Non Secretory Multiple Myeloma in a Nigerian: A Case Report

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Abstract
Non secretory multiple myeloma is a rare variant of multiple myeloma characterized by the absence of paraproteins in the serum/or urine. It may present a diagnostic challenge, hence the need for a high index of suspicion while excluding multiple myeloma as a cause of bone pain and lytic lesions. The objective of this study was to report a case of non secretory myeloma, which has not been previously reported in a Nigerian. A 55year old female teacher presented with a 2 month history of painful swelling on the sternum, with no antecedent trauma. Bone marrow aspiration cytology and skeletal surveys revealed plasmacytosis and multiple osteolytic lesions, respectively. Urinary and serum paraproteins were not detected; neither was Cyclin D1 over expression. She was managed as a case of non secretory multiple myeloma with good response to therapy.

Key words: Non secretory multiple myeloma, Bone pain, Paraproteins, Plasmacytosis, Osteolytic lesions, Cyclin D 1 over expression

Introduction

Multiple myeloma (MM) is a B cell malignancy, characterized by the clonal proliferation of plasma cells within the bone marrow. It classically presents with elevated serum levels of monoclonal immunoglobulins, measurement of which has important implications for diagnosis, prognosis and management. Monoclonal immunoglobulins are absent in the serum or urine in about one to five percent of MM cases, these are referred to as Non secretory multiple myeloma (NSMM).[1] Internationally, MM has an incidence of approximately 86,000 per year and accounts for 0.8% of all cancer deaths.[2] NSMM presents a diagnostic dilemma as definitive diagnosis is dependent partly on the demonstration of monoclonal increase in bone marrow plasma cells. Furthermore, due to the absence of serum markers of disease, they present a unique problem with regards to monitoring of response to therapy as well as identification of disease progression compared to patients with the secretory variant.[3] In spite of these differences, reports comparing treatment responses in the two variants have

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Table 1: Summary of results of investigations

2/11/09	Chest X-ray:	Multiple luscencies with punched out appearances in the ribs & clavicles. CTR normal, lung fields clearIMP: ?Multiple myeloma ?Metastasis ?Leukaemia
11/1/09	Upper GI Endoscopy:	Oedematous erythema of the lower end of the esophagus, no ulcers, no erosionsImpression: GERD
25/11/09	Serum electrophoresis:	Test electrophoregram 'T' shows normal electrophoretic bands
30/11/09	Skull X-ray:	Multiple luscencies with well defined outlines in the calvarum. Mandibles are spared. Impression ?Multiple myeloma ?Metastasis
2/12/09	Bence Jones protein:	Negative
2/12/09	Total Serum calcium: Serum Phosphate:	2.1 (2.1 – 2.6) mmol/L Not done
9/12/09	ParkedCell Volume: White Blood Cell Count: Erythrocyte Sedimentation Rate(ESR): platelets normal & adequate	.31L/L 4.8 x 10^9/L 7mm 1st hr Normocytic normochromic red cells(rbc),
	Neutrophils: Lymphocytes: Monocytes: Eosinophils:	22% 73% 01% 04%
11/12/09	Retroviral screening: Peripheral blood film: Platelets: White Blood Cells: Reticulocyte index:	Negative Normocytic normochromic RBC Normal Normal 0.2%
17/12/09	Repeat ESR:	2mm 1st hr
17/12/09	Serum protein:	Total protein 64 (62 – 80)g/l Albumin 31 (28 – 40)g/l Globulin- 33 (23-35)g/l
17/12/09	Serum Uric acid:	202 (130 – 390)mmol/L

been conflicting.[3,4] Even though NSMM has been fairy reported in literature internationally, to the best of our knowledge, no case has been reported from Nigeria. We present a case report of a known peptic ulcer disease (PUD) patient who presented to the medical outpatient department of our facility with painful swelling of the left clavicle and was subsequently

diagnosed with and managed for NSMM, to emphasize its existence in our population.

Case summary

A 55yr old post-menopausal secondary school teacher who hails from and lives in Nnewi, South Eastern Nigeria, was referred to the haematology unit (from the medical outpatient department) of our facility on account of 2 months history of swelling on the antero – superior border of the sternum. The swelling progressively increased in size and was associated with a non radiating, moderate to severe pain, with restriction of movement and routine activities. There was significant weight loss as well as history of frequent handling of chemicals in the school laboratory, but none of exposure to established carcinogens, antecedent trauma to the chest or swelling in any other part of the body.

Skeletal survey revealed multiple luscencies in the ribs and pelvis and punched out lytic lesions in the skull (figure 1). Serum electrophoresis showed no monoclonal band (figure 2) and Bence Jones protein was not detected in the urine.

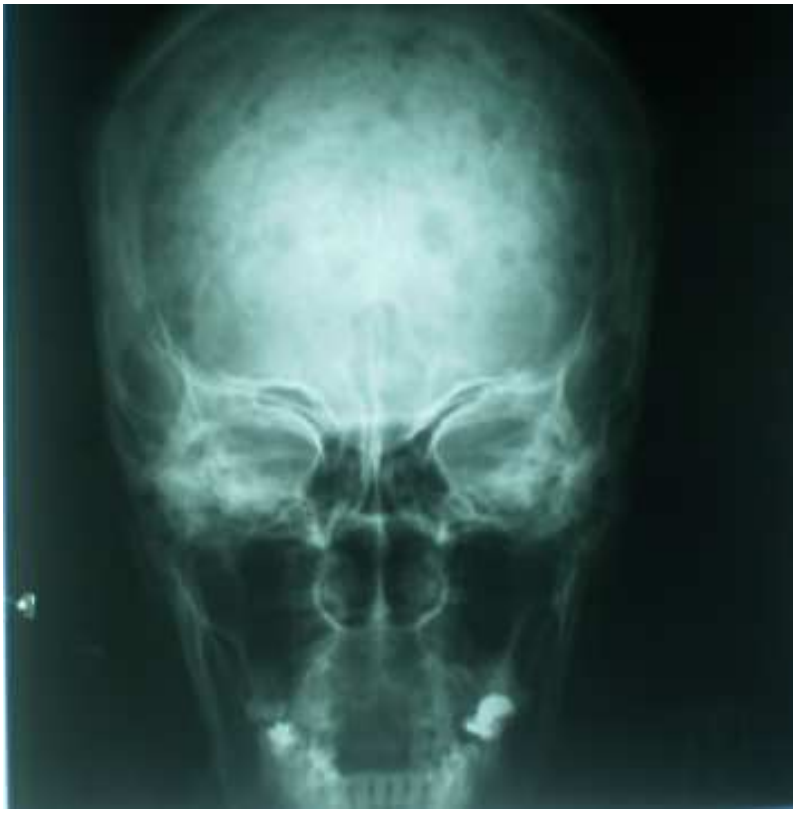


Fig. 1: X- ray of skull showing prominent osteolytic coin lesions

On further evaluation, bone marrow aspiration was done, cytology of which showed increased numbers of malignant bone marrow plasma cells (>30%) (Figure 3). More so, immunoglobulin heavy chain (IgH) translocation (Cyclin D1 over expression t (11:14) q (13:32)) done with multiplex PCR and Real Time PCR- TaqMan chemistry) was

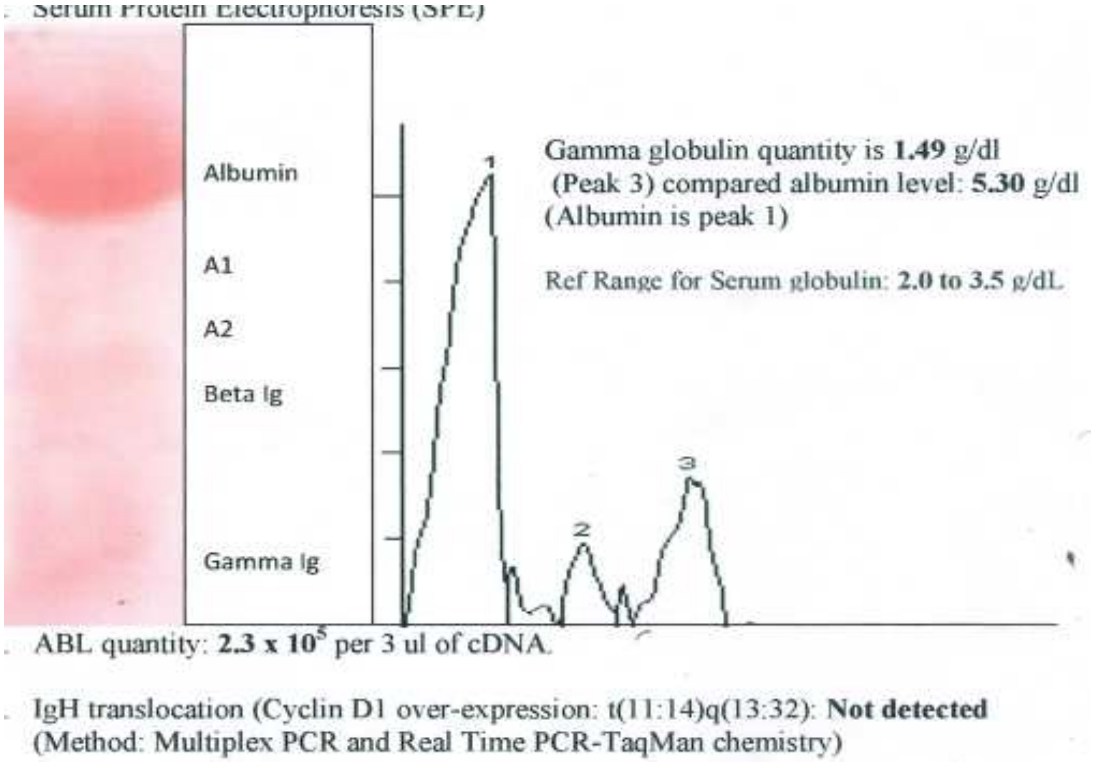
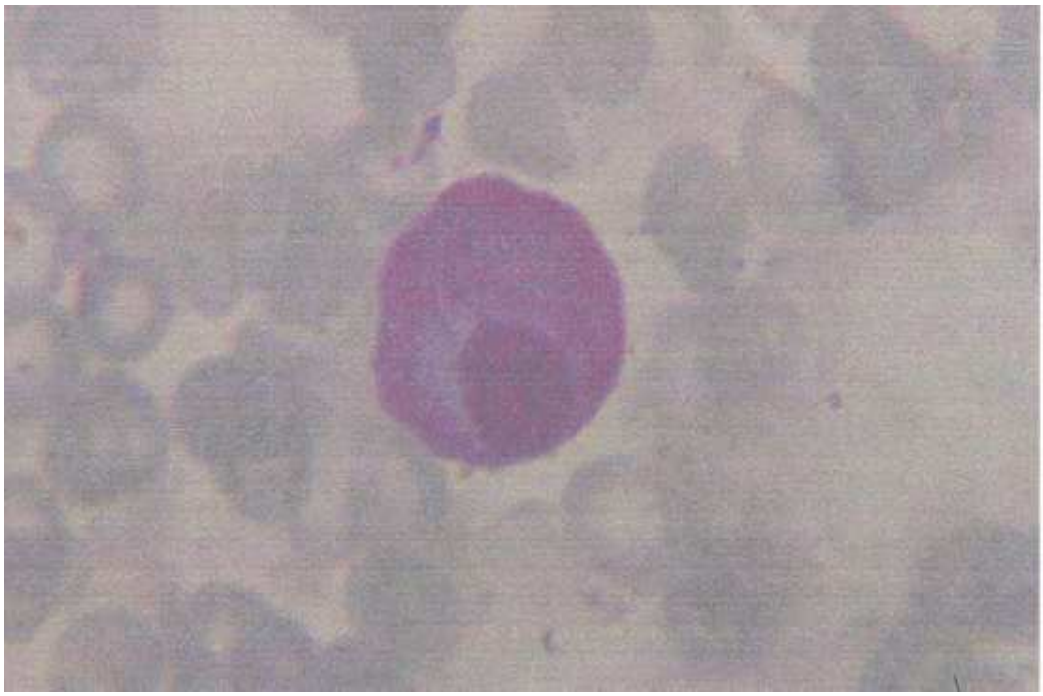


Fig. 2: Serum protein electrophoresis showing an apparently normal result



negative. A diagnosis of NSMM was thus made and patient was commenced on chemotherapy with appropriate support and did well subsequently. A list of the investigations done for this patient is included in table 1. Written informed consent was obtained from the patient and ethical approval secured from the research and ethics committee of our institution.

Discussion

The diagnosis of MM is confirmed by the presence of bone marrow plasmacytosis of at least 10%, demonstration of monoclonal immunoglobulins in the blood and/or urine and the presence of appropriate symptoms.[5] Up to 50-70% of patients with MM will present with bone pains, arising from lytic lesions and pathological fractures, while up to 10-40% may be asymptomatic.[5] Our patient was symptomatic but was classified as having the rare variant of MM, known as NSMM.

Patho-physiologically, myeloma cells interact with bone marrow stromal cells, leading to the production of osteoclast activating factor (OAF). OAF stimulates stromal cells and osteoblasts, leading to copious production of cytokines which cause activation of osteoclasts and inhibition of osteoblasts; a prelude to bone demineralization and loss of bone density which are hallmarks of MM. Extensive out-pouring of cytokines, especially by osteoclasts drive the growth and proliferation of MM cells. This vicious cycle continues and produces the characteristic symptomatology of MM.[6]

NSMM is defined as the myeloma variant in which there is absence of monoclonal immunoglobulin (M band) in serum and/or urine, in spite of clinical symptomatology similar to multiple myeloma.[1] There are three types of NSMM; the non producers (monoclonal immunoglobulins are not produced at all), the non secretors monoclonal immunoglobulins are produced but are degraded intracellularly and not secreted),[7]and lastly a false non secretory type, in which monoclonal immunoglobulins are either not available in the plasma because they are budded off as cytoplasmic vesicles,[8] or are rapidly cleared from the plasma by proteolysis or deposition in tissues.[9] In the last category of NSMM, immunohistochemistry has identified cytoplasmic M band in up to 85% of cases,[9] Even though conventional immunochemical techniques fail to detect M band in the serum or urine in NSMM, the use of more sensitive techniques such as free light chain detection assay, has identified up to 60% of apparently NSMM patients as having free light chains in the serum.[10] The diagnosis of true NSMM is therefore said to be on the decline with the application of these tests with capacity for better detection of paraproteins in the serum and urine.[11] Analysis for cytoplasmic immunoglobulins as well as serum free light chain assay were not done for our patient because the facility for these were not available in our centre when she presented.

NSMM has been found to have a very high prevalence of translocation t(11;14)(q13;q32). Avet-Loiseau *et al* found a prevalence of 79% in their data set and postulated that although the molecular effects of the dysregulated gene (Cyclin D1) were obscure; clones with this chromosomal aberration may have low secreting features, and a better prognosis than classical MM.[12]

Although this translocation was not detected in the case reported above; and as at the time of this report, the patient was doing well on therapy and remained stable, it is yet to be seen whether this chromosomal aberration, will be the hall mark of cases of NSMM in the black race and whether it will have a similar prognostic implication as earlier reported. A study that will ascertain these facts needs to be undertaken in the West African sub region.

Figure 3: A malignant plasma cell with perinuclear halo

Conclusion

A high index of suspicion of NSMM is important in the evaluation of patients of Nigerian origin, presenting with features of MM with no detectable serum or urine paraproteins.

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