Case Report and Review of the Literature

Low-secretory multiple myeloma

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Introduction

Multiple myeloma (MM) is an incurable malignancy arising from postgerminal B lymphocytes. It is estimated to account for 10-15% of haematological malignancies and 1% of all malignancies.[1-3] Non-secretory multiple myeloma (NSMM) is a rare variant of MM, where no monoclonal immunoglobulin (M-protein) can be demonstrated in either the urine or serum. NSMM is estimated to occur in 1-5% of all myeloma cases. So-called 'low-secretory' forms also exist, where the degree of immunoglobulin production does not fulfil the diagnostic criteria, but monoclonal production does occur.[4] The lack of M-protein in NSMM may be due to the inability of the plasma cell to excrete the immunoglobulin, an inherent low synthetic capacity, or intra- or extra-cellular degradation of the M-protein upon production.[5] Patients typically present with fatigue, bone pain and recurrent infections.[6]

Bone involvement is common in this disorder with an estimated 80% of patients having radiographic abnormalities upon diagnosis. The majority present with focal lytic lesions (~60%), with osteoporosis (~20%), pathological fractures (~20%) and spinal compression fractures (~20%) seen in the remainder.[7] Metastatic disease is a significant contributor to patient morbidity, since it significantly affects the patient's ability to perform activities of daily living. The humerus is the second-most common site affected after the femur.[8] Surgical intervention is aimed at providing pain relief and restoration of limb function, and is usually not indicated in patients with a very short life expectancy,[9] but this practice remains controversial.[8]

In this report we describe a patient with a low-secreting myeloma, presenting with a pathological fracture, in which establishment of the diagnosis according to the World Health Organization (WHO) criteria required creative sampling.

Table I. Summary of laboratory findings

	26/1 Admission	30/1	5/2	9/2	16/2	18/2	19/2
UKE							
Urea	4.1						5.9
Creatinine	93						92
Anion gap	15						13
CMP							
Calcium	2.48						2.40
Albumin	40						39
Magnesium	0.83						0.85
Phosphorus inorganic	1.16						1.20
LFT							
Bilirubin total	13						
ALP	114						**123**
GGT	17						
Tumour markers							
PSA	0.38						
Full Blood Count							
Haemoglobin	13.5						14.9
MCV	90.3						88.1
MCH	32.6						31.3
RDW	13.4						13.2
Platelets	221						281
White cell count	6.43						6.94
ESR	14						
CRP							5.3
Bone marrow aspirate			3% very abnormal plasma cells		3% plasma cells		
Bone marrow biopsy			Failed investigation	Failed investigation	Failed investigation		
Protein electrophoresis	**Monoclonal band of 1.30g/L Immunoparesis**					Normal pattern No immunoparesis	
Bence Jones protein		**0.23g/ 24 hours Kappa**					
Immunoglobulin levels							
IgG					**5.01**		
IgM					**<0.25**		
IgA					**0.31**		

Case report

A 54-year-old male patient presented to his local practitioner with a painful left arm, after having fallen. At this time, he also complained of a progressively enlarging lump on his forehead, present for 7 months. The practitioner applied a backslab for the left arm and referred him to the Steve Biko Academic Hospital casualty department. Prior to going to the casualty unit, he was instructed to have X-rays taken of his skull. No X-rays were performed on the arm at this point. The practitioner was promptly contacted by the radiologist, who reported multiple lytic lesions on skull X-ray.

The patient was admitted to the Steve Biko Academic Hospital, under the care of the Internal Medicine Department, with a provisional diagnosis of possible multiple myeloma. Laboratory examinations were conducted (summarised in *Table I*), but essentially showed a normal renal function, albumin level and haemoglobin. The first serum protein electrophoresis showed a monoclonal band (1.30 g/L), which could not be typed, as well as immunoparesis. A follow-up serum protein electrophoresis three weeks later however showed a normal pattern with no immunoparesis. The reason for this discrepancy is unknown. The urine Bence Jones protein estimation showed a free kappa band, quantified at 0.23 g/24 hours.

None of these findings qualify as diagnostic criteria for multiple myeloma used at the time.

In order to establish a diagnosis, a bone marrow aspirate and trephine biopsy was performed. The aspirate was that of a bloody tap (markedly haemodiluted) containing very few bone marrow elements, with a plasma cell count of 3%. This did also not contribute to the diagnosis. These findings were confirmed on flow cytometry. The plasma cells present did however show a worrying morphological feature, viz. 'flaming'.

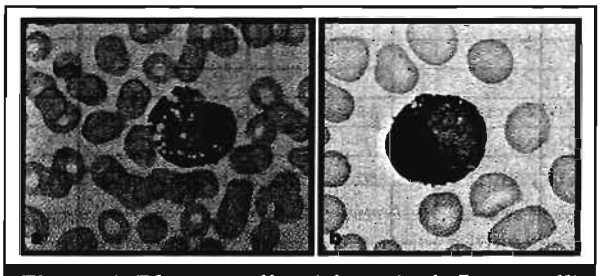

Figure 1: Plasma cells with typical 'flame cell' appearance (eosinophilic cytoplasmic edge). The surrounding red blood cells in the figure show a degree of rouleaux formation, although this is not a prominent feature.

This is typically associated with IgA type multiple myeloma, but has also been described in IgG and IgM type MM (see *Figure 1*).

This feature was reported and further examination and investigations for MM were advised. The trephine biopsy failed. Two more bone marrow examinations were performed (of which only one included an aspirate), all of which failed. Immunoglobulin sub-fraction quantification did show immunoparesis. Full body X-rays were performed showing classic lytic lesions on skull radiograph and right clavicle (*Figure 2*) as well as a pathological left humerus fracture (*Figure 3*). At this point the patient fulfilled two minor (if the first electrophoresis is accepted, three) and no major criteria (see *Table II*).

Three weeks after his initial admission, the patient was referred to the Department Orthopaedic Surgery, Tumour and Sepsis Unit for management of the pathological fracture. The patient was taken to theatre and the fracture was fixated with a reamed intramedullary nail, and a formal biopsy of the fracture site was performed (*Figure 3*). Additionally, during the procedure, some of the reamings were used to make smears. These smears were immediately stained and examined. It showed plasma cell predominance, accounting for >90% of the nucleated cells (*Figure 4*). This is not described as an accepted sampling technique, but may supply valuable information in cases where the diagnosis remains elusive. The final diagnosis of non-secreting multiple myeloma was made on histology from the fracture site biopsy.

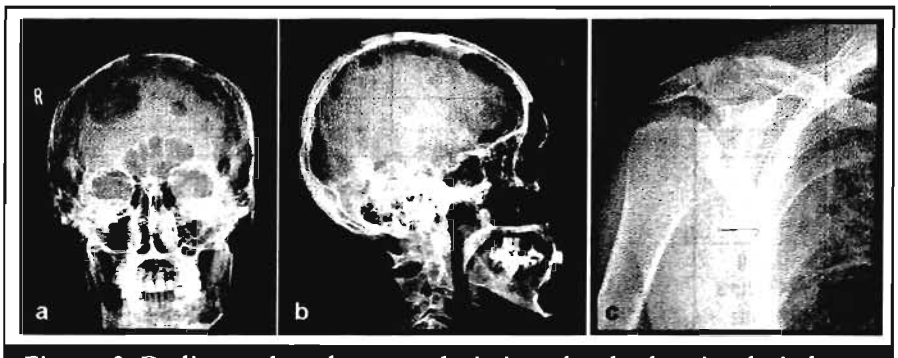

Figure 2: Radiographs taken on admission clearly showing lytic bone lesions. A) Skull AP. B) Skull lateral. C) Lytic lesion seen at the right acromioclavicular junction

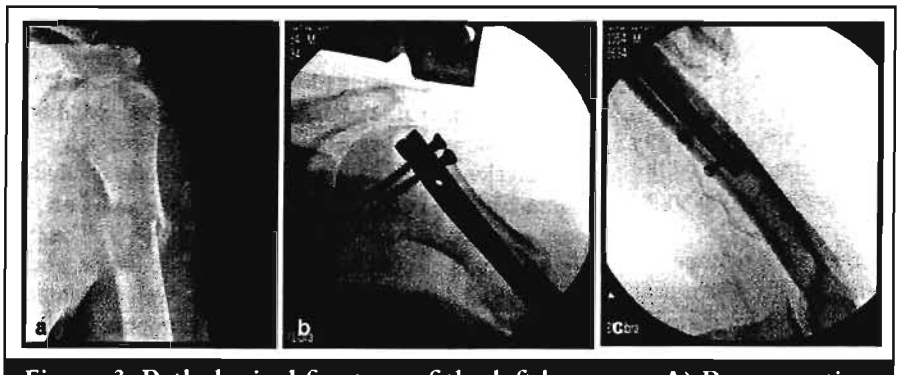

Figure 3: Pathological fracture of the left humerus. A) Pre-operative X-ray showing fracture site. B) Intra-operative X-rays showing proximal fixation. C) Distal fixation of intramedullary nail

Another diagnostic tool is now also available, specifically in the diagnosis of non-secretory and low-secretory multiple myelomas. It is not only used in the diagnosis, but also serves as a useful tool in the monitoring of these patients. The serum-free light chain analysis (FLC) measures the levels of free κ and λ chains and compares their ratio.[10] This assay was performed with results displayed in *Table III*.

Of note is the fact that with the change in diagnostic criteria as given by the WHO (*Table II*), the diagnosis of multiple myeloma can now be made earlier, as this patient would have complied with the diagnostic criteria on admission with a monoclonal band of 1.30g/dL.

Table II: Previous and current World Health Organization criteria for the diagnosis of multiple myeloma

	Previous WHO criteria	Current WHO criteria
Major criteria	1. Plasmacytoma on tissue biopsy	1. M-protein in serum or urine
	2. Bone marrow infiltration with >30% plasma cells	• No levels of seru or urine Mprotein in included
	3. Monoclonal globulin spike on serum electrophoresis	• M-protein in most cases in >30 g/L of IgG or >25 g/L
	• IgG >35 g/L	for IgA or >1 g/24 hours of urine light chains but
	• IgA >20 g/L	lower levels are also acceptable
	• Concentrated urine >1 g/24h of κ or λ light chains	2. Bone marrow clonal plasma cells or plasmacytoma
		• Usually exceed 10% of nucleated cells in the marrow
Minor criteria	1. Bone marrow infiltration with 10-30% plasma cells	but no minimal levels is designated as 5% of MM
	2. Paraprotein less than level defined above	cases have levels below 10%
	3. Lytic bone lesions	3. Related organ or tissue impairment
	4. Immunoparesis defined as:	• C – Hypercalcaemia
	• IgM <0.5 g/L	• R – Renal insufficiency
	• IgA<1 g/L	• A – Anaemia
	• IgG <6 g/L	• B – Bone lesions
Require-ments	• 2 major	
	• 1 major + 1 minor	
	• 3 minor (always including minor criteria 1 and 2)	• All three criteria required

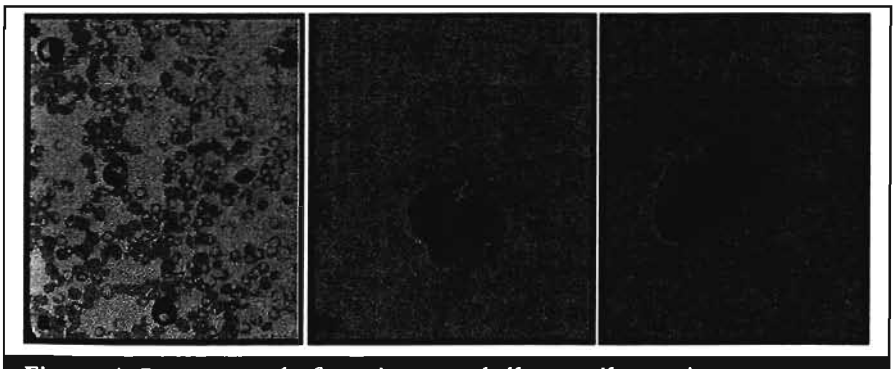

Figure 4: Smears made from intramedullary nail reamings. A) Showing a plasma cell appearance. B) Binuclear plasma cell. C) Two plasma cells showing a 'flame-cell' appearance

Table III. Serum free light chain assay analysis of patient

Test	Result	Reference
s-Kappa FLC	**2 810. mg/L**	3.30 – 19.40
s-Lambda FLC	10.20 mg/L	5.71 – 26.30
Kappa/Lambda ratio	**275.49**	0.26 – 1.65

Sampling at the site of lytic lesions renders a more representative sample and offers a targeted approach to sampling one of the end-organs affected

Conclusion

Patients suspected of having multiple myeloma should be aggressively investigated in order to definitively establish or exclude the diagnosis since a delay in diagnosis will affect treatment response and outcome. Sampling at the site of lytic lesions renders a more representative sample and offers a targeted approach to sampling one of the end-organs affected. In cases of suspected low- or non-secretory MM, a serum-free light chain analysis should be part of the routine testing, as this may offer a more sensitive result as compared to conventional Bence Jones analysis.

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