CASE REPORT

Coexistence of JAK2 and BCR-ABL mutation in patient with myeloproliferative neoplasm

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ABSTRACT

The World Health Organisation (WHO) classifies myeloproliferative neoplasm (MPN) into BCR-ABL positive chronic myeloid leukaemia (CML Ph^+) and Ph^-MPN. The JAK2 V617F mutation is specific for Ph^-MPN and occurs in approximately 50% of primary myelofibrosis. Earlier reports suggest that the occurrence of JAK2 and BCR-ABL mutations are mutually exclusive. However, recent reports have documented the coexistence of BCR-ABL and JAK2 mutation in the same patient mostly following treatment with tyrosine kinase inhibitors (TKIs). We thus report a 60-year-old male with atypical clinical and laboratory features of MPN and the presence of both BCR-ABL and JAK2 Mutations.

Key words: BCR-ABL, CML, JAK2, mutation, myelofibrosis

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INTRODUCTION

Chronic myeloid (myelogenous) leukaemia (CML) is a clonal myeloproliferative neoplasm characterised by a reciprocal rearrangement and fusion of the BCR genes on chromosome 22 and ABL gene on chromosome 9. This mutation leads to the productions of an oncoprotein that can be *p190, p210 or p230* depending on the breakpoints of the BCR-ABL. This oncoprotein is constitutively active leading to uninhibited cell proliferation that is the main driving factor for the progression of the disease.[1,2]

Chronic myeloid leukaemia is said to have a uniform worldwide incidence of 1-2/100,000.[3] In the United States of America, the incidence is 1.1 and 2 per 100,000 population in female and males, repectively.[2] The mean age at diagnosis of CML is put at 60-65 years even though about 30% of new diagnosis are less than 45 years old.[2,4] The median age at diagnosis of CML in Nigeria is 38 years and very uncommon by age 60.[3,5]

Janus Kinases (JAK) are a group of proteins involved in normal cell signalling.[6] However, reports have shown that the V617F somatic mutation of JAK2 gene on chromosome 9 and the finding that it is found in all Philadelphia-negative (Ph−) myeloproliferative diseases such as polycythaemia vera (PV) and essential thrombocythaemia (ET) but absent in Philadelphia-positive (Ph+) CML.[7-9] Recent reports however indicate that some cases of CML may also paradoxically present with both Ph+ and JAK2V617F mutations.[10,11] This case report is to highlight the occurrence of both Ph+ and JAK2V617F mutations in a patients in our centre.

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CASE REPORT

A 60-year-old male retired soldier presented with a 4-month history of recurrent low-grade fever, cough, abdominal distention and remarkable weight loss. He was chronically ill looking, wasted, moderately pale, splenomegaly of 16 cm, and hepatomegaly of 6 cm. Haematological investigation showed packed cell volume (PCV) of 21.7% (37.0-53.0%), total white blood cell (WBC) count of 30.5 × 10^9/L (3.0-13.2 × 10^9/L) with differentials of granulocyte of 36.3%, lymphocyte 53.6%, medium sized (MID) 10.1%. Platelet count was 324 × 10^9/L. Other investigations revealed erythrocyte sedimentation rate (ESR) >80 mm in the first hour. Chest radiograph (hilar opacities), mantoux test (negative) and sputum acid bacilli (negative). The patient was then classified as smear-negative tuberculosis. He was then placed on empirical anti tuberculosis therapy according to the Nigerian national guideline for tuberculosis therapy. However, there was no clinical response after 4 weeks.

On haematological review he was found to be emaciated, mildly pale, mildly dehydrated without significant peripheral lymphadenopathy. The chest was clinically clear, and the cardio-vascular system was stable. He has an enlarged spleen measuring 24 cm below the left coastal

margin. Repeat haematological investigations revealed a PCV of 20.8%, WBC count of 48.8 × 10^9/L differentials were neutrophils 70%, lymphocyte 8%, monocyte 4%, band forms 2%, metamyelocyte 10% and myelocyte 6%. The platelet count was 769 × 10^9/L. The peripheral blood film showed 416 nucleated red blood cells (NRBC) per 100 WBC, macrothrombocyte, leuco-erythroblastosis, tear drop poikilocytes, target cells, fragment cells and hypogranular granulocyte with bizarre segmentation. Bone marrow aspiration (BMA) revealed myeloid:Erythroid reversal and increased megakaryocytopoiesis. Biopsy findings were consistent with increase dysplastic megakaryocyte and moderate fibrosis.

These laboratory and clinical findings led to a diagnosis of CML (accelerated phase) to rule out cellular phase of myelofibrosis (MF); thus, cytoreductive therapy was started with hydroxyurea (HU) for 3 months while awaiting results of molecular biologic test. The test turned out positive for BCR-ABL1 (e14a2/e13a2) 61.6%. The patient was then commenced on Imatinib at 400 mg once daily. However, response to Imatinib was sub-optimal; thus, JAK2 analysis was requested on the same sample, and it turned out to be positive for the JAK2 mutation (exon14V617F). He was then maintained on Imatinib, blood transfusion support, erythropoietin and regular follow-up, but the patient died in a peripheral hospital about 10 months after diagnosis.

DISCUSSION

It was initially hypothesised that occurrence of both BCR-ABL and JAK2V617F mutation could be mutually exclusive in CML or exist in independent clones.[12-15] However, the possibility of a coexistence mutation has so far been shown to occur on a background of a previous treatment with a tyrosine kinase inhibitor (TKI).[10,13,16] Other studies show that simultaneous occurrence of the two is possible without TKI therapy.[10,15-18]

The presentation of this case although atypical warrants that a diagnosis of CML in acceleration be entertained. Also, due to the thrombocytosis, leucoerythroblastosis and marrow fibrosis thus myelofibrosis (MF) was a strong differential diagnosis. The brief response to empirical anti-tuberculosis agents may be due to recrudescence of latent TB due immunosuppresion that accompanies malignancies.

In this patient, simultaneous occurrence of BCR-ABL and JAK2V617F gene mutation in the major exons e13/14 and exon 14, respectively, is noted. Literature is still controversial as to the possibility of a single clone carrying both mutation, or they are independently derived from different susceptible polyclonal stem cells.[13,15-18] This does not exclude the possibility that the BCR-ABL–positive clone might have represented a sub-clone of JAK2V617F mutated cells, which had growth advantage either by direct suppression of BCR-ABL by the JAK2V617F cells or as a result of treatment with TKI.[10,13,15-18] This case represents the appearance of BCR-ABL and JAK2V617F in a patient before TKI therapy in our centre for the first time.

This case report underscores the need for haematologist and other physicians alike to be vigilant, especially if myeloproliferative neoplasm (MPN) patients present with atypical features.

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