CASE REPORT

Potential Link Between Janus Kinase 2 Mutation and Renal Artery Stenosis Leading to Refractory Secondary Hypertension - A Case Report

Lakshmipriya V, Vanishree Murugavel, Jayaganesh

Abstract

Polycythaemia vera (PV) is a rare BCR/ABL negative chronic myeloproliferative neoplasm characterized by increased red cell mass, splenomegaly and JAK2 V617 mutation in nearly all patients. The frequency of acquired Janus kinase 2 (JAK 2) V617 mutation is about 95% in PV patients.Herein,we report a case of renal artery stenosis leading to uncontrolled hypertension in apatient with PV having JAK2 V617F mutation, high haematocrit levels and erythrocytosis.A syndrome of refractory secondary hypertension, renal artery stenosis and erythrocytosis could be seen in the same patient.However, renovascular hypertension may be a thrombotic complication of primary erythrocytosis seen in PV patients and may lead to secondary erythrocytosis. Thus, patients with PV having JAK2 V617 mutation must be evaluated for thrombosis and optimally managed when hypertension coexist.

Keywords

Erythrocytosis, Hypertension, JAK 2 Mutation, Polycythaemia, Thrombosis

Introduction

Polycythaemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are BCR/ABL negative chronic myeloproliferative neoplasms (MPN) characterized by clonal expansion of an abnormal hematopoietic stem cell[1,2]. PV is a relatively rare disease and its incidence has been estimated to be 2.3–2.8 per 100,000 persons/year with a male/female ratio of 1.2:1[1]. There current molecular abnormalities, mainly represented by the V617F mutation in JAK2 exon 12, which involves 95% of PV patients[3].

A guanine-to-thymidine substitution at nucleotide position 1849 leads to a valine to phenylalanine exchange at amino acid position 617, which is localized in pseudo-kinase JAK homology-2 (JH2) domain of the exon 12[4]. The V617F mutation finally results in a gain of function of JAK2 which activates downstream pathways, including JAK-STAT, PI3K/Akt, and ERK1/2 MAPK signaling[5-7]. A JAK2V617F-mutated status and a high V617F allelic burden have been variably associated with increased risk of thrombosis which has been reviewed by Alessandro *et al* [5]. Most patients die from thrombosis or haemorrhage, but upto 20% succumb to myelodysplasia or acute myeloid leukaemia[3]. We report a case of renal artery stenosis occurring in a patient with polycythaemia vera (PV).

Case report

A 52-year-old male, known smoker and known case of systemic hypertension on treatment for 3 years presented

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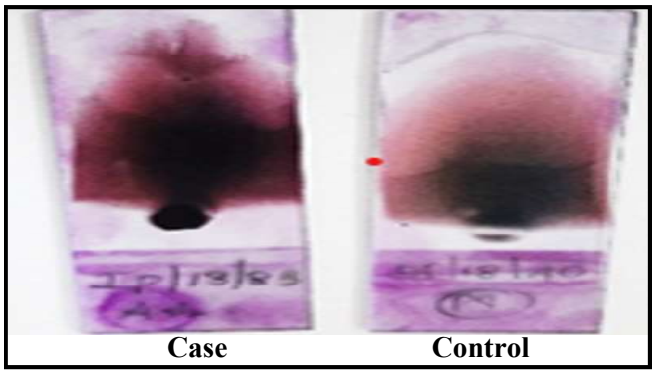

Figure 1 : Peripheral blood film of the patient is darker in comparison to a normal smear.

with complaints of eye pain which was on and off for past 6 months, associated with blurring of vision and also had a complaint of pain in right hypochondrium and lumbar region. During evaluation,the patient presented with high blood pressure levels (mean BP 180/100 mmhg). On physical examination,tenderness was noted over right iliac fossa and hypogastric region.

On further evaluation, CT Abdomen-plainre vealed right contracted kidney with cysts and perinephric stranding – Chronic parenchymal disease (Eccentric calcification of right renal artery causing mild luminal narrowing), left mild bulky kidney with cysts – likely compensatory hypertrophy. USG Kidney doppler showed a right

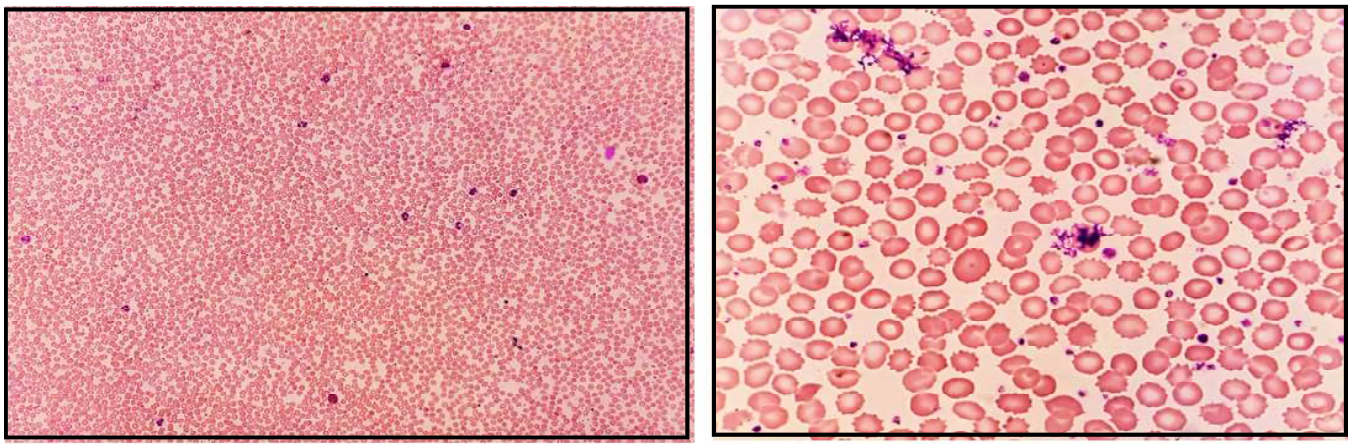

Figure 2: (A) 100X Peripheral smear showing increased RBC and total leucocyte count. (B) 400 X Peripheral smear showing thrombocytosis.

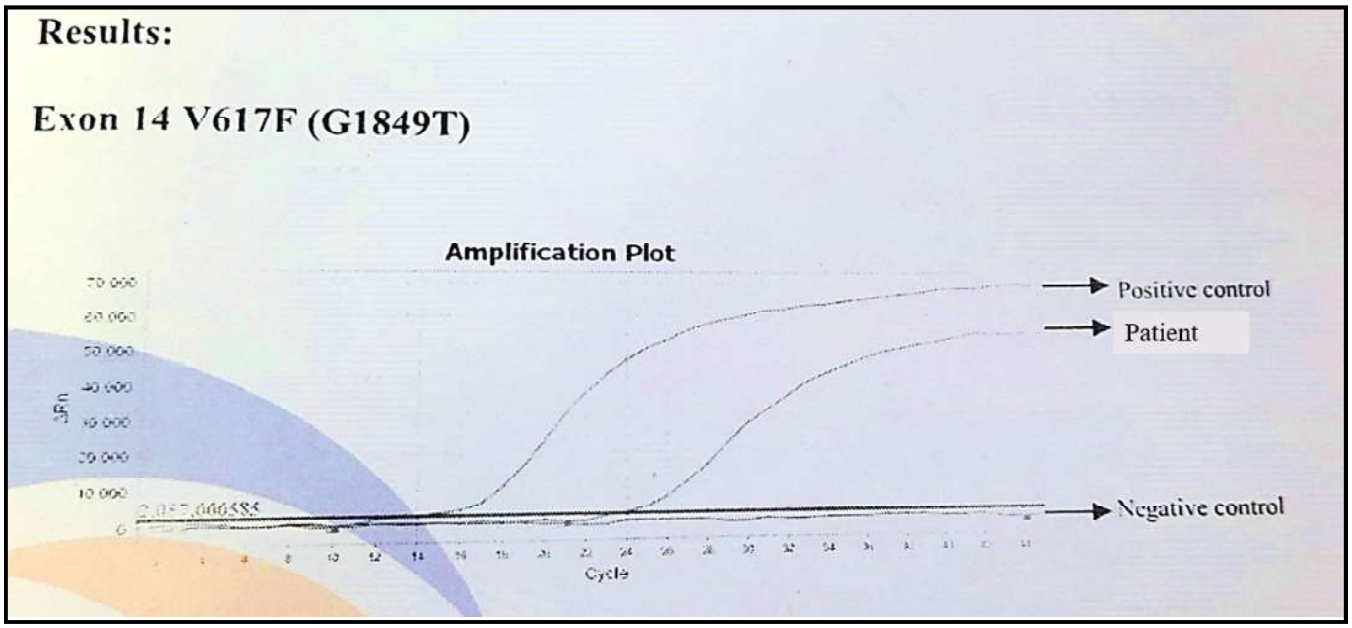

Figure 3: Real time Polymerase chain reaction for JAK2 Exon 14V617F mutation was detected in 22nd cycle.

segmental artery upper pole increased waveform – Possibilty of Right renal artery stenosis**.** USG Carotid and vertebral artery doppler showed a mixed echogenic focus at level of bifurcation of Common carotid artery causing 25-30% luminal occlusion.

On Ophthalmic examination revealed- Grade 1 Hypertensive Retinopathy.Complete blood count showed a haemoglobin of 15.7 g/dL, haematocrit of 51 %, red blood cell count of 6.51millions/cumm,white blood cell count of 15,240/microlitre, and platelet count of 9.7 lakhs/ cumm. Erythropoietin was 2.30mU/mL which was in the subnormal range.

Peripheral blood film from this case of PV showed a darker film in comparison to a normal smear because of high hemoglobin and high red cell count (*Figure 1*) and peripheral blood smear showed erythrocytosis, leucocytosis and thrombocytosis (*Figure2A and 2B*). Figure 1-Peripheral blood film of the patient is darker in comparison to a normal smear

Also, JAK2 mutation was sent, and results came back positive (*Figure 3*). The patient was then diagnosed with JAK2-positive polycythaemia vera according to the World Health Organization (WHO) Diagnostic Criteria (2016) for Polycythaemia Vera.

Discussion

PV is characterized by clonal stem-cell proliferation of red blood cells (RBCs), white blood cells (WBCs), and platelets. Increased RBC mass results in hyperviscosity of the blood which results in increased risk for thrombosis[2]. A diagnosis of PV was made in our patient based on the findings ofan elevated cell count of trilineage series, JAK2 V617 mutation,subnormal levels of erythropoietin and high haematocrit value. Major changes to its diagnostic criteria were made in the 2016 revision of the World Health Organization (WHO) classification, with both hemoglobin and hematocrit diagnostic thresholds lowered to 16.5 g/dL and 49% for men, and 16 g/dL and 48% for women, respectively[1].

As shown in our patient, primary erythrocytosis due to polycythaemia vera may lead to atherosclerosis and subsequent atherosclerotic renal artery stenosis. This possible pathophysiological explanation, was also provided by Bhadauria *et al*, which states that hyperviscosity due to increased red cell mass, endothelial damage due to leucocyte activation with subsequent thrombus formation, abnormalities in platelet function, hyperhomocysteinaemia, hypercoagulable state and hyperexpression of activating genes such as JAK2 and STATS are all features characteristic of PV, together with other risk factors that may contribute to the development and progression of atherothrombosis,which is further supported in our case due to the fact that renal artery stenosis occurred following a period of high haematocrit levels [5,6,8,9]. If a patient presents with refractory hypertension, renal artery stenosis and erythrocytosis together, wes hould consider two possible causes:(i)renal artery stenosis with secondary refractory hypertension which may lead to secondary erythrocytosis,(ii) PV causing primary erythrocytosis which may result in renal artery stenosiswith secondary hypertension possibly due to an atherothrombotic mechanism[6].

PV patients are stratified into two thrombotic risk classes: a low-risk group, in the case of younger patients (age < 60 years) with no previous thromboses, and a high-risk group, in the case of patients older than 60 years and/or with a previous thrombotic complications[1].

The primary management of PV is phlebotomy combined with low-dose aspirin which usually improves symptoms immediately. Cytoreductive chemotherapy is recommended to control RBC volume in patients who are poorly tolerated to phlebotomy, those in whom the thrombotic risk remains high, or those having symptomatic splenomegaly. The cytoreductive agents used for the purpose includes hydroxyurea, interferon-alpha (IFN-a), and busulfan[9]. Understanding the molecular pathogenesis of diseases—for example, knowing the role of BCR-ABL in CML and now JAK2V617F in PV and some cases of ET and IMF has laid the foundation for investigating small molecule inhibitors for JAK2[6].Ruxolitinib (Jakafi), a JAK1/JAK2 inhibitor, was approved by the FDA in December 2014 for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea which showed a superior response[10].

Conclusion

We should remember that patients with syndrome of erythrocytosis, renal artery stenosis and refractory secondary hypertension should be evaluated for JAK2 mutation and managed appropriately targeting to low haematocrit levels. And also, JAK2V617F mutational status might be a new disease associated risk factor that would deserve to be incorporated in the current risk stratification. Whether drugs targeting the JAK2/STAT pathway may improve the management of thrombosis in PV patients which is a challenge for future studies.

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Conflicts of Interest

There are no conflicts of interest.

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