Clinical Profile of Subjects with Myeloproliferative Neoplasms other Than Chronic Myeloid Leukemia

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ABSTRACT

Introduction: Myeloproliferative neoplasms (MPN) are rare heterogeneous group of disorders characterized by increased proliferation of the erythroid, megakaryocytic, and myeloid lineages. The Janus-associated Kinase-2 mutation JAK2 V617F in MPNs has been described as a frequent genetic event in majority of patients with polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (IMF). Study aimed to clinical and laboratory evaluation of subjects with myeloproliferative neoplasms other than CML, as diagnosed by 2008 WHO criteria

Materials and Methods:
All patients presenting to outpatient department and admitted as inpatient, with clinical features suggestive of MPN were evaluated (after thorough history and physical examination) with complete hemogram, biochemical investigations, bone marrow aspiration, biopsy and cytogenetics. Analysis for JAK2 V617F mutation was performed. Diagnosis was made using revised WHO 2008 diagnostic criteria.

Results: A total of 36 patients were evaluated. IMF was more common than PV and ET in our study. IMF patients were older compared to PV and ET. PV patients common symptoms were headache, flushing, erythromelalgia. Symptomatic anemia and splenomegaly were common in IMF. Thrombosis and bleeding were common in ET. JAK2 V617F mutation was detected in 75% of patients with PV, 71.4% in ET and 33.3% in IMF. JAK2 V617F detection was associated with older age of presentation, greater risk of thrombosis and higher values of hemoglobin, total leukocyte and platelet counts. Only one patient with PV developed Acute Myeloid Leukemia after one year of diagnosis.

Conclusion: The 2008 WHO classification of myeloproliferative neoplasms is useful in diagnosing these patients and as the emphasis is on molecular abnormalities such as JAK2 V617F, it is easy to exclude secondary causes. The JAK2 V617F mutation also serves as a good prognostic marker indicating more severe forms of disease in positive patients. Regular follow up is essential to detect occurrence of other neoplasms like acute myeloid leukemia and evolution into other forms of MPNs.

Keywords: Myeloproliferative Neoplasms (MPN), Polycythemia Vera (PV), Essential Thrombocythemia (ET), Idiopathic Myelofibrosis (IMF), Janus Associated Kinase -2 mutation.

INTRODUCTION

Myeloproliferative neoplasms (MPN) are rare heterogeneous group of disorders characterized by increased proliferation of the erythroid, megakaryocytic, and myeloid lineages.[1] They are characterized by a predilection to extramedullary hematopoiesis, myelofibrosis, and transformation at varying rates to acute leukemia.[2] Non CML (chronic myeloid leukemia) myeloproliferative neoplasms include polycythemia vera (PV), idiopathic myelofibrosis (IMF), essential thrombocytosis (ET), chronic neutrophilic leukemia (CNL), and 2008

WHO classification also includes mast cell disease (MCD), hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia not otherwise specified (CEL-NOS).[6]

The revisions in the 2008 WHO diagnostic criteria for PV, ET and IMF were instigated by the discovery of Janus Kinase 2 (*JAK2*) V617F mutation.[3,4] This mutation is present in nearly all patients with PV, approximately 50% of each of those with ET and IMF, 20% of those with atypical MPNs, and 0% of those with CML.[4,5] Since, there are very few studies available from India; we sought to look for the clinical profile, frequency of *JAK2* V617F mutation and impact of *JAK2* V617F mutation in patients with MPN other than CML. Study aimed to clinical and laboratory evaluation of subjects with myeloproliferative neoplasms other than CML, as diagnosed by 2008 WHO criteria

MATERIAL AND METHODS

A prospective study of subjects with myeloproliferative neoplasms other than CML was conducted in Department of General Medicine, and Department of Pathology, Nizam's Institute of Medical Sciences (NIMS), Hyderabad over 2 years. The study was designed and conducted in accordance with Good Clinical Guidelines; written informed consent was obtained from each subject before inclusion into the study. The protocol was approved by the Institutional Ethics committee, NIMS. All patients were recruited from the outpatient clinics and inpatient wards of Department of General Medicine, NIMS. Total of 36 patients with myeloproliferative neoplasms were evaluated in this study.

After clinical history and examination patients were investigated according to the protocol of the study. Bone marrow aspiration, biopsy and cytogenetics were performed in the pathology department. JAK2 V617F mutation analysis, BCR-ABL quantitative assay and serum erythropoietin assays were performed with the help of outside laboratory. Both male and female patients aged 18 years and above with clinical profile suggestive of myeloproliferative neoplasms and satisfying 2008 WHO diagnostic criteria were included into the study.

STATISTICAL ANALYSIS

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on

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Parameter	Diagnosis		
	PV (n=10)	IMF (n=16)	ET (n=8)
At presentation			
Hb (gm/dl)	19.02±1.29	9.56±4.42	11.03±3.06
PCV (vol%)	59.26±7.11	30.64±14.06	34.66±8.91
TLC (/mm³)	14840±8407	13768.8±10097	26475.0±20260
Platelet count (lakh/mm³)	4.24±2.02	3.15±2.50	12.89±8.68
At 3rd month follow up			
Hb (gm/dl)	15.36±1.26	9.64±2.93	11.04±2.67
PCV(vol%)	48.35±4.34	30.28±9.42	35.10±8.05
TLC (/mm³)	11470.0±4093	10860.0±9831	12912.0±9020
Platelet count (lakh/mm³)	4.63±1.46	2.56±2.55	6.51±2.36
At 6th month follow up			
Hb (gm/dl)	13.50±3.97	10.13±3.42	10.52±3.22
PCV(vol%)	41.00±13.50	30.01±9.09	31.60±9.64
TLC (/mm³)	10087.0±3739	10444.4±7733	8560.0±5657
Platelet count (lakh/mm³)	3.06±1.22	2.79±2.67	7.04±3.29

Table-1: Showing Hemogram among PV, IMF, ET

JAK2 V617F mutation	Diagnosis		
	PV (n=8)	IMF (n=9)	ET (n=7)
Detected	6(75.0%)	3(33.3%)	5(71.4%)
Not detected	2(25.0%)	6(66.7%)	2(28.6%)
Inference	JAK2 detection rate is statistically less in IMF with 33.3% with P=0.226		

Table-2: Showing JAK2V617F mutationin PV, IMF, ET

Clinical signs	JAK2		P value
	Detected (n=14)	Not detected (n=10)	
Hemoglobin (gm/dl)			
M <13, F <12	4(28.5%)	7(70.0%)	0.111
M 13-17; F 12-15	5(35.7%)	1(10.0%)	0.345
M >17; F >15	5(35.7%)	2(20.0%)	0.659
TLC (/mm³)			
<4000	0 (0%)	2 (20%)	0.150
4000-10000	2 (14.2%)	5 (50%)	0.075+
>10000	12 (85.7%)	3 (30%)	0.009**
Platelet count (lakh/mm³)			
<1.5	0 (0%)	5 (50%)	0.005**
1.5-4.0	4 (28.5%)	3 (30%)	1.000
>4.0	10 (71.4%)	2 (20%)	0.041*

Table-3: Showing Hemogram in relation to JAK2

Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Chi-square/ 2x3 Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Significant figures: + Suggestive significance (P value: 0.05<P<0.10);* moderately significant (P value: 0.01<P ≤ 0.05);** strongly significant (P value: P≤0.01).

RESULTS

In the present study a total of 36 patients were included.

Mean age was 45.9 years. Males were commonly affected than females. Out of 36, patients with PV were 10 (27.8%), IMF were 16 (44.4%), ET were 8 (22.2%) and one (2.8%) each of hypereosinophilic syndrome and PDGFRA rearranged myeloid neoplasm with eosinophilia (PRMNE). Duration of illness widely varied among the patients. Earliest presentation was 1 month and longest duration of illness being 30 years.

Symptoms of Headache (80%), facial flushing (60%), pigmentation (60%) and erythromelalgia (50%) were common in PV patients. Fatigue (81.3%), generalised weakness (75%), loss of appetite (68.8%), loss of weight (62.2%) and abdominal discomfort (62.2%) were common in IMF and paraesthesias (62.5%), abdominal discomfort (62.5%) in ET. Splenomegaly was present in 27 (79.4%) {14(87.5%) out of 16 in IMF, 7 (70%) out of 10 in PV and 6 (75%) out of 8 in ET} and hepatomegaly in 5 (14.7%) out of 34 classic MPN patients. Arterial and venous thrombotic events were common in ET (87.5%) > PV (40%) > IMF (12.5%).

In PV mean hemoglobin (Hb) was 19.02 gm/dl, hematocrit (PCV) 59.26 vol%. Mean total leukocyte count (TLC) was 14840/mm³ and platelet count 4.24 lakh/mm³. In patients with ET mean hemoglobin was 11.03 gm/dl, mean leukocyte count was 26475/mm³ and mean platelet count was 12.89lakh/mm³. In IMF mean hemoglobin was 9.56 gm/dl, mean hematocrit 30.64 vol%, mean leukocyte count was 13768/mm³, and mean platelet count was 3.15 lakh/mm³ (Table 1).

JAK2 V617F mutation

In PV 8 patients underwent *JAK2* mutation analysis, 6 (75%) were detected to be positive. In ET out of 7 patients who underwent *JAK2* mutation analysis 5 (71.4%) were detected to be positive for the mutation and in IMF out of 9 patients who underwent *JAK2* V617 F mutation analysis 3 (33.3%) were detected to be positive (Table 2). Mean age of *JAK2* V617F positive patients was 47.21±16.59 yrs and 40.50±12.98 for negative ones.

The overall presence of *JAK2* V617F mutation in MPN was associated with a higher hemoglobin level, a higher TLC (*P<0.01*) and higher platelet counts (*P<0.05*) (Table 3). Patients

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with *JAK2* V617F mutation had higher splenomegaly (85.7%) as compared to mutation negative patients (50%), (Table 4). Thrombotic events were also slightly higher in *JAK2* V617F positive patients compared to negative ones though statistically not significant (Table 5).

DISCUSSION

Classic MPNs, PV, IMF and ET, are among the most frequent hematologic neoplasms, usually affecting the adult elderly population. They are relatively indolent disorders,[7] resulting in a modest reduction of lifespan when compared with control population. Thrombosis, hemorrhage, evolution to post-polycythemic or post-thrombocythemic myelofibrosis, and AML transformation represent the most clinically relevant issues in the course of classic MPN.[8-10] Most thrombotic events occur at or in the two years before diagnosis.[11] Recent data indicate that at least 40% of patients with splanchnic vein thrombosis not attributable to other causes actually harbour the *JAK2* V617F mutation; therefore, *JAK2* V617F genotyping represents a first-line test for these conditions.[12,13]

In our study IMF was more frequent compared to PV and ET and affected older people than that of PV, ET. Though these disorders were described to occur in 6th or 7th decades, patients in our study were comparatively younger.

Vascular complications occurred in 3 PV patients in the form of ischemic stroke in 2 patients and both ischemic stroke and deep venous thrombosis (DVT) of lower limb in 1 patient. Only one PV patient progressed to acute leukemia (AML-M2) within one year of diagnosis who was treated with hydroxyurea. All PV patients received low dose aspirin and periodic phlebotomies. Patents with erythromelalgia had a good response with low dose aspirin. Three patients who came under high risk category received hydroxyurea.

In ET, ischemic stroke occurred in 2 patients and both ischemic stroke and coronary artery disease (CAD) in one patient. Venous thrombosis was found in 3 patients and all had portal vein thrombosis with portal hypertension and esophageal varices. All patients received low dose aspirin. Three patients who had portal vein thrombosis and esophageal varices were considered as high risk category and treated with hydroxyurea.[1] In IMF, thrombotic events were found only in 2 out of 16 patients. One patient had DVT of right leg and one patient had CAD. Patients were managed with component transfusions, hydroxyurea for symptomatic splenomegaly and one patient received thalidomide.

A total of 25 patients underwent *JAK2* V617F mutation analysis. 15 were detected to be positive for the mutation. In PV 6 (75%) out of 8, in ET 5 (71.4%) out of 7 and in IMF 3 (33.3%) out of 6 patients were detected to be positive. Higher percentage of ET patients were detected to have *JAK2* V617F mutation in our study in contrast to that reported in studies from West where *JAK2* V617F positivity in ET is around 50%. This may be explained because of ethnic variation as similarly observed in AIIMS study but requires confirmation with larger population studies. JAK2 Y617F positive patients were older compared to others. Splenomegaly (85.7%) and thrombosis (64.2%) were more frequent in *JAK2* V617F positive patients. Mean hemoglobin, mean leukocyte and platelet counts were higher in patients with *JAK2* V617F mutation when compared to patients

| Spleen size (cm) | JAK2 | | P value |
	Detected (n=14)	Not detected (n=10)	
<12	2(14.2%)	5(50.0%)	0.075+
>12	12(85.7%)	5(50.0%)	
Table-4: Showing Spleenic size in relation to JAK2			

| Thrombosis | JAK2 | | P value |
	Detected (n=14)	Not detected (n=10)	
Arterial thrombosis	6(42.8%)	2(20.0%)	0.088+
Venous thrombosis	3(21.4%)	2(20.0%)	1.000
Total	9(64.2%)	4(40.0%)	0.111
Table-5: Showing Thrombosis in relation to JAK2			

without the mutation.

CONCLUSION

The 2008 WHO classification of myeloproliferative neoplasms is highly useful in diagnosing patients with MPN and as the emphasis is on molecular abnormalities such as JAK2 V617F, it is easy to exclude secondary causes. *JAK2* V617F mutation screening helps to prove clonality in these diseases. *JAK2* V617F mutation screening can also be used for other indications such as unusual thrombotic complications like abdominal vein thrombosis, unexplained erythrocytosis and thrombocytosis. Detection of this mutation may have a significant role in identification of subsets who would respond to JAK2 inhibitor therapy. It may also serve as a prognostic marker in future to indicate more severe forms of disease.

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