Case Report

Story of red faces: two cases with management strategies

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ABSTRACT

Polycythaemia rubra vera (PRV) is a myeloproliferative neoplasm of stem cells that lead to trilineage haemopoietic cell hyperplasia, which carries a risk of thrombotic complications. Untreated cases may lead to myelofibrosis and leukaemia. An individual with erythrocytosis is screened by Janus Kinase-2 gene (JAK-2) ^{V617F} mutation analysis. Here, two cases with ruddy cyanosis were discussed with focus on importance of JAK2 mutation study for diagnosing PRV along with other clinical and laboratory work up. This study highlights the role of phlebotomy in preventing thrombotic complications in addition to other antiplatelet and cytoreductive drugs.

Key words: *antiplatelet drug, cytoreduction therapy, Janus Kinase-2 Gene (JAK2), phlebotomy, polycythaemia rubra vera, thrombosis.*

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INTRODUCTION

Initial description of polycythaemia rubra vera (PRV) was stated by Vaquez in 1892.[1] Primary polycythaemia, often called polycythaemia vera (PV) or PRV or erythraemia, is a clonal myeloproliferative-myeloaccumulative disorder with ability of erythroid progenitor cells to proliferate in the absence of erythropoietin, as it involves multipotent hematopoietic progenitor cell, the hallmark of PRV is trilineage hematopoietic cell hyperplasia. Here, excess red blood cells are produced as a result of an abnormality of the bone marrow; often with excess white blood cells and platelets.[1,2] PRV occurs slightly more often in men than female, with the median age at diagnosis to be 60 years; however, about 10% of patients are less than 40 years at diagnosis.[3] 2005 and 2007 were the milestone years in the diagnosis of PV.[3] In 2005, identification of presence of (JAK-2)^{V617F}, a gain-of-function mutational state in Janus kinase-2 (JAK-2) gene in exon 14 of chromosome 9 and in 2007, among case of JAK 2^{V617F} (exon 14) negative erythrocytosis an invention of JAK-2 exon 12 mutation had played landmark role in the pathogenesis

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of PRV.[3,4] The V 617F point mutation in exon 14 is most prevalent approximately in 96 % of patients, whereas mutations (small deletions or insertions) in exon 12 of JAK2 are found in about 3% of patients of PV.[5] Here, two cases of PRV are discussed with clinical and laboratory findings along with treatment strategy specially the role of venesection.

CASE REPORTS

Case 1

A 50-year-old male, smoker, hypertensive, diabetic businessman presented with the complaints of dizziness and weakness for two months and reddish dis-colouration of face for same duration. Dizziness was not associated with vomiting. There was no jaundice and shortness of breath. Patient had plethoric face and conjunctival injection. Systemic examination was unremarkable. On investigation, haemoglobin was 20 g/dl, RBC 6.1 x 10^{12}/L, Hct. 56.4%, MCV 92.9fl, MCH 33.3 pg, MCHC 35.9 g/dl, RDW-SD 42.2 fl, ESR 6 mm in 1st hour, O_2 saturation was 87%, total count was -7.69x10^9/L, Neutrophil-57%, Lymphocyte -32%, Monocyte-07%, Eosinophil was-03% and Basophil-00%, platelet count was 1,86000/mm^3, LFT as normal, serum creatinine 1.2mg/dl, blood group 'O' Rh'D' negative, PBF showed non-specific morphology, bone marrow aspiration study showed: hypercellular marrow with increased M:E ratio, erythropoiesis, mildly hyperactive and micronormoblastic, granulopoiesis, also hyperactive and maturation showed left shift, megakaryocytes also increased in number and showed mild dysmegakaryopoiesis. Chest X-ray, ECG and other investigation findings were within normal limit. USG of whole abdomen showed mild splenomegaly. Cytogenetic analysis specific for JAK-2 mutation study showed identification of JAK-2^{V617F} (exon 14). A diagnosis of PRV was made as per WHO 2016 criteria and patient was advised for phlebotomy as first line of treatment.[3,5] Before first venesection, patient's blood pressure was 140/80 mm of Hg, pulse was 64/m, serum ferritin initially was 570 ng/ml and after periodic five venesections his blood pressure was within normal limit, pulse was same and serum ferritin was low (140 ng/ ml). That patient was on oral antihypertensive and oral anti-diabetic drug and was advised to take 3 litres of water per day and counseling was given to avoid alcohol and smoking.

Case 2

A 56-years-old, hypertensive, dyslipidaemic, diabetic, farmer presented with vertigo, headache, uncontrolled blood pressure, intermittent weakness of right lower limb and confusion for three days. On physical examination, his face was plethoric and conjunctiva was reddened. His pulse was 80 b/m, regular and BP was 110/80 mm of Hg without any organomegaly or lymphadenopathy. Investigations revealed hemoglobin 19.5 gm/dl, red cell count 8.01 million/µl, Hct. 59.60%, MCV 75.6 fL, MCH 24.2 pg, MCHC 32.6, WBC 16.13 k/µl with ESR 5 mm in 1st hour. Platelet was 5 x 10^9/ L. PBF showed nonspecific morphology with erythrocytosis, thrombocytosis and leukocytosis. His bilirubin level was 1.78 mg/dl, SGPT 55u/l, SGOT 35u/l, HbA_1C was 7.4%, uric acid level was 8.0 mg/dl and ferritin level was normal (118.0 ng/ml). Bone marrow study revealed hypercellular marrow with increased M:E ratio, erythropoiesis hyperactive and micronormoblastic, granulopoiesis also hyperactive and maturation showed segmented form with few myelocytes, megakaryocytes are increased in number and shows dysmegakaryopoiesis. Non-contrast computed tomography of brain (CT scan) revealed left sided cerebral infarct and white matter ischaemic changes. USG of whole abdomen showed normal finding. His JAK-2 mutation study was also positive and diagnosed as a case of PRV as per WHO criteria.[1,3] He was treated with phlebotomy about 400 ml every alternative day, till HCT was <45%. Before 1st phlebotomy his blood pressure was 120/70 mm of Hg and after 5th phlebotomy was 110 / 60 mm of Hg. He was also given oral hydroxyurea (500 mg twice daily; target to keep WBC less than 3000/µl and Hct. 40-45%. Oral aspirin (75mg/day) was given along with other medications e.g. allopurinol, beta-blocker, ACE inhibitor, calcium channel blocker and proton pump inhibitor. Patient was advised with restriction on supplemental iron and consult at Transfusion Medicine and Clinical Haematology OPD with CBC report twice weekly for1st two months, then monthly for six months and three monthly for life long.

DISCUSSION

These two case reports outlined the clinical features, diagnostic workup and management of with PRV. PRV is a myeloproliferative neoplasm with incidence of 2.6 per 100000.[4] The status of JAK2 mutation analysis has tremendous role to screen out individuals with

erythrocytosis and a major criterion for PRV diagnosis according to WHO criteria (2008, proposed revised criteria 2014 and revised criteria 2016) and British Committee for standards in Haematology (BCSH).[5,6] Polycythaemia vera study group (PVSG) in USA since 1960 credited for developing the first consensus on diagnostic criteria and important clinical trials to assess the beneficiary role of phlebotomy while PVSG found, fatal leukemogenic aspect of chlorambucil and P32 in that study.[6] In PVSG, red cell mass, an isotope assay (RCM) was the cornerstone of diagnosis.[9] In 2005, JAK-2 mutation brings the genetic paradigm of PRV.[3] WHO criteria (2008) and BCSH criteria (2007) incorporates JAK-2 mutation as one of the major criteria.[3] Studies showed 35% patients of PV with positive JAK-2 mutation and bone marrow morphology, had low haemoglobin level, while majority of them fulfilled the BCHS –Haematocrit (Hct) criteria, which suggested that Hct is better indicator of raised red cell mass (RCM) than haemoglobin (Hb).[3] To identify 'masked PV' WHO criteria for PV has been updated in 2016.[6] This updated WHO criteria lower the Hb threshold than previous and included bone marrow findings as a major criterion for diagnosis unless the haemoglobin is greater than 18.5 g/dl.[5] The major life-threatening complications in PV are leukaemic transformation, fibrotic progression and thrombosis.[6] Thromboembolic event prevention is the main focus of treatment strategy to reduce morbidity and mortality in PRV secondary to increased whole blood viscosity.[1, 3]

Thrombotic risk increases with advanced age more than 65 years, prior history of thrombosis, increase of JAK2 ^{V617F} allele burden, hypercholesterolemia and smoking.[3,6,7] About one third presents with symptoms due to thrombosis, three quarters arterial thrombosis and a quarter is venous thrombosis along with features include stroke, myocardiac infarction, deep vein thrombosis and pulmonary embolism. Thrombosis may be due to quantitative platelet abnormality and ischemia may due to stroke, myocardial infarction and arterial or venous thrombosis. [3] The incidence of thrombosis in people with PRV ranges from 4 to 11.4 events/100 patients per year.[7] Study shows up to 8% of all ischaemic strokes usually occurs due to haematological disorders.[7] Studies showed haematological transformation to AML or MDS causes 13% deaths among polycytaemia, beside this, incidence rates of solid malignancies among them are 0.6 to 1.6 per 100 persons per year.[8]

As the hallmark of polycythemia is an elevated hematocrit, with hematocrit >55% seen in 83% of cases, reduction of the red cell mass and maintaining it at a safe level by phlebotomy–hematocrit level <45% in men and <42% in women, < 36% in pregnancy– is the first principle of therapy in PV.[3] First-line therapies include aspirin and phlebotomies markedly reduce the incidence of thrombotic events and prolong survivality.[3] Phlebotomy has been one of the treatment of choice and corner stone of therapy for PV since 1900s.[4] Maintaining of haematocrit target of less than 45% showed that, thrombosis or cardiovascular deaths were less prevalent among these group;[6] while aspirin accepted as another corner stone of therapy to decrease risk of thrombosis.[6] Cytoreductive treatment with hydroxyurea (HU) and conventional or pegylated interferon-á reserved for high risk or inadequately controlled disease as first line or second line treatment in addition to anagrelide.[3] Beside these busulfan or pipobroman or radioactive phosphorus 32 (P^{32}) are also second line treatment but leukaemogenic with restricted use for those with short life expectancy.[3]

Traditionally in clinical practices use of HU as a first-line therapy for cytoreduction was accepted and established by the PVSG, showing there was lower incidence of thrombosis but showed leukaemogenic transformation, although the incidence was lower than chlorambucil and P^{32}.[5] In the Department of Transfusion Medicine and Clinical Haematology of BIRDEM General Hospital, the main treatment strategy of PV patients consists of phlebotomy, antiplatelet drug and cytoreduction therapy. Phlebotomy was found to be equally beneficial in men and women, and among hypertensive patients and non-smokers. It is safe with instant restoration of coagulant activity toward normal by reducing blood viscosity leads to improve blood flow, platelet function and keep balance between coagulation factor concentration and red cell number.[11] Therapeutic venesection or phlebotomy done in Transfusion Medicine Department of BIRDEM by withdrawing of 450 ml of blood similar to other studies of aggressive phlebotomy[11] two to three times in a week

and has been performed until hematocrit reaches below 45% as per WHO guideline. Once hematocrit lowered, CBC has been checked for every 4 to 8 weeks' similar to other clinical practices.[2] Aggressive phlebotomy is a rapid way of reducing the increased red blood cells down to normal levels, maintaining the haematocrit level at lower than 45%.[6] The shorter interval is appropriate for patients with hematocrits that are over 64 percent. Patients with impaired cardiovascular functions are better treated with smaller phlebotomy at more frequent intervals. After phlebotomy, as the blood increases its plasma content, the hematocrit falls, so the red blood cells are becoming diluted.[3] The immediate effect of phlebotomies is to reduce the hematocrit, which results in improvement of symptoms such as headaches.[3] Studies showed, overusing of phlebotomy may cause iron deficiency, due to abnormal RBC morphology and eventually reactive thrombocytosis.[2] Here, if patients developed symptoms due to iron deficiency iron supplement may be needed accordingly.

On the other hand, those at high thrombotic risk or with progressive thrombocytosis or splenomegaly, a myelosuppressive agent should be used. Study showed HU, an oral antimetabolite which prevents DNA synthesis by inhibiting the enzyme ribonucleoside reductase can be use among all ages. In BIRDEM, HU has been used as a cytoreductive drug. In younger patients, interferon or anagrelide may be considered.[2] In BIRDEM among the PRV patients anti-platelet treatment with aspirin or clopidogrel has been chosen, recommended by other studies.[3] Low dose aspirin used in those with thrombotic or ischemic complications unless contraindicated and withdrawal done in case of bleeding or gastric intolerance. Study showed PV with thrombocytosis produces a platelet response in 75% cases with administration of anagrelide.[7] Various studies showed, use of HU or anti–platelet medications has a combined well tolerated effects

while, periodic phlebotomies help to maintain normal haematocrit level among PRV patients. While in PRV with pruritus or gout treatment modalities like aspirin, cyproheptadine, interferon alpha, photo chemotherapy with psoralens and ultraviolet light has been helpful. [1, 3, 5-7] Ruxolitinib, a JAK1/2 inhibitor is an effective therapy for those patient with high symptom burden, but has risk of thrombotic events, Herpes zoster, non-melanoma skin cancer etc. It acts as a second line therapy in resistant or intolerant cases patients with severe pruritus, symptomatic splenomegaly, or post-PV myelofibrosis symptoms. Ruxolitinib significantly improve requirement of phlebotomy and reduction in splenomegaly.[12] These cases demonstrated that JAK2 mutation study has led to the diagnosis and management of PRV. Although phlebotomy is a simple option but regarding the management of polycythaemia, it is an effective first-line treatment.

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