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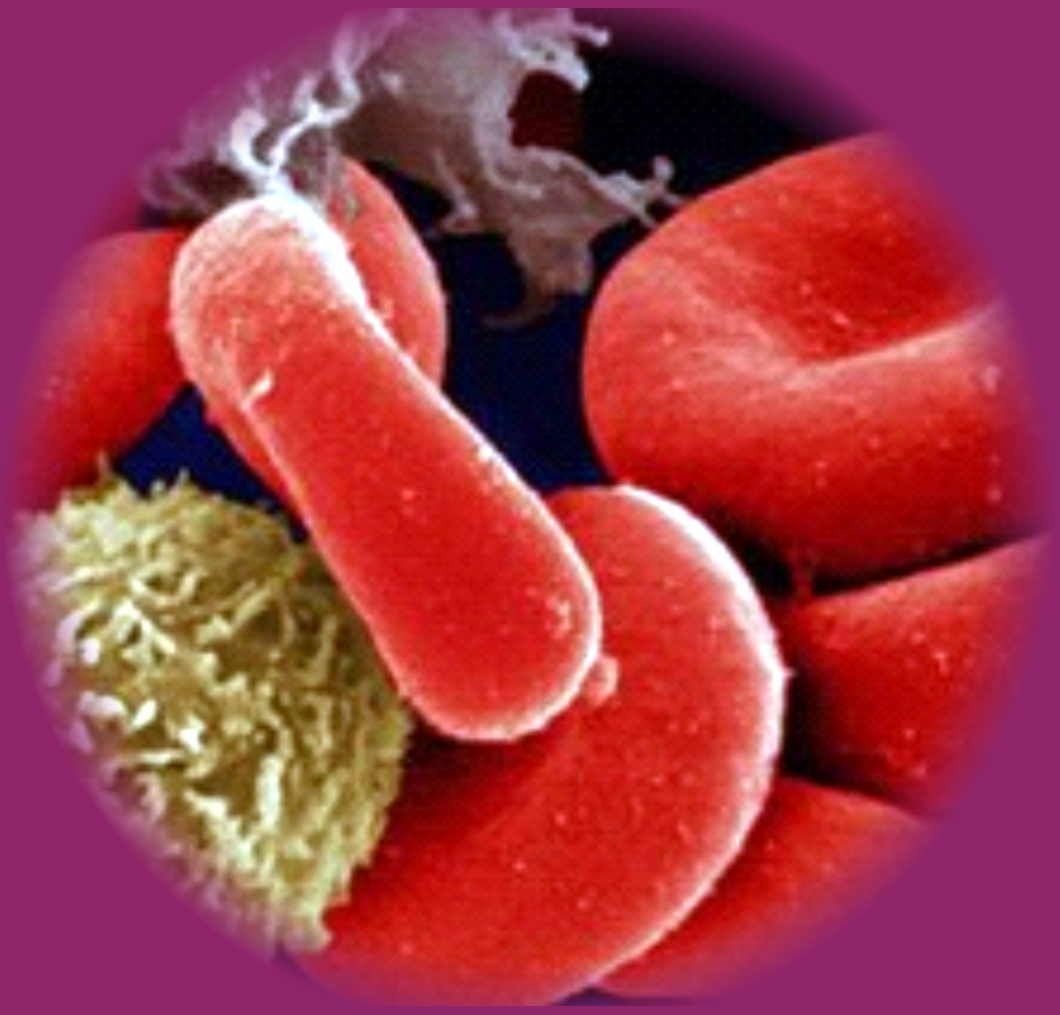

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Multiple Myeloma as a Secondary Malignancy in a 44-year old Male Nigerian with Chronic Myeloid Leukaemia: A Case Report

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SUMMARY

The occurrence of multiple myeloma (MM) and chronic myeloid leukaemia (CML) in the same patient is very rare. Cytopenias may develop in patients with CML during the course of treatment with tyrosine kinase inhibitors (TKIs) as a result of drug-related bone marrow suppression or disease progression. This report describes a rare case of MM which presented with persistent anaemia and neutropenia after 35 months of diagnosis of CML in a 44-year old male Nigerian who was treated with Imatinib mesylate. During the course of investigation of the cause of the cytopenias, bone marrow aspiration revealed plasmacytosis of 40%. Serum protein electrophoresis and immunofixation revealed elevated monoclonal IgG 19.2g/L (reference: 7.0 – 16.0g/L) and *kappa* (*k*) light chain 32.9mg/L (reference: 3.3 – 19.4mg/L). Serum free-light chain ratio was 4.3 (reference: 0.26 – 1.65). Urinary Bence-Jones protein (BJP) was detected, identified on immunofixation as *k* light chain protein. Serum beta-2-microglobulin was 2.4mg/L (reference: 1.0 - 2.0mg/L). The patient was treated with chemotherapy and autologous stem cell transplant (Auto-SCT) at the Hammersmith Hospital, London, United Kingdom. To our knowledge, this is the first report of the development of secondary MM in a Nigerian CML patient on Imatinib therapy and also the first report of the treatment of such with Auto-SCT.

Keywords: multiple myeloma, chronic myeloid leukaemia, cytopenias, Imatinib mesylate

INTRODUCTION

Multiple myeloma (MM) is a malignancy of lymphoid origin, characterised by monoclonal proliferation of malignant plasma cells in the bone marrow which secrete monoclonal proteins that are detectable in serum and/or urine. Diagnosis of MM is based on the presence of bone marrow plasmacytosis of at least 10%, in addition to detection of monoclonal protein in the serum, significant monoclonal light chain protein in the urine with manifestations of end-organ damage such as anaemia, renal failure, hypercalcaemia or lytic bone lesions. [1] Multiple myeloma is mainly a disease of the elderly with a median age of 60 years at diagnosis, commoner in males and Africans. [2] Majority of Nigerian patients present with advanced disease which is associated with a shortened survival. [2] Treatment for MM in our centre involves mainly alkylating agents like Melphalan or Cyclophosphamide in combination with steroids such as Prednsolone or Dexamethasone and immunomodulatory agents such as Thalidomide. [2] Stem cell transplant for MM is not an option for most Nigerian patients due to lack of facilities, financial constraints or advanced age at presentation.

Chronic myeloid leukemia (CML) is a triphasic clonal disorder of myeloid origin characterized by the presence of the Philadelphia (Ph) chromosome which is an acquired reciprocal chromosomal translocation involving chromosomes 9 and 22 i.e. t(9;22) (q34;q11). This results in the formation of a chimeric BCR/ABL fusion protein which is a constitutionally active tyrosine kinase that confers a high proliferative capacity on the malignant myeloid cells. [1, 3] Chronic myeloid leukaemia is a rare disease with an estimated incidence of one to two cases per 100,000 per

year. [3] The median age at diagnosis of CML in Nigerians is about 37 years compared to about 53 years in Caucasians. [3] The conventional treatment of CML involves the use of cytoreductive agents such as Hydroxyurea. There was significant progress in the treatment of CML following the development of targeted therapy with the approval of the first-line tyrosine kinase inhibitor (TKI), Imatinib mesylate by the United States' Food and Drug Administration (FDA) in 2001. [3] Imatinib has been available free for Nigerian patients since 2003 via the Max Foundation's initiative; the Glivec International Patient Assistance Programme (GIPAP) in conjunction with Novartis Pharmaceuticals. The use of TKIs has resulted in significant improvement in prognosis and survival of CML patients such that allogeneic stem cell transplant is only considered in patients who are intolerant or resistant to all TKIs. [3] The concomitant occurrence of MM and CML. in the same patient is very rare with few reports in literature. [1, 4]

No single case of myeloma occurred as a second cancer among the 51(3.5%) of 1,445 CML/MPNs patients treated with tyrosine kinase inhibitors (TKIs). [5]. Multiple myeloma in CML patients may be detected during routine investigation of cytopenias and/or myelodysplasia. [6] The co-existence of the two malignancies may worsen the clinical course and complicate the treatment of the affected patient. There is no identifiable aetiological link between the two diseases because the malignant cells in MM are lymphoplasmacytic while those in CML are myeloid, thus they are completely different. [1] Cases of patients having the two malignancies concurrently have been reported both before and since the Imatinib mesylate era. [1, 4]

CASE REPORT

A 44-year old male Nigerian presented at the haematology clinic in April 2011 with a six-month history of abdominal swelling and fever. Physical examination showed an apparently healthy looking man, weighing 105kg, with a height of 1.72m, hepatomegaly of 8 cm below the right costal margin and splenomegaly of 6cm below the left costal margin. Complete blood count (CBC) at presentation revealed haematocrit of 43%; platelet count of 216 x 10^9/L and total white blood cell count (WBC) of 76 x 10^9/L. The pulse rate was 72/min while the blood pressure (BP) was $^{130}/_{90}$ mmHg. The peripheral blood film confirmed leucocytosis comprising mainly of myelocytes, metamyelocytes and segmented neutrophils (Figure 1).

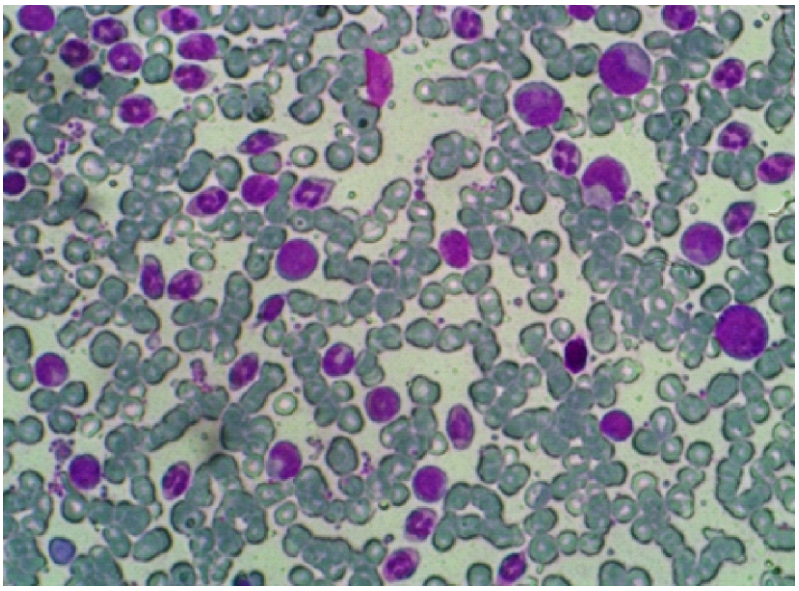

Figure 1: CML in chronic phase - Peripheral blood film showing leucocytosis comprising of granulocytes at different stages of maturation. Leishman stain, x 400 magnification.

Cytogenetic analysis showed the presence of Philadelphia chromosome and deletion of long arm of chromosome 7 (7q-). [7] Quantitative polymerase chain reaction (qPCR) analysis revealed the presence of BCR-ABL transcripts of 32%. Imatinib (Glivec©, Novartis Pharma AG, Basel Switzerland) was commenced at a dosage of 400mg daily in May 2011.

He achieved complete haematological remission (CHR) within the first month of therapy. Imatinib-related significant neutropenia developed after three months of therapy, which resolved after withdrawal of the drug for seven days. However, he developed persistent anaemia and neutropenia after 34 months of using Imatinib (Table 1) which required frequent treatment-interruptions and subsequent reduction of Imatinib dosage; initially to 300mg and eventually to 200mg daily with no improvement. The plasma level of Imatinib was assayed while he was on the 200mg dose and was found to be within the effective therapeutic range at 1,330ng/ml (reference: greater than 1000ng/ml) after 13 hours of drug administration. There was no response to treatment with erythropoietin and granulocyte-colony stimulating factor (G-CSF). He was in complete molecular remission (CMR) at this time (Table 2).

Table 1: Haematological parameters at diagnosis of multiple myeloma and after stem cell transplant

Parameter	July 2014	June 2016
Haemoglobin (g/dL)	11.0	14.0
WBC (x 10^9/L)	1.5	4.6
Absolute Neutrophils count (x 10^9/L)	0.6	2.8
Platelets (x 10^9/L)	297.0	246.0

Table 2: Serial BCR-ABL analysis by qPCR

Month	BCR-ABL %
FEB 2013	0.020
MAY 2013	0.006
JAN 2014	0.010
JUL 2014*	0.007*
OCT 2014	0.007
NOV 2015#	0.003#
JUN 2016	0.0023

** Myeloma diagnosed*
 # Nine months after autologous stem cell transplant

A bone marrow aspiration done to investigate the cytopenias surprisingly revealed plasmacytosis of 40% (Figure 2). Subsequently, serum protein analysis revealed IgG*k* paraprotein and elevated serum free light chain ratio (Figure 3). [8] Urinary BJP was positive which was identified on immunofixation as *k* light chain protein 0.9mg/L (reference: 0mg/L). Serum beta-2-microglobulin was mildly elevated at 2.4 mg/L (reference range: 1.0 - 2.0 mg/L). In view of the anaemia, bone marrow plasmacytosis and biochemical findings (Table 3), a diagnosis of multiple myeloma, ISS stage 1 was made.

He elected to seek further treatment at the Hammersmith Hospital, London, United Kingdom where he was treated with six cycles of Cyclophosphamide, Thalidomide and Dexamethasone (CTD) followed by autologous stem cell transplantation (Auto-SCT) for MM in February 2015. Imatinib therapy for CML continued during treatment for MM. He is presently on 300mg Imatinib daily and Zoledronate 4mg monthly. [9] Two years after Auto-SCT; he remains in complete molecular remission of CML and serum paraprotein is undetectable.

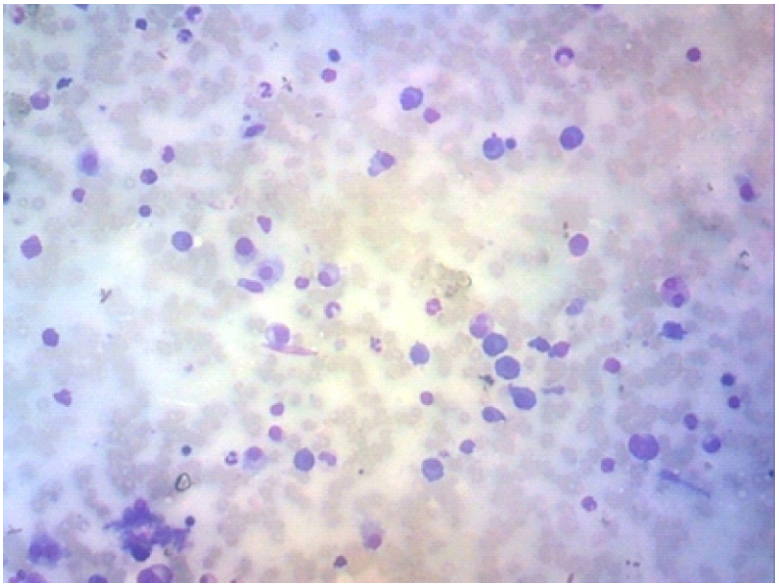

Figure 2: Multiple myeloma - bone marrow aspirate showing increase in plasma cells (black arrows). Leishman stain, x 100 magnification.

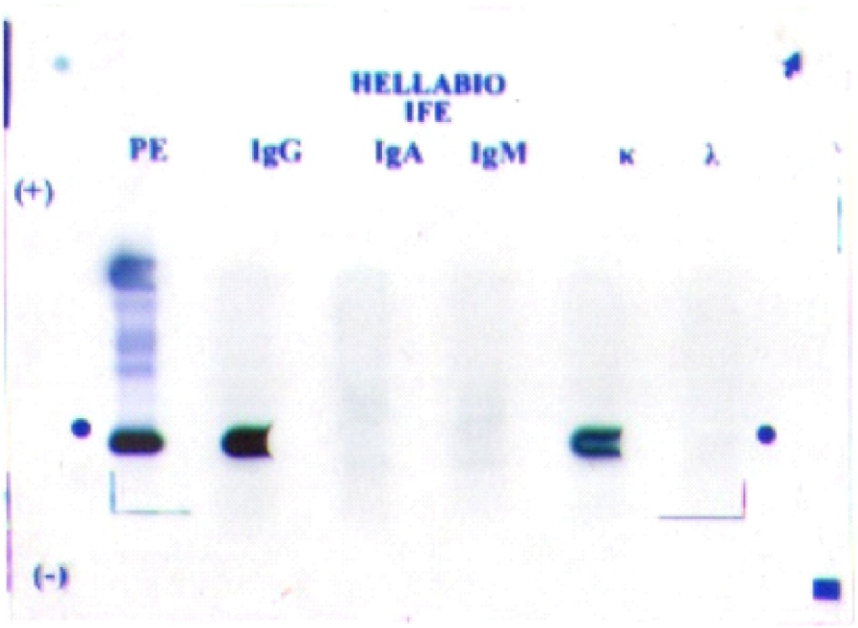

Figure 3: Multiple myeloma – Serum protein immunofixation electrophoresis showing the electrophoretic pattern with a monoclonal band in the gamma-globulin identified as IgG kappa. Hellabio gel IFE kit, Amido black stain

Table 3: Biochemical parameters at diagnosis of multiple myeloma and after stem cell transplant

Parameter	July 2014	February 2015	Reference range
Total protein (g/L)	79.0		66.0 - 83.0
Albumin (g/L)	47.7		35.0 - 52.0
Globulin (g/L)	31.3		20.0 – 45.0
Albumin/Globulin ratio	1.5		0.9 – 2.7
Alpha-1-globulin (g/L)	2.4		2.1 – 3.5
Alpha-2-globulin (g/L)	7.0		5.1 – 8.5
Beta-globulin (g/L)	6.6		6.0 – 9.4
Gamma-globulin (g/L)	15.3		8.0 – 13.5
IgG (g/L)	19.2	4.6	7.0 – 16.0
IgA (g/L)	0.24	0.8	0.70 – 3.50
IgM (g/L)	0.12	0.2	0.5 – 2.50
Serum Kappa (mg/L)	32.9	18.5	3.3 – 19.4
Serum Lambda (mg/L)	7.6	6.6	5.7 – 26.3
Serum Free light chain ratio	4.3	2.8	0.26 – 1.65
Serum Calcium	2.2	2.4	2.1 – 2.6
Serum Creatinine	88.0	68	57.0 – 113.0

DISCUSSION

Multiple myeloma was diagnosed in the patient during the investigation of anaemia and neutropenia that were assumed to be Imatinib-related. Similar cases have been previously documented. [1, 4] The cytopaenias were not related to Imatinib therapy as there was no improvement on dosage reduction. The plasma levels of Imatinib remained within the therapeutic range even on the reduced dosage, thus the molecular response was sustained. Diagnosis of MM was based on presence of bone marrow plasmacytosis of 40%, significant serum level of monoclonal IgG, significant urinary kappa light chain excretion, hypoglobulinaemia of normal immunoglobulins and haemoglobin (Hb) of 11.0 g/dL (our laboratory reference: 14.0 -16.0g/dL for males) in line with the diagnostic criteria for MM. [1, 4] Diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was excluded based on the presence of anaemia. [1]

The diagnostic karyotype was associated with a 7q- abnormality. The additional chromosomal abnormality was not indicative of disease progression or clonal evolution because it was present at diagnosis. [7] Chromosome 7q contains critical tumour suppressor genes that are inactivated by deletions thus predisposing to increased risk of malignancies. [10] The impact of this additional chromosomal abnormality on the course of the patient's CML is unknown as 7q- is more commonly found in acute myeloblastic leukaemia and myelodysplastic syndrome in which it confers a high risk of resistance to treatment. [11] However, 7q- has also been described as a secondary clonal mutation in patients with lymphoid malignancies such as multiple myeloma and chronic lymphocytic leukaemia. In such patients, a large clone size is associated with a risk for subsequent development of therapy-related acute myeloid leukaemia or MDS. [12] The *IgG κappa* myeloma was diagnosed early, when the patient still had normal serum albumin and calcium levels. The only myeloma-related end-organ damage present in the patient at diagnosis of the secondary malignancy was mild anaemia with Hb 11 g/dL. There were no lytic bone lesions and the renal function was normal. The MM was detected at an early early stage because he was being followed-up for CML. This is in contrast to patients with primary MM seen in our centre who typically present with advanced end-organ damage. [2] In addition, he was younger than most patients with primary MM. [2] Lytic bone lesions and renal impairment were also absent in some previously reported cases of secondary myeloma. [1, 4]

Myeloma was treated with CTD regimen, followed by Auto-SCT. This is the first report of the use of Auto-SCT in a patient with concurrent CML and MM. Most of the previously reported patients were older than 65 years hence, were ineligible for stem cell transplantation. [1] The presence of plasma cells and monoclonal paraprotein did not impact negatively on the

course of the CML, as evidenced by the maintenance of complete molecular remission from the time of diagnosis of MM to the post-transplant period (Table 2).

There was no clonal chromosomal evolution, thus suggesting lack of a common pluripotent stem cell or common clonal origin for the two diseases. In a previous report of a similar case, fluorescent in-situ hybridisation (FISH) testing showed that the plasma cells did not express the Ph chromosome. [4] Imatinib therapy continued during the treatment for myeloma because immunosuppressive chemotherapy was also used for stem cell mobilisation. In a situation where stem cell transplant is not an option, Imatinib therapy may be suspended during active myeloma therapy to prevent synergistic myelosuppression. [4] The risk of relapse or progression of the untreated tumour is higher when chemotherapy is given for only one of the diseases. [4] Zoledronate and other bisphosphonates have been associated with inhibition of proliferation and induction of apoptosis in CML cell lines; alone or in combination with Imatinib. [9] Thus, the continuous use of prophylactic bisphosphonate in this patient will further enhance haematologic and molecular response to Imatinib.

In conclusion, it should not be assumed that all cases of cytopenias in CML patients are related to TKI therapy or disease progression, hence patients should be adequately investigated. Concurrent CML and MM is a potentially treatable disorder and does not always portend disaster.

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/2. Cytogenetics with FISH, CISH.

/3. Haematopathology – diagnosis of Lymphomas.

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Deadline for abstract submission 12.00 pm June 30 2018

Late breaking Abstract submission July 12-16 2018.

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