Unusual presentation of JAK2-negative polycythemia

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ABSTRACT

Polycythemia vera is a relatively rare disease occurring in 0.02–2.8 per million population. Globally, about 95% of PV is due to *J*AK2V617F mutation in the chromosome 9p. The remaining 5% were found to have a wide range of mutations including JAK2 exon12 mutation and calreticulin (CALR) mutation. In India, the incidence of JAK2-negative polycythemia is relatively high, reaching up to 18%. Polycythemia usually presents as symptoms secondary to hyperviscosity or as symptoms secondary to increased histamine release by the cells. Herein, we describe a 46-year-old Indian male presented with a headache and found to be in hypertensive urgency, which was later found to be secondary to *JAK2*-negative polycythemia.

Key words: *Erythrocytosis, JAK2-negative polycythemia, Polycythemia vera, Secondary hypertension*

Polycythemia vera (PV) is a myeloproliferative disorder with relatively rare incidence. An incidence of 0.02–2.8/100,000 population per year was reported by several studies [1,2]. PV has no sex predilection, although the PV study group (PVSG) found that the disorder affects more males than females [3]. *JAK2V617F* is the most common mutation associated with a myeloproliferative disorder; it is a somatic mutation in the short arm (p) of chromosome 9. The main role of the gene is in the JAK2/STAT pathway which signals for cell growth and proliferation. Other conditions associated with a mutated JAK2 gene are primary myelofibrosis (PMF), essential thrombocythemia (ET), Crohn's disease, and Budd–Chiari syndrome. The allelic frequency of *JAK2V617F* is upward of 95% in PV, and roughly 50% in ET and PMF, as estimated by sensitive detection methodologies [4,5]. In India, the incidence of JAK2-negative PV is relatively high ranging up to 18% in some studies [6].

The symptoms of PV are usually secondary due to hyperviscosity of blood, excess histamine secretion by the cells, or due to splenomegaly. It is very unusual for polycythemia to present as hypertension; after an extensive search of the literature, we were able to find only one reported case of PV presenting as hypertension [7]. Here, we describe a case of *JAK2*-negative polycythemia presented as hypertensive urgency.

CASE REPORT

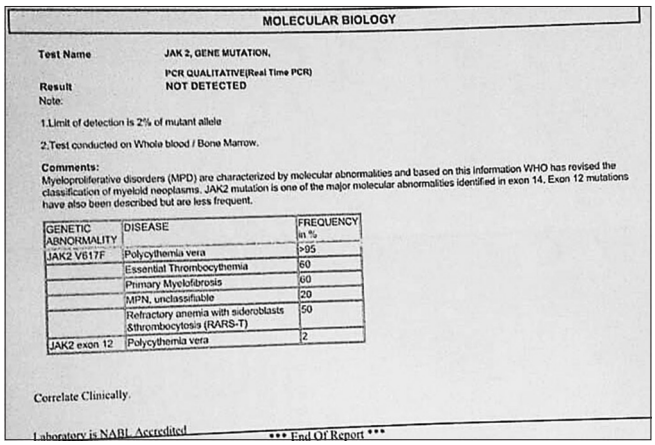
A 46-year-old male patient came to the department with a chief complaint of a headache for 1 day. There was no history of weakness of limbs, nausea, or loss of consciousness, but he reported numbness of both upper and lower extremities since few months for which he never consulted a doctor. His medical history and family history were negative for any significant information. His sleep, appetite, and bowel habits were unchanged and normal. He is not on any medications currently, and there is no known allergy. He neither smokes nor drinks alcohol.

On examination, he was conscious and oriented, with a blood pressure of 200/100 mmHg in the right arm in supine position, pulse rate of 90/min, and respiratory rate of 16/min were noted. No pallor, icterus, cyanosis, clubbing, lymphadenopathy, or edema were present. Abdominal examination revealed mild splenomegaly. Cardiovascular, respiratory, and nervous system were found to be normal on examination. A provisional diagnosis of a hypertensive headache was made, for which he was given oral antihypertensive medications and paracetamol. The blood pressure was moderately reduced, but headache was completely relieved by medication.

Laboratory investigation revealed hematocrit 0.64, hemoglobin 22.4 g %, white blood cell count of 9300 cells/mcL, platelet 214,000/mcL, and RBC 6.29 million cells/mcL. Coagulation assays, kidney and liver function tests, and arterial blood gas analysis were normal. Ultrasound abdomen confirmed the splenomegaly. Serum erythropoietin level was 2.60. All the secondary causes of erythrocytosis were ruled out; other causes of secondary hypertension were also ruled out from history, physical examination, and normal serum electrolyte levels. Cytogenetic analysis for *JAK2V617* mutation was done, which was negative (Fig. 1).

A diagnosis of PV was made on the basis of the British Committee for Standards in Haematology (BCSH) guidelines [8]. The criteria used for the diagnosis of PV are given in Table 1. Diagnosis of PV was made as A1 + A2 + A3 +A4 and B3 + B4 are present in our case.

The patient was treated with multiple periodic phlebotomies; 350 ml of blood removed for a total of 4 times in a month, and



MOLECULAR BIOLOGY

Test Name: JAK 2, GENE MUTATION, PCR QUALITATIVE(Real Time PCR)

Result: NOT DETECTED

Note:

1.Limit of detection is 2% of mutant allele

2.Test conducted on Whole blood / Bone Marrow.

Comments:
Myeloproliferative disorders (MPD) are characterized by molecular abnormalities and based on this information WHO has revised the classification of myeloid neoplasms. JAK2 mutation is one of the major molecular abnormalities identified in exon 14, Exon 12 mutations have also been described but are less frequent.

GENETIC ABNORMALITY	DISEASE	FREQUENCY in %
JAK2 V617F	Polycythemia vera	>95
	Essential Thrombocythemia	60
	Primary Myelofibrosis	60
	MPN, unclassifiable	20
	Refractory anemia with sideroblasts &thrombocytosis (RARS-T)	50
JAK2 exon 12	Polycythemia vera	2

Correlate Clinically.

Laboratory is NABL Accredited

••• End Of Report •••

Figure 1: Cytogenetic analysis for *JAK2V617* mutation

his blood pressure came down to normal reference range and remained within reference range even after discontinuation of antihypertensive medications. His hemoglobin and hematocrit values also came down to a reference level.

DISCUSSION

The American College of Cardiology and American Heart Association (ACC/AHA) guidelines classify the blood pressure into various stages; Stage 1 hypertension as an average systolic blood pressure (SBP) of 130–139 mmHg or a diastolic blood pressure (DBP) of 80–89 mmHg and Stage 2 hypertension as an average SBP of 140 mmHg or greater or a DBP of 90 mmHg or greater [9]. Most cases of hypertension are primary; the incidence of secondary hypertension varies in different age group. In hypertensive adults, 5–10% is having secondary hypertension. The main causes of secondary hypertension are renal artery stenosis, aldosteronism, pheochromocytoma, obstructive sleep apnea, Cushing's disease, thyroid diseases, medication-induced, etc. Polycythemia as a cause of secondary hypertension is reported rarely in literature [1].

For the diagnosis of PV, three sets of diagnostic criteria were described; the PVSG criteria (1975), the British Committee for Standards in Haematology (BCSH) criteria (1996), and the World Health Organization (WHO) criteria (2001). Among the three, the BCSH criteria are considered the most accurate with the acceptable level of sensitivity and ability to differentiate PV and other causes of erythrocytosis [10].

The mutations described recently in *JAK2V617F*-negative polycythemia are *JAK2* exon12 mutation [11] and CALR mutations [12]. Among this, JAK2 exon12 mutation was associated with isolated erythrocytosis compared to the *JAK2V617F*-positive PV where there is elevated leukocyte and/or platelet count. The analysis of *JAK2* exon12 and *CALR* mutations is not available widely. There is no significant difference in the presentation of *JAK2*-positive and negative polycythemia, but there is a noted significant difference in the clinical outcome of *JAK2V617F*-positive and negative PV [13,14]; *JAK2*-positive PV has a worse prognosis compared to *JAK2*-negative PV.

Primary familial and congenital polycythemia (PFCP) is

Table 1: Diagnostic criteria for PV

JAK2-positive PV *(both criteria should to be present)*
A1. High hematocrit (>0.52 in men, >0.48 in women) or raised red cell mass (>25% above predicted)
A2. Mutation in JAK2
JAK2-negative PV (in the presence of A1+A2+A3+either one other A or two B criteria
A1. Raised red cell mass (>25% above predicted) or hematocrit≥0.60 in men, ≥ 0.56 in women
A2. Absence of a mutation in JAK2
A3. No case of secondary erythrocytosis
A4. Palpable splenomegaly
A5. Presence of an acquired genetic abnormality (excluding BCR-ABL) in hematopoietic cells
B1. Thrombocytosis (platelet count>450×10^9/l)
B2. Neutrophil leukocytosis (neutrophil count>10×10^9/l in non-smokers, and>12.5×10^9/l in smokers)
B3. Radiological evidence of splenomegaly
B4. Endogenous erythroid colonies or low serum erythropoietin

PV: Polycythemia vera

a rare differential diagnosis for JAK2-negative polycythemia. PFCP is inherited in an autosomal dominant manner in the majority of cases, but some people with PFCP have no relatives with the disease. In about 12–15% of people with PFCP, it is caused by mutations in the *EPOR* gene [15]. However, in most people, the genetic cause is not yet known. Although PFCP has been largely reported in children and young adults, certain forms like the autosomal recessive Chuvashia form have been reported in people >40 years of age [16] but are limited to the Chuvashia region of Russia. Here, we excluded the PFCP since there is palpable splenomegaly, the absence of family history and the higher age of our patient.

Since the patient gives a history of witnessing a fire accident 2 days before presentation, we have also considered the possibility of acute stress disorder presenting as a headache and hypertension in the patient, but a detailed psychiatric history and lack of other symptoms excluded the diagnosis.

The primary management of PV is phlebotomy combined with low-dose aspirin. Patients usually report an immediate improvement of their symptoms. Cytoreductive chemotherapy is recommended to control RBC volume in patients in whom phlebotomy is poorly tolerated, those in whom the thrombotic risk remains high, or those whose splenomegaly continues to be symptomatic. The cytoreductive agents used for the purpose are hydroxyurea, interferon-alpha (IFN-α), and busulfan. 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, it showed a superior response compared to the best available treatment [17]. Splenectomy can be considered in patients with painful splenomegaly.

Median survival in patients PV is 1.5–3 years in the absence of therapy, which has been extended to approximately 14 years overall, and to 24 years for patients younger than 60 years of

age, because of new therapeutic tools [18]. The major causes of morbidity and mortality are thrombosis, hemorrhagic complications, peptic ulcer disease, myelofibrosis, and transformation to acute leukemia or myelodysplastic syndrome.

CONCLUSION

Even though it is a rare for polycythemia to present as hypertension, clinicians should consider this possibility while evaluating a newly diagnosed hypertension.

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