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EVALUATION OF VASO OCCLUSIVE/THROMBOTIC EVENTS IN PATIENTS WITH JAK 2 POSITIVE POLYCYTHEMIA VERA AT A TERTIARY CARE HOSPITAL IN SOUTH INDIA

Arathy A.	Physician Assistant, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India.
Dr. Neeraj Sidharthan*	Associate Professor, Department of Clinical Hematology, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India. *Corresponding Author
Dr. Manoj Unni	Associate Professor, Department of Clinical Hematology, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India.
Dr. Rema G	Assistant Professor, Department of Clinical Hematology, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India.
P. Gangadharan	Head of Department Cancer Registry, Consultant Biostatistician, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041
Ajil Shaji	Biostatistician, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi- 682041
Sumi Soman	Junior Research Fellow, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi- 682041
Dr. Sharanya Jayashankar	Fellow in Clinical Hematology, Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India.
Chirag Sunil Lalwani	Third Professional MBBS (Part 1), Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India.
Hamsini Movva	Third Professional MBBS (Part 1), Amrita School of Medicine, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi-682041, India.

ABSTRACT

Introduction: Polycythemia Vera (PV) is a chronic myeloproliferative disorder with abnormally increased hemoglobin and hematocrit. JAK2 mutation is detected in up to about 95% patients with PV. Patients are at riks for arterial and venous occlusive/ thrombotic events

Methods: Consecutive patients diagnosed with PV and JAK2 mutation positive at a single centre from January 2013 to December 2017 were analysed in the study. Arterial occlusive and thrombotic venous events before or at diagnosis were studied. Age at diagnosis, sex, splenomegaly, PCV, leukocyte count and platelet count at diagnosis were analysed as potential risk factors for thrombosis. The data was subsequently documented into an excel sheet following which a statistical analysis was done using SPSS(v24).

Results: One hundred and thirty four patients with Jak 2 positive polycythemia were included in the analysis. Thrombotic episodes were documented in 48 (35.8%) at or before diagnosis. Arterial events predominated in 35 (72.9%) of them followed by venous events in 10(20.8%) and both arterial and venous events in 2 (6.25%) patients. Patients who had splenomegaly at diagnosis had significantly more thrombotic episodes (p 0.004).

Conclusion: The medical literature from India on Polycythemia has been sparse (10,11). Our single centre study shows that the clinical profile and thrombotic episodes in Indian patients with JAK2 positive PV appear similar to those described in the western literature. Prospective multi center studies should look carefully into the risk factors predicting thrombosis in PV.

KEYWORDS : Polycythemia Vera, Thrombosis , JAK2 mutation

INTRODUCTION

Polycythemia Vera (PV) is an abnormal elevation of hemoglobin and hematocrit in the peripheral blood. It is a chronic myeloproliferative disorder more commonly seen in males aged above 55 years whose major morbidity and mortality are contributed by thrombo haemorragic events and progression to acute leukaemia or myelofibrosis (1).

Polycythemia can be initially classified as relative and absolute. Absolute polycythemia is associated with an increase in the red blood cell mass whereas in relative polycythemia there is a modest elevation of the hematocrit without an increase in the red cell mass(2).Absolute polycythemia can be due to secondary causes like smoking , hypoxia , stress , congenital causes and erythropoietin secreting tumors or it can be primary (PV)

Janus Kinase 2 (JAK 2) is a tyrosine kinase that transduces signaling pathways in hematopoietic cells often triggered by growth factors like erythropoietin. Acquired JAK2 mutation (termed JAK2 V617F) is reported in Polycythemia and related myeloproliferative disorders and makes the normal hematopoietic progenitor cells hypersensitive to thrombopoietin, erythropoietin, and myeloid progenitor cells, leading hematopoietic myeloproliferation. JAK2 mutation is detectable in upto about 95% of patients with polycythemia vera.

Due to the overproduction of red blood cells in the marrow, there are abnormally high numbers of circulating red blood cells. Consequently, the blood thickens and increases in volume, a condition called hyperviscosity which impedes the proper flow through the vessels.

This is associated with a high frequency of major arterial and venous

thrombotic complications in addition to platelet-mediated microvascular circulatory disturbances of thrombocythemia which increases the risk of life-threatening conditions such as myocardial infarction , stroke, or pulmonary embolism (3,4). Medical literature has been sparse from India in describing the thrombotic complications in JAK2 positive PV patients.

Aim

To assess the thrombotic events in a cohort of JAK 2 positive polycythemia vera patients from January 2013 to December 2017 at a tertiary care hospital in South India.

Methods

This is a retrospective observational cohort study . The details from electronic medical records of consecutive Jak 2 positive adult polycythemia vera patients who were diagnosed between the 1st January 2013 and 1st December 2017 were collected from the cancer registry department at Amrita Institute of Medical Sciences (AIMS)

The 2016 World Health Organization guidelines for establishing a diagnosis of PV include these major criteria:

1) An increased red cell mass (based on hemoglobin >16.5g/dL or hematocrit >49% in a males, or hemoglobin >16 g/ dL or hematocrit >48% in females)
2) A bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid , granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes.
3) The presence of a JAK2 V617F or JAK2 exon 12 mutation.

The sole minor criterion is a subnormal serum erythropoietin level, The diagnosis is established based either based on all three major critera or with first two major criteria and a minor criteria. Bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis, if major criterion 3 and minor criterion are present.

Arterial and venous occlusive / thrombotic events either prior to or at the time of diagnosis were documented. The data was subsequently documented into an excel sheet following which a statistical analysis was done using SPSS(v24) . Age at diagnosis, sex, splenomegaly, PCV, leukocyte count and platelet count at diagnosis were analysed as poteintal risk factors for thrombosis. The study was conducted during a period of 6 months.

RESULTS

One hundred and thirty four patients with Jak 2 positive polycythemia were included in the analysis. Males were 95(70.9%) in number. Mean age was 59.3 years . Twenty seven of patients (20%) were active smokers. Eighty two patients (61.2%) were symptomatic at presentation. The symptoms are enumerated. Headache was the most common presenting symptom in 23(34.14%) patients followed by tingling and numbness of limbs in 17(20.7%) patients. Other major presenting symptoms were chest pain in 5(9.75%) patients, giddiness in 5(6.09%), fatigue in 6(7.31%), pruritus in 5(6.09%), fever in 4(4.87%), Erythromelagia in 6(7.31%) , multiple joint pains in 1(1.21%), gingival bleed in 1(1.21%), dyspnoea in 1 (1.21%) and abdominal pain in 8(1.21%) patients.

The mean Hemoglobin, total leucocyte count and platelet count at diagnosis were 18.8g/dl(16-25g/dl), 14,058/mm3(4600 - 54,000) and 4,02,297/mm3(22,0000 -9,60,000) respectively. The mean value of lactate dehydrogenase and uric acid at presentation were 394.32(153 to 1088) and 6.24(1.6 to 14.5)patients. Serum erythropoietin was done in 75(55.9%) patients and were low in 31(21.1%), normal in 35(26.1%) & high in 7(6.7%) patients respectively. Splenomegaly was documented by examination and sonologically in 38(28.4%) patients. In 48(35.8%)patients bone marrow biopsy was performed.

Thrombotic and vaso occlusive episodes were documented in 48 (35.8%) at or before diagnosis. Arterial events predominated in 35 (72.9%) of them followed by venous events in 10(20.8%) and both arterial and venous events in 2 (6.25%) patients. There were thus 51 vascular events , out of which coronrary artery disease was the most frequent one accounting for 27(52.9%) of them, followed by cerebrovascular accident in 12 (23.5%) , deep vein thrombosis in 5 (9.8%) , cortical venous sinus thrombosis in 2 (3.9%), pulmonary embolism in 2 (3.9%) , portal venous thrombosis in 2 (3.9%) and mesenteric vein thrombosis in 2 (3.9%).

Patients who had splenomegaly at diagnosis had significantly more thrombotic episodes (p =0.004). This was consistent in both univariate and multi variate analysis. However, age, hematocrit, leukocyte count and platelet count at diagnosis was not statistically significant between those who had thrombosis and those who didn't.

Table 1. Details of arterial occlusive and venous thrombotic events in a cohort of patients with JAK2 positive PV

Thrombotic events in 134 JAK 2 positive polycythemia patients		
	Number	Percentage
1.Patients with Thrombosis	48	35.80%
Arterial	35	72.90%
Venous	10	20.80%
Arterial and venous	3	6.30%
2.Vascular Events	51	
Coronary Artery Disease	27	52.94%
Cerebro-vascular accident	11	21.57%
Deep Vein Thrombosis	5	9.81%
Cortical Venous sinus thrombosis	2	3.92%
Pulmonary Embolism	2	3.92%
Portal-Venous Thrombosis	2	3.92%
Mesentric Vein Thrombosis	2	3.92%

DISCUSSION

PV is estimated to have an incidence of 1/36000 to 1/100000 and prevalence 1 in 3300 (5).In our cohort the median age was 59.3 years, which is within the age range 50-70 years described in literature (5).

Thrombotic episodes at or before diagnosis were documented in 35.8% of our patients. This is much similar to the overall reported rates of thrombosis of 39-41 % in PV (6)(7). Around 3/4ths of our patients had arterial thrombosis, consistent with the previously reported literature (8). Coronary artery disease was the most common arterial event (52.94%) in our cohort, again similar to the previous reports (8). Patients with splenomegaly at diagnosis had significantly higher thrombotic episodes. S. Cerquozzi et al (9) has described association of palpable splenomegaly with venous thrombosis. We looked at the thrombosis occurring before or at diagnosis, and it is known that most of the thrombotic episodes in PV occur in this time. However, a major limitation of our study was that it was cross sectional and did not look at the thrombotic events after diagnosis. High hematocrit, leukocytosis and thrombocytosis have been previously described as risk factors for thrombosis, but in our cohort these were not found to be significant, probably because of the lack of follow up data. We will be looking into these with a prospective study which will also look into the effect of JAK2 burden in predicting thrombosis.

CONCLUSION

The medical literature from India on Polycythemia has been sparse (10,11). Our single centre study shows that the clinical profile and thrombotic episodes in Indian patients with JAK2 positive PV appear similar to those described in the western literature. Prospective multi center studies should look carefully into the risk factors predicting thrombosis in PV.

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