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CASE REPORT

NON-SECRETORY MULTIPLE MYELOMA IN A 37 YEAR OLD PREGNANT WOMAN IN OWO: A CASE REPORT

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ABSTRACT

Introduction: This is a case report of non-secretory multiple myeloma in a young woman.

Case report: A 39-year old pregnant woman presented with chest pain, weight loss, generalized joint pain, body weakness, bilateral knee joint swelling and fractures of the left humerus and distal femur. Investigations revealed leukocytosis, elevated plasma alkaline phosphatase, negative serum protein electrophoresis and Bence Jones protein, anaemia and elevated erythrocyte sedimentation rate. Skull X-ray showed moth-eaten appearance in keeping with myelomatosis. She had intrauterine foetal death; and was managed subsequently as a case of non-secretory multiple myeloma with chemotherapy and had a tremendous improvement.

Conclusion: This case illustrates the occurrence of patients with multiple myeloma who do not secrete immunoglobulins in our environment.

Keywords: multiple myeloma; non-secretory; protein electrophoresis

INTRODUCTION

Non-secretory multiple myeloma (NSMM) is a rare myeloma subtype whose diagnosis was established few years ago by the demonstration of monoclonal plasma cells ≥ 10% in the bone marrow, negative results on serum- and urine protein electrophoreses and immunofixation studies.[1] NSMM is commonly misdiagnosed if serum free light chain test is not evaluated; as NSMM could be light chains only, with small amounts of monoclonal proteinuria. Multiple myeloma (MM) on the other hand, is a malignancy of plasma cells, defined by the infiltration of bone marrow and the presence of CRAB features (skeletal lesions, anaemia, bone pain, renal insufficiency and hypercalcaemia); as well as three specific biomarkers: clonal bone marrow plasma cells ≥ 60%, serum free light chain (FLC) ratio ≥ 100 (if the FLC concentration is > 100mg/L) and more than one focal lesion on magnetic resonance imaging (MRI).[1] The multiple myeloma (MM) cell represents the neoplastic variant of normal plasma cells known to secrete non-functional clonal immunoglobulin (Ig); either complete Ig (heavy and light chains) or as part of Ig (heavy chain or light chain). The presence of these proteins in the blood and urine helps in the evaluation of patients suspected to have multiple myeloma.[2]

The non-secretory MM is characterized by the absence of detectable monoclonal components either in the serum or urine. This represents a very small subset of multiple myeloma population; accounting for about 3-5% of the total MM population. However, with improvement in the evaluation of these patients with NSMM, most of them have been

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reclassified as oligo-secretor; producing primarily serum free light chains in the absence of heavy chain. Hence, the proportion of true NSMM is about 1-2% of the MM population. The NSMM patients have been postulated to have a defect in immunoglobulin synthesis leading to no measurable protein in the blood or urine.[2]

The revised International Myeloma Working Group (IMWG) diagnostic criteria for monoclonal gammopathy of undetermined significance, smoldering multiple myeloma and multiple myeloma itself are presented below: [3]

Definition of monoclonal gammopathy of undetermined significance

i. Serum M-protein (IgG or IgA) <3 g/dL and/or urinary <500 mg/24 h; ii. clonal plasmocytes (CP) in bone marrow <10%; iii. absence of organ damage resulting from proliferation of clonal plasmocytes or amyloidosis.

Definition of smoldering multiple myeloma

Both criteria must be met: i. serum M-protein (IgG or IgA) ≥3 g/dL and/or urinary ≥500 mg/24 h and/or clonal plasmocytes in bone marrow 10–60%; ii. absence of organ damage resulting from proliferation of clonal plasmocytes or amyloidosis

Definition of multiple myeloma

Both criteria must be met: i. Clonal plasmocytes in bone marrow ≥10% or extramedullary plasmacytoma; ii. ≥1 of the following types of organ damage resulting from CP proliferation:

• hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal or >2.75 mmol (>11 mg/dL)

• renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 µmol/L (>2 mg/dL)

• anemia: hemoglobin concentration >2 g/dL below the lower limit of normal, or a hemoglobin concentration <10 g/dL

• bone lesion(s): ≥1 osteolytic lesion on skeletal radiography, CT or PET/CT – ≥1 of the following biomarkers of malignancy (SLiM):

• clonal plasmocytes in bone marrow ≥60%

• involved: uninvolved sFLCr ≥100

• >1 focal lesions (≥5 mm in size) on MRI

In this case report, we evaluated and managed a 39-year old pregnant woman who presented with classical features of non-secretory multiple myeloma.

CASE REPORT

A 39-year old gravida 8 and para 4^{+3} (4 Alive) at 16 weeks gestation presented in one of the "annexes" of the Federal Medical Centre, Owo, in Ondo State, Nigeria, with chest pain, weight loss, generalized body weakness, headache, blurring of vision, generalized joint pain, foaming urine and bilateral knee joint swelling. She was not a known diabetic, hypertensive, asthmatic or peptic ulcer patient.

She had fracture of the left humerus and bilateral distal femoral fractures. Full blood count revealed leucocytosis, elevated plasma total calcium and alkaline phosphatase enzyme activity. Urine tested for Bence Jones protein was negative and serum protein fractions were within their reference intervals. Other features seen in this patient included anaemia and elevated erythrocyte sedimentation rate (ESR). Her haemoglobin genotype was AA.

High vaginal swab yielded *Candida albicans* possibly a normal flora overgrowth. Vital signs were stable. She was transfused with packed red cells and transferred to Obstetrics and Gynaecology Department. At this point, the foetal heart rate could not be picked with sonicade. Further radiological evaluation revealed intra uterine foetal death (IUFD) at 17^{th} week gestation. This was followed by induction of labour which later culminated in retained placenta. This was treated appropriately. Orthopedic surgeon evaluation led to the application of a U-slab to

immobilize both upper limbs while skin traction was applied to both lower limbs. Analgesics, haematinics, antifungals (Mycoten pessaries) and antibiotics were commenced. Skull X-ray result was in keeping with myelomatosis with multiple lytic lesions showing a "moth-eaten appearance" (Figure 1).

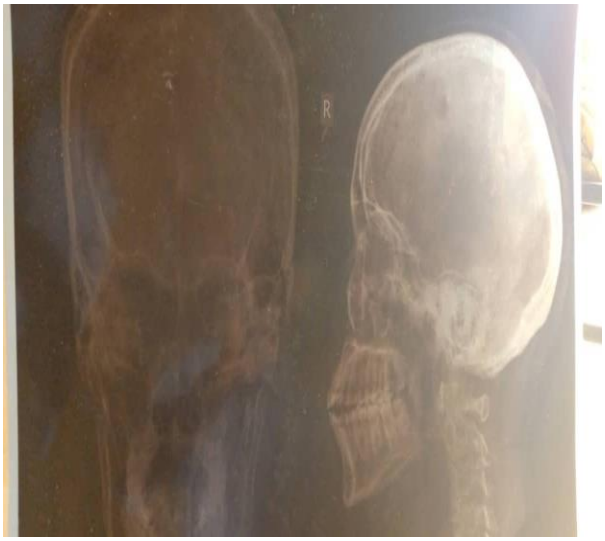

Figure 1: A moth-eaten appearance on skull x-ray showing areas of bone destruction with ragged edges.

She had open reduction and internal fixation (ORIF) with interlocking nails (ILN), disc plates and screws for bilateral supracondylar femoral fracture. Bone marrow study showed evidence of an increased fraction of plasma cells (>30%). Immunoglobulin quantification and urine free light chain estimation could not be done due to financial constraints. She was planned for chemotherapy about 6 months after admission in the hospital (mephalan 8mg/m^2 orally, day 1 – 4, prednisolone 60mg/m^2 orally day 1 – 4, thalidomide 100mg orally day 1 – 28, zolendronic acid 4mg IV over 5 minutes monthly and allopurinol). Routine pre-chemotherapy laboratory investigations (renal- and liver function tests and full blood count) were done before the commencement of chemotherapy. Surface area (SA) was calculated using SA(m^2)= (4x + 7)/(x + 90); where x= weight (kg). Liberal fluid intake was advised. Renal parameters were measured closely. Much improvement was noticed progressively as she could sit unaided.

Physiotherapy was commenced, and patient improved tremendously. Full blood count result in remission phase was essentially normal (WBC-4.6 X10^3/µL, haemoglobin concentration -11.9g/L, platelet count of 186 X10^9 µL) and the blood count parameters improved progressively (figure 2 and table 1). Her other investigation results are provided in tables 2 and 3.

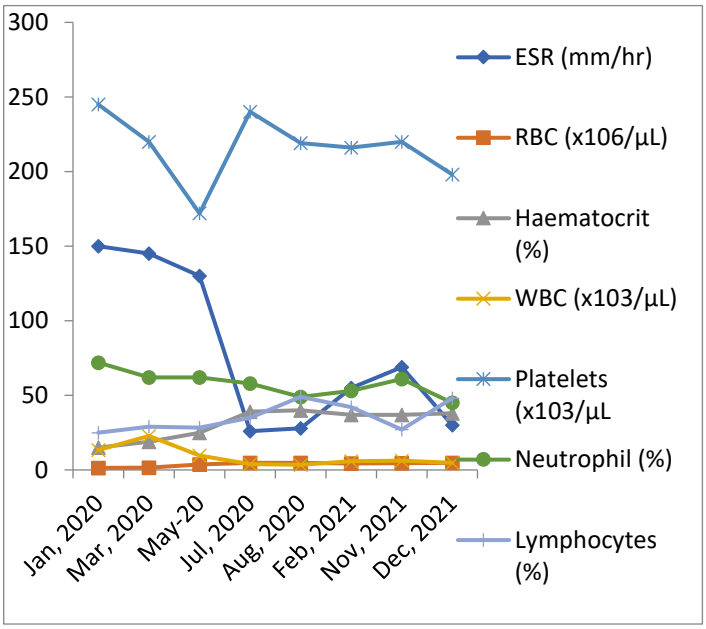

Figure 2: Line plots of erythrocyte sedimentation rate and blood count parameters per time. A sharp decline in ESR noted upon the commencement of chemotherapy.

Her vital signs were stable, however, recurrent bilateral trigger finger of the thumb was recorded as a complication from the surgery. This was managed with Depo-Medrol (a steroid) injection as patient was reluctant to have surgical correction of the trigger finger. She has been amenorrheic for the past one year. She was discharged home after about 8 months on admission (8/1/2020-28/8/2020); while the follow-up continued at various clinics (Haematology, Orthopaedics, Physiotherapy and Obstetrics and Gynaecology) in the hospital till date. The results of subsequent full blood count tests were normal.

Table 1: Pattern of erythrocyte sedimentation rate and some full blood count parameters and time.

Months	ESR (mm/hr	RBC ($x10^6$/µL)	PCV (%)	WBC ($x10^3$/µL)	PLT ($x10^3$/µL	NEUT (%)	LYM (%)
Jan, 2020	150	1.4	15	13.4	245	72	25.0
Mar, 2020	145	1.6	19	22.8	220	62	29.1
May 2020	130	3.7	25	9.8	172	62	28.3
Jul, 2020	26	4.7	39	3.9	240	58	35.0
Aug, 2020	28	4.8	40	3.5	219	49	49.0
Feb, 2021	55	4.4	37	5.9	216	53	42.0
Nov, 2021	69	4.5	37	6.2	220	61	27.0
Dec, 2021	30	4.7	38	4.7	198	45	48.0

ESR:Erythrocyte sedimentation rate, RBC: Red blood cell, WBC:White blood cell, PCV: Packed cell volume, NEUT: Neutrophils, LYM: Lymphocytes

Table 2: Other investigation results

Categories	Investigations	Results
Microbiology	High vaginal swab for microscopy, culture and sensitivity	Direct Gram staining yielded epithelial cells++, Gram negative bacilli (+) and pus cells (+). Culture yielded growth of *Candida albicans* which was resistant to nystatin and fluconazole but sensitive to voriconazole.
Histology	Bone biopsy	Sections of bone biopsy showed necrotic bony spicules with delicate blood vessels. Nil neoplastic cells.
Clinical chemistr	Urinalysis	Urinalysis was essentially normal.
	Urine Bence Jones Protein (BJP) Serum free light chain assay	Bradshaw BJP Negative Jacobson &Milner Negative Negative
	Thyroid study	Euthyroidism
	Plasma total calcium, inorganic phosphate and alkaline phosphatase(ALP)	TCa 3.30mmol/L [2.15-2.55] Pi 2.14 mmol/L [0.88-1.44] ALP 99 IU/L [53-128]
	Glucose assay	Euglycaemia
	Liver and Renal function tests	Essentially normal
Other Haematology tests	Haemoglobin genotype Blood group	AA A Rhesus Positive
Radiology	Obstetrics scan	Intrauterine foetal death Hepatomegaly

Table 3: Serum protein electrophoresis results were within their respective reference intervals.

Analytes	Results	Reference intervals
Total protein	7.5g/dL	[6.4-8.6]
Albumin	4.3 g/dL	[3.5-5.5]
Alpha-1 globulin	0.31 g/dL	[0.2-0.4]
Alpha-2 globulin	0.88g/dL	[0.5-1.0]
Beta-1 globulin	0.39g/dL	[0.5-1.1]
Beta-2 globulin	0.68g/dL	[0.3-0.6]

DISCUSSION

Non-secretory myeloma is a rare myeloma subtype diagnosed as the demonstration of plasma cells ≥10% in the bone marrow with negative results on serum and urine electrophoresis and immunofixation studies; as well as evidence of end organ damage as a result of plasma cell proliferative disorder specifically hypercalcaemia, renal inefficiency, anaemia and bone lesions.[4] In this case, the patient presented with fractures of the left humerus and bilateral distal femoral fractures, abnormal bone marrow findings, elevated white cell count, elevated erythrocyte sedimentation rate (ESR), negative urine and serum protein electrophoresis, hypercalcaemia, hyperphosphataemia, intrauterine fetal death, hepatomegaly and negative urine Bence Jones Protein.

Upon the commencement of chemotherapy; a considerable improvement in the patient was noticed. These include: reduction in the ESR, white blood and neutrophil counts, improvement in the red cell count, normocalcaemia and normophosphataemia. Stability in platelet and lymphocyte counts was observed throughout the course of management of the patient. The general condition of the patient was fine after several courses of the chemotherapy. However, patient had candidiasis which can be adduced to the effect of the chemotherapy and pregnancy state.

We were unable to evaluate the patient for CD138 and translocation study [(t(11:14)] which have been documented to occur in patient with NSMM in 83% of the cases.[5] The overall survival of patient with NSMM has been documented to be higher than those patients with secretory multiple myeloma. Multivariate analysis of the factors responsible for survival in NSMM include the age and the time-period of diagnosis which were reported to significantly correlate with a better outcome.[6]

Our patient was a 39-year old woman. Several cases of non-secretory multiple myeloma have been reported among young adults. Ferjani *et al.* reported NSMM in a 22 year old man with symptoms resembling Gorham's disease.[7] In another case report by Yadav *et al.*, NSMM was seen in a 32 year old Indian woman presenting with diffuse sclerosis of affected bones interspersed with osteolytic lesions.[8] Furthermore, a rare case of NSMM was reported in a 23 year old female presenting with bilateral limb weakness, who was initially diagnosed with Pott's disease.[9] These reports indicate that NSMM is not limited to older adults of more than 50 years of age.

Our patient received mephalan, prednisolone and thalidomide in the course of treatment. A combination therapy with lenalidomide, bortezomid and dexamethasone was used by Nooka *et al* for induction followed by early or late transplant.[10] The authors reported a 3-year overall survival of >85% in all the patients with secretory and non-secretory multiple myeloma.[10] In another study, a gain in overall survival was achieved with the use of newer agents in both secretory and non-secretory multiple myeloma.[11]

A close look at the literatures showed that Gorham's disease and Pott's disease are the differential diagnoses of NSMM.[9] Gorham's disease, also called Gorham-Stout disease or vanishing bone disease is a rare and poorly understood disease condition characterised by progressive loss of bone tissues (osteolysis)

due to proliferation of blood vessels (angiomatosis) within the bone. This disease commonly affects the skull, spine, ribs and pelvis.[9]

In comparison with secretory multiple myeloma, non-secretory multiple myeloma patients have been reported to have lower incidence of renal failure and hypogammaglobulinaemia, lower median percentage of bone marrow plasma cells, higher incidence of neurological presentations and longer survival.[10]

Our centre is a low resource hospital; the use of new cross-sectional imaging modality is not available; we rely solely on serial bone marrow examinations for the quantification of neoplastic plasma cell in the monitoring of this patient.

CONCLUSION

A negative serum protein electrophoresis, a major diagnostic modality for multiple myeloma, does not rule out the disease. Physician should be aware of the presence of non-secretory multiple myeloma patients in our environment as majority of them do well on chemotherapy.

Abbreviations: CT – computed tomography; IgG – immunoglobulin G; IMWG – International Myeloma Working Group; M-protein – monoclonal protein; MRI – magnetic resonance imaging; PET/CT – positron emission tomography/computed tomography; sFLCr – serum free light chain ratio.

REFERENCES

1. Corso A, Mangiacavalli S. Non-Secretory Myeloma: Ready for a new Definition? Mediterr J Hematol Infect Dis. 2017; 9(1):e2017053. doi: 10.4084/MJHID.2017.053.
2. Chawla SS, Kumar SK, Dispenzieri A, Greenberg AJ, Larson DR, Kyle RA, Lacy MQ, et al. Clinical course and prognosis of non-secretory multiple myeloma. Eur J Haematol. 2015; 95(1):57–64. https://doi.org/10.1111/ejh.12478.
3. Rajkumar SV. Multiple myeloma: Update on diagnosis, risk stratification and management. Am J. of Haematology 2022; 97(8):1086-1107.
4. Terpos E, Apperley JF, Samson D, Giles C, Crawley C, Kanfer E, et al. Autologous stem cell transplantation in multiple myeloma: improved survival in nonsecretory multiple myeloma but lack of influence of age, status at transplant, previous treatment and conditioning regimen. A single-centre experience in 127 patients. Bone Marrow Transplant. 2003; 31:163–70. https://doi.org/10.1038/sj.bmt.1703818.
5. Avet-Loiseau H, Garand R, Lodé L, Harousseau JL, Bataille R Intergroupe Francophone du Myélome. Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. Blood. 2002; 101(4):1570–1571. https://doi.org/10.1182/blood-2002-08-2436.
6. Charliński G, Jurczyszyn A. Non-secretory multiple myeloma: Diagnosis and management. Adv Clin Exp Med. 2022; 31(1):95-100. doi: 10.17219/acem/141455.
7. Ferjani HL, Mariem M, Affess H, Maatallah K, Kaffel D, Jenri M, et al. Non-secretory multiple myeloma in a young man mimicking The Gorham's disease: Case Report and Literature Review. Rom J Intern Med. 2022; 60(1):77-84.
8. Yadav RR, Singh A, Mathur SP,Mangal Y, Singh M. Non-secretory multiple myeloma presenting with diffused sclerosis of affected bones interspersed with osteolytic lesions. Br J. Radiol. 2009; 82(974):e29-31.

9. Neeravari A, Netravati P, Mohammed R, Ragupathi AR, Nagarajappa AH. Atypical imaging features of non-secretory multiple myeloma. Annal of Diagn Pathol; 2011; 268:72-79.
10. Nooka A, Langston A, Waller EK, Heffner LT, Gleason C, Muppidi S, et al. Early versus delayed autologous stem cell transplant (ASCT) in patients receiving induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD) for newly diagnosed multiple myeloma (MM). J Clin Oncol. 2013; 31(15_suppl):8540. DOI: 10.1200/jco.2013.31.15_suppl.8540