant Chemical Pathologist Unilabs, Bewlay House, 32 Jamestown Road, London, for assistance with paraprotein studies. We also thank Professor Cole and Dr. O. Talabi of Department of Medicine, UCH and Professor Y. Aken'ova of the Department of Haematology, University College Hospital, for their miscellaneous assistance.

REFERENCES

- Kyle RA, Gertz MA, Witzig TE *et al.* Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proc* 2003; 78:21-33.
- Riches P. Paraproteinaemias. In: *Clinical Biochemistry: Metabolic and Clinical Aspects*. Marshall WJ, Bangert SK eds, Churchill Living Stone, Edinburgh 1995. pp. 493-506.
- Brown LM, Gridley G, Potters LM *et al.* Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. *Cancer Causes Control* 2001;12:17-25.
- Solimando DA. Overview of Hypercalcaemia of Malignancy. *Am J Health System Pharma* 2001; 58: (suppl) 54-7.
- Baris P, Brown LM, Silverman DT *et al.* Socioeconomic Status and Multiple Myeloma Among US Blacks and Whites. *Am J Public Health* 2000;90 1277-81
- Marshall WJ. Plasma proteins. In *illustrated Textbook of clinical chemistry*. Gower Medical Publishing, London 1988 PP.215-17,209 and 276
- Aguanno J, Gorren M, Ladenson JH *et al.* Multiple myeloma and hypercalcaemia *Clinchem*. 1979; 25:1821-1825.
- Demaeyer E., Adiels – Tegman M. The Prevalence of Anaemia in the World. *World Health Stat Q* 1985; 38:302-376.
- Sun T, Erichson RB, Lien Y.Y., WU C – H. Multiple Myeloma Protein with Three Light Chains. *Clin. Chem*. 1982, 28:1227-1230.
- Alper CA. Plasma Protein Measurement as a Diagnostic Aid. *N. Engl J Med*. 1974, 291:287 – 290
- Riches P. Immunological Investigations of Lymphoid Malignancies. In *Clinical Immunology*. Gooi H.C. Chapel H, eds, Oxford University press UK, 1990, pp111-138.
- Grimm R.G., Leon A.S., Huminghaku D.B., Leuzk, Hanna P, Blackburn H. Effects of Thiazide Diuretics on Plasma Lipids and Lipoproteins in Mildly Hypertensive Patients. *Ann Int Med*. 1981; 94:7-11
- Marshall WJ Metabolic Aspects of Malignant Disease In *An Illustrated Textbook of Clinical Chemistry*. Gower Medical Publishing London 1988, pp273-284
- Calmon AC. Interpretations of Serum Protein Electrophoretic Pattern Cancer Cachexia. *Brit J Hospital Med*. 1982; 27:28-34.
- Beeler M.F., Caltrou P.G.s Interpretations in *Clinical Chemistry: A Textbook Approach to Chemical Pathology* American Society of Clinical Pathologists Press Chicago, 1983, 150-3.