

## Immunoglobulin A Myeloma in a Newly Diagnosed Sickle Cell Disease Patient

### Abstract

Several neoplasms including hematological malignancies occurring in very few patients with sickle cell syndromes have been reported in literature, particularly as survival among these patients and diagnostic accuracy have continued to improve. Multiple myeloma (MM) has rarely been reported in patients with hemoglobin (Hb) S + C. We report a 65-year-old retired banker who was recently diagnosed with HbS + C. This patient developed MM with markedly elevated erythrocyte sedimentation rate, mild anemia, 80% bone marrow plasmacytosis, and elevated serum immunoglobulin A level, while plain X-ray of the lumbosacral spine showed multilevel vertebral collapse.

**Keywords:** Anemia, immunoglobulin A, multilevel vertebrae collapse, multiple myeloma, plasmacytosis, sickle cell disease

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### Introduction

Reports of hematological malignancies in patients with sickle cell disease (SCD) are sparse – only two cases (Hodgkin's disease and Acute myeloblastic leukemia) were reported before 1960.<sup>[1]</sup> Since then, there has been significant improvement in the care of patients with SCD and hence increased survival in these patients. Therefore, more hematological malignancies are now being reported including acute lymphoblastic leukemia, chronic myeloid leukemia, multiple myeloma (MM), non-Hodgkin's lymphoma, and cutaneous T-cell lymphoma.<sup>[1]</sup> To the best of our knowledge, this is the first report of MM in a patient with hemoglobin (Hb) S + C; previous reports of MM in SCD were in HbS (sickle cell anemia) and in HbS-beta<sup>+</sup>-Thal.<sup>[2]</sup>

MM and SCD have different etiopathogenesis. While MM is an acquired neoplasm of terminally differentiated B lymphocytes, SCD is an inherited disorder caused by a mutation in position of beta globin chain of hemoglobin molecule resulting in structural defect in the beta globin chain with consequent malfunction with reduced oxygen tension. The occurrence of this malignancy in a SCD patient is very uncommon and deserves reporting.

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### Case Report

Patient is a 65-year-old male, a retired bank manager, who was first seen at the Haematology Day Care Unit in August 2016 having been referred from the Geriatric Center of the University College Hospital on account of a 5-month history of severe (score 7 of 10) and recurrent pain of the rib cage and low back. The pain was nonradiating and severe enough to disturb his normal daily activities. He had no associated constitutional symptoms. He presented to the source of referral at the onset of the illness where his hemoglobin electrophoresis was determined as HbS + C for the very first time ever. Analgesia was prescribed to him and this resulted in significant relief of the pain. Further questioning revealed that he had bone pain crisis in childhood but SCD was not diagnosed. However, the last episode of such was 35 years ago. He was never transfused with blood. He was married in a nuclear family with five children who are all well and alive. He does not smoke cigarette but stopped taking alcohol about 5 years ago.

Examination at presentation revealed a middle-aged man in no obvious distress, afebrile, tinge of jaundice, fair hydration status, no significant peripheral lymphadenopathy, and no pedal edema.

**How to cite this article:** Olaniyi JA, Shonde-Adebola KB. Immunoglobulin a myeloma in a newly diagnosed sickle cell disease patient. *Int J App Basic Med Res* 2018;8:177-80.

Received: 30 October, 2017.  
Accepted: 11 January, 2018.

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#### Access this article online

**Website:**  
www.ijabmr.org

**DOI:**  
10.4103/ijabmr.IJABMR\_107\_17

#### Quick Response Code:



Vital signs were within normal and breath sounds were vesicular. Moderate tenderness was elicited over the lower three ribs bilaterally. He was managed as a newly diagnosed HbS + C patient in moderate bone pain crisis and discharged home to complete investigations on outpatient basis and to return in a week for review with results. He, however, defaulted follow-up appointment only to return 4 weeks after with a more terrible pain and inability to stand from sitting and lying positions. He decided to go to a private facility from where he was referred back to the Hematology Department because an abdominal ultrasonography result revealed splenomegaly and para-aortic lymphadenopathy and hence a lymphoma was strongly suspected. Laboratory investigations revealed a full blood count with anemia (packed cell volume 27%), white blood cell 2700/mm<sup>3</sup>, and platelet count of 186,000/mm<sup>3</sup>. He had an elevated prostate-specific antigen of 15.6 ng/ml (0–4). Radiological findings include cervical spondylosis; anterior wedging of L2 vertebral body; and reduction in the height of T9, L1, L2, and L3 vertebral bodies. Further physical examination mainly established moderate tenderness over the anterior lower ribs and the flanks bilaterally and over the lumbosacral spine. At this point, working diagnosis was metastatic prostatic carcinoma rule out lymphoma in an HbS + C.

He was admitted for pain control and further evaluation. A bone marrow aspiration carried out revealed bone marrow plasmacytosis of 80% including binucleate forms and a few plasmablasts, which were suggestive of MM [Figure 1]. Further investigations such as serum protein electrophoresis, immunoglobulin quantitation, serum- and urinary-free light chains, skull and pelvic X-rays, urinary Bence Jones protein, and beta-2 microglobulin were requested to further confirm diagnosis. Patient could only afford beta-2 microglobulin and immunoglobulin quantitation. Result of beta-2 microglobulin was 2.7 ng/L (within normal limit) and immunoglobulin quantitation showed elevated immunoglobulin A (IgA) of 17.6 µg/dl; hence, a diagnosis of IgA myeloma was made in International Staging System-stage 1.

He was commenced on chemotherapy with melphalan (PO 7.5 mg/m<sup>2</sup> × 5 days), prednisolone (PO 60 mg/m<sup>2</sup> × 5 days), and thalidomide 100 mg daily in a 42-day cycle. Neurosurgeons equally co-managed on account of the vertebral and lumbar spine lesions and pain. He was initially kept on strict bed rest to stabilize the spine. He later had magnetic resonance imaging of lumbosacral spine and flexion/extension radiological study of the lumbosacral spine which was found satisfactory. He was subsequently commenced on ambulation, after a thoracolumbar spine orthosis was applied.

He has tolerated so far, five cycles of chemotherapy, as well as, physiotherapy very well and have made a significant improvement. The bone pain has resolved and he is now fully ambulant without support. He has also received three doses of intravenous zoledronic acid 4 mg monthly.

## Discussion

SCD is an inherited chronic hemolytic anemia and varied clinical manifestation ranging from very bad clinical to types with good clinical course as determined by many well-known and well-established genetic and environmental factors. The diagnosis of SCD in our patient for the first time at age 65 years shows that his disease runs a very mild clinical course. Even though he experienced occasional but mild bone pain in childhood, bone pain crisis event subsided after the age of 35 years. His mildly elevated hemoglobin F and A2 levels (suggestive of beta thalassemia co-inheritance) may somehow contribute to this mild clinical course of disease [Table 1]. The resurgence of bone pain before diagnosis of MM is most probably attributable to hyperviscosity caused not only by sickle cell vaso-occlusion but also by high plasma level monoclonal IgA produced by the clone of abnormal plasma cells in the bone marrow. This phenomenon was equally observed by Anderson *et al.*, who postulated that the increased frequency of vaso-occlusive crisis that occurred in their patient in the months before diagnosis of myeloma was due to this cell-protein interaction with resulting enhancement of whole blood viscosity and the sickling phenomena.<sup>[3]</sup>

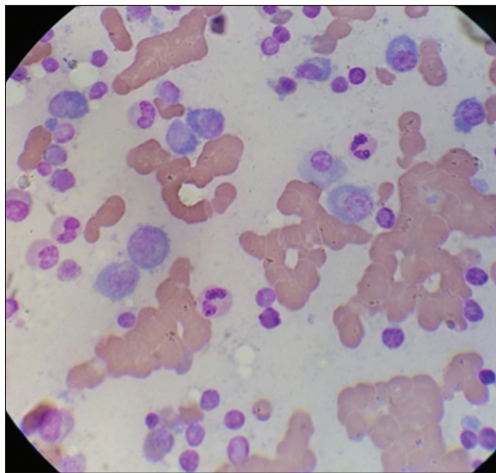
MM is a B-cell malignancy characterized by the accumulation of terminally differentiated clonal plasma cells in bone marrow, the production of a monoclonal immunoglobulin detectable in serum and/or urine, and the presence of lytic bone lesions.<sup>[4]</sup> MM has rarely been reported in patients with HbS + C. Certain factors have been shown to increase the risk of plasma cell dyscrasias in patients with sickle cell syndromes. These include increased level of interleukin-6, renal dysfunction, a combination of vaso-occlusion and hyperviscosity, and increased survival.<sup>[1]</sup> Our patient is 65 years old which is the documented median age at diagnosis of myeloma cases.<sup>[5]</sup> He had a high level of hemoglobin F of 4.6%, which could have ameliorated his SCD and in turn contributed to his survival. He had an elevated erythrocyte sedimentation rate of 140 mm/h, which was responsible for the heightened vaso-occlusion due to additional insult from hyperviscosity state.

The diagnosis of symptomatic MM requires the presence of an M-protein in serum and/or urine with decreased normal immunoglobulins (immunoparesis), the presence of increased bone marrow plasma cells or plasmacytoma, and related organ or tissue impairment (end-organ damage including bone lesions. Our index case has elevated serum immunoglobulin-A (17.6 g/L), low levels of immunoglobulins G (5.3 g/L) and M (0.3 g/L), 80% bone marrow abnormal plasmacytosis, and multilevel vertebral lesions (L2 vertebral collapse, osteopenia of T2-T10, anterior wedge compression of L1, and severe back pain and paraparesis) [Figure 2]. Bone disease is seen in 80% of newly diagnosed symptomatic MM patients, and spine is the site that is most frequently affected by

**Table 1: Relevant laboratory parameters**

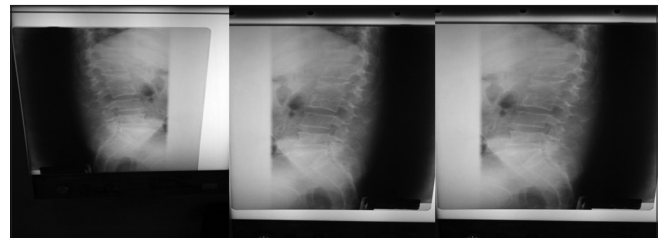
Date	Investigation	Result	Reference range
September 16, 2016	$\beta$ 2 microglobulin	2.7 ng/L	0-3 $\mu$ g/mL
September 2, 2016	Immunoglobulin quantitation	IgA=17.6 g/L $\uparrow\uparrow\uparrow$ IgG=5.3 g/L $\downarrow$ IgM=0.3 g/L $\downarrow$	0.7-4.0 7-16 0.4-2.3
September 2, 2016	E/U/Cr/Ca <sup>2+</sup>	Within normal limits Urea=34 mg/dl Cr=0.9 mg/dl Ca=8.6 mg/dl UA=6.2 mg/dl PO3- =4.1 mg/dl	15-45 0.5-1.5 8.5-10 2.0-7.0 2.5-4.5
	LFT	Total protein=8.1 g/dl, albumin=4.2 g/dl Immunoglobulin 3.9 g/dl AST, ALP, gamma GT within normal limits	5.5-8.0 3.5-5.0
	ESR	140 mm/h $\uparrow\uparrow\uparrow$	0-20
	Hemoglobin quantitation	HbS=45.8% HbC=42.2% HbF=4.6% A2=3.1% A1C=9.7%	
	PSA	15.6 ng/mL $\uparrow\uparrow$	0-4
	Fasting plasma glucose	92 mg/dl	(Normal)
	Malarial parasite	Not seen	
	Urinalysis	Normal	
	CEA	3.0 ng/mL	

ALP: Alkaline phosphatase; AST: Aspartate transaminase; CEA: Carcinoembryonic antigen; PSA: Prostate specific antigen; ESR: Erythrocyte sedimentation rate; LFT: Liver function test;  $\downarrow$ : Reduced;  $\uparrow$ : Increased or elevated



**Figure 1: The bone marrow aspiration cytology at high magnification, showing severe rouleaux, increased plasmacytosis, mild depression of erythropoiesis, and sequential maturation of myeloid series**

myeloma-induced osteoporosis, osteolysis, or compression fractures.<sup>[5]</sup> It is important to note that our patient did not prevent with laboratory evidence of renal impairment and hypercalcemia which are important components of the CRAB criteria. Furthermore, there was no laboratory evidence hypoalbuminemia or elevated beta-2 microglobulin which puts his disease stage at ISI Stage I.



**Figure 2: The scanned X-ray images of the spine showing L3/L4 vertebral collapse**

This patient had a stable hematocrit in the range between 24% and 28% and has never required blood transfusion even though he is a SCD patient and receiving standard chemotherapy for MM. The patient has responded excellently to applied standard chemotherapy (melphalan, thalidomide, and prednisolone) as he is now fully ambulant.

This case highlights the unexpected and rare coexistence of SCD (HbS + C) and MM and unusual delay in the SCD in our environment in spite of the positive history of recurrent bone pain. Therefore, hemoglobin genotyping should be ensured for all as at now, routine medical examination for all should be encouraged, and SCD patients being followed up should be screened for certain malignancies when suspected before it gets to an advanced stage. A stitch in time saves nine.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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