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Clinico-pathological profile and outcomes of patients with polycythaemia vera, essential thrombocythaemia and idiopathic myelofibrosis: a tertiary care center experience from southern Pakistan

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ORIGINAL ARTICLE

CLINICO-PATHOLOGICAL PROFILE AND OUTCOMES OF PATIENTS WITH POLYCYTHAEMIA VERA, ESSENTIAL THROMBOCYTHAEMIA AND IDIOPATHIC MYELOFIBROSIS: A TERTIARY CARE CENTER EXPERIENCE FROM SOUTHERN PAKISTAN

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Background: The "Philadelphia Negative Classic Myeloproliferative Neoplasms" include polycythaemia vera (PV), essential thrombocythaemia (ET) and idiopathic myelofibrosis (IMF). These three disorders share several clinical and laboratory features including *JAK2* V617F mutation. Our objectives were to determine the clinico-pathological profile and outcomes of Pakistani patients with polycythaemia vera (PV), essential thrombocythaemia (ET) and idiopathic myelofibrosis (IMF) in order to have an insight regarding behaviour of these conditions. **Methods:** A retrospective analysis of all the cases of PV, ET and IMF diagnosed at our institute from January 1995 to December 2013 was performed. Age, gender, clinical presentation, laboratory investigations, treatment provided and duration of follow-up were included for analysis. Appropriate statistics were utilized for calculation of data. **Results:** A total of 58 patients were diagnosed as PV, ET or IMF during the study period. Male to female ratio was 1.1:1. Forty five percent (n=27) patients came to medical attention due to abnormal laboratory results, 3 had cerebrovascular events, 3 had pruritus, and 1 patient each with gangrene and Budd-Chiari syndrome. Haemorrhage was not seen in any patient. Sixty percent (n=35) patients were treated with phlebotomy, hydroxyurea and aspirin alone or in combination. None of the patients transformed to myelofibrosis (MF) or myelodysplasia (MDS) during the mean (±SD) follow-up period of 57.2±50 months. One patient with ET transformed to acute myeloid leukaemia 9 years after the diagnosis. **Conclusions:** This study demonstrated a relatively more benign form of PV, ET and IMF with lesser frequency of symptoms, good response to treatment and less likelihood of transformation to MF, MDS or AML.

Keywords: Myeloproliferative neoplasms, Polycythaemia vera, Essential thrombocythaemia, Idiopathic myelofibrosis, Pakistan

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INTRODUCTION

The Myeloproliferative Neoplasms (MPNs) are clonal disorders of haematopoietic stem cells characterized by overproduction of one or more myeloid cell lineages. Conditions which are considered myeloproliferative neoplasms under the classification used by the World Health Organization[1] include chronic myelogenous leukaemia (CML), polycythaemia vera (PV), essential thrombocythaemia (ET), idiopathic myelofibrosis (IMF), chronic neutrophilic leukaemia (CNL), chronic eosinophilic leukaemia-not otherwise specified (CEL-NOS), mastocytosis, and myeloproliferative neoplasms unclassifiable (MPN-U). Located in Philadelphia chromosome (Ph), BCR-ABL1 gene is found positive only in CML.

The three classic Ph-negative MPNs (PV, ET and IMF) share several clinico-pathological features. All three are characterized by marrow hyper cellularity, risk of thrombosis, haemorrhage and leukemic transformation. *JAK2* V617F mutation is another feature which is shared by these three conditions. It is found positive in approximately 95%, 60% and 50% cases of PV, ET and IMF respectively. *JAK2* V617F mutation is often said to be associated with more aggressive nature of these conditions. In PV and ET, it has been found associated with higher haemoglobin[2,3] and granulocyte levels,[4,5] a greater incidence of pruritus,[2] a higher rate of fibrotic transformation[2] and thrombosis[6]. Lower platelet counts and increased risk of transformation to PV in *JAK2* positive ET[7,8] and more aggressive disease phenotype with shortened overall survival have been described with *JAK2* positive IMF.

Patients with PV and ET come to medical attention either due to abnormal laboratory results or may have symptoms related to myeloproliferation like pruritus, thrombosis, headaches, erythromelalgia, visual disturbances and haemorrhage. Most patients with IMF on the

contrary present with debilitating fatigue, anaemia, early satiety secondary to marked splenomegaly and constitutional symptoms.[9]

Transformation into acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and myelofibrosis (MF) are major causes of death in PV.[10] Median survival in PV if treated is 10 years. Most patients with ET enjoy a normal life expectancy without associated disease-related complications[11] as evolution into either AML or MF is unusual.[12] Median survival in IMF according to the series used for constructing the International Prognostic Scoring System (IPSS) was reported to be 69 months.[13]

The goal of treatment in PV and ET is to relieve symptoms and prevent thrombosis without increasing the risk of bleeding.[14] Several therapeutic modalities based on risk stratification of these conditions have been described.[14] The role of phlebotomy, low-dose aspirin, hydroxyurea, interferon-alpha[15] and anagrelide is well documented.

Literature search revealed lack of studies from Pakistan addressing these three conditions. Therefore, we aimed in determining clinico-pathological profile and outcomes of patients with PV, ET and IMF diagnosed at our centre. This study will provide an insight to the clinicians dealing with these three Philadelphia-negative classic myeloproliferative neoplasms.

MATERIAL AND METHODS

This was a retrospective analysis performed in the Section of Hematology, The Aga Khan University Hospital. An exemption (2967-Pat-ERC-14) was granted by institutional ethical review board for conducting this study. All patients diagnosed as PV, ET or IMF from January 1995 to December 2013 were included in the analysis. Medical records were retrieved with the help of institutional data management system.

The diagnosis of all three disorders was made in accordance with the WHO criteria in use at the time of first presentation (WHO criteria 2001 and 2008). Before that, diagnosis was made based on Polycythaemia Vera Study Group Criteria (PVSG).

Age, gender, clinical presentation, laboratory investigations, treatment provided and duration of follow-up were included for analysis. Statistical package for social sciences (SPSS-19) was utilized for data analysis (SPSS Inc., Chicago, IL, USA). Frequency and percentage were calculated for categorical variables and mean and standard deviation were computed for quantitative variables.

RESULTS

A total of 58 patients were diagnosed as PV, ET or IMF during the study period. Male to female ratio was 1.1:1 with mean±SD age of 57.3±13.3 for males and 56.3±16.6 for females. The mean age and gender distribution of study population with respect to the diagnosis is shown in table-1.

For PV and ET, the most common reason for consultation was abnormal complete blood count (CBC) findings carried out as routine testing. Three of 6 patients with IMF presented with constitutional symptoms. Two patients (1 male, 1 female) with PV and one female with ET presented with stroke. None of the patients with PV or ET had erythromelalgia or haemorrhage. Other key presenting features and *JAK2* V617F mutation status are detailed in table-1. Haematological parameters of study population are shown in table-2.

Thirty seven out of 58 patients (64%) continued their follow-up in haematology outpatient department. Of those who were treated, combination of phlebotomy, hydroxyurea and aspirin was the most common strategy for PV patients (Table 3). Twelve patients who required therapeutic phlebotomies, mean±SD haematocrit were 54.9±6.7 at the time of diagnosis. The mean±SD units of whole blood (450ml each approximately) taken out were 5.0±6.0 over the mean±SD follow-up period of 77.8±59.5 months. Interferon alpha and anagrelide were not utilized in any patient. Most of the patients with ET received hydroxyurea and aspirin in combination. None of the patients with PV and ET transformed into MF or MDS with a mean±SD follow-up period of 71.3±57.2 and 52±47 months respectively. Evolution into AML was seen in one female patient with ET. She developed AML 9 years after the initial diagnosis and subsequently succumbed to this aggressive condition. All four patients with IMF were treated differently (Table 3) with only one patient requiring red cell transfusions. Three patients with IMF (1 on no treatment, 1 on hydroxyurea and 1 on aspirin only) remained stable with a median follow-up of 32±18.7 months. Treatment details and follow-up duration of study population are shown in table-3.

JAK2 V617F mutation was found positive in 89.3%, 58.3% and 66.7% of patients with PV, ET and IMF respectively (Table-1). Of 31 symptomatic patients, 25 (81%) were positive for this mutation including patients with cerebrovascular events, gangrene and Budd-Chiari syndrome (Table 4). Similarly, haematological parameters were higher in patients with *JAK2* V617F positive mutation status except for the platelet count which was low (Table-4). Single patient with ET who transformed to AML was negative for this mutation.

Table-1: Age, gender, clinical features and *JAK2* V617F mutation status of study population

	PV	ET	IMF
Number of Patients (%)	28 (48.3%)	24 (41.4%)	6 (10.3%)
Males	19 (67.8%)	5 (20.8%)	6 (100%)
Females	9 (32.2%)	19 (79.2%)	0
Age in years (Mean±SD)			
Males	52.5±12.6	61.4±8.3	59.5±19.8
Females	64±14.8	53.6±15.9	-
Presenting symptoms			
Constitutional symptoms (night sweats, weight loss, fever)	3 (10.7%)	0	3 (50%)
Abnormal laboratory findings	14 (50%)	13 (54.2%)	-
Symptoms influencing daily activities (fatigue, insomnia, inactivity)	4 (14.3%)	4 (16.6%)	1 (16.7%)
Complaints related to myeloproliferation (Bone pains, itching)	3 (10.7%)	5 (20.8%)	1 (16.7%)
Cerebrovascular event	2 (7.1%)	1(4.2%)	-
Gangrene	1 (3.6%)	-	-
Budd-Chiari	1 (3.6%)	-	-
Symptoms of splenomegaly	0	1(4.2%)	1 (16.7%)
Palpable Splenomegaly	8 (28.6%)	-	4 (66.7%)
***JAK2* V617F Mutation[(a)]**			
Positive	25 (89.3%)	14 (58.3%)	4 (66.7%)
Negative	3 (10.7%)	10 (41.7%)	2(33.3%)

(a) JAK-2 mutation analysis in 9 patients was performed during follow-up period when this test became available in 2008; all were positive

Table-2: Haematological parameters of study population

Diagnosis	Sex	Haemoglobin (g/dl)	Haematocrit (%)	RBC (X 10^{12}/L)	MCV (fl)	MCH (pg)	WBC (X 10^9/L)	Platelets (X 10^9/L)
PV	Male (n=19)	18.2±2.0	56.4±6.2	8.8±6.1	75.1±17.0	24.9±3.7	20.4±13	470±182
	Female (n=9)	17.1±2.2	54.3±6.7	6.8±0.9	81.1±13.1	26.0±4.4	22±13.8	569±228
ET	Male (n=5)	11.6±1.9	37.7±6.1	4.0±0.1	83.6±3.4	27.5±1.6	16.1±10.4	1375±781
	Female (n=19)	13±1.4	39.8±4.5	4.9±0.7	84.8±8.5	27.8±3.1	11.5±3.7	968±442
IMF	Male (n=6)	11.4±2	34.6±7.0	3.7±0.4	74.1±14.3	24.5±5.9	20.3±17	636±623

Table-3: Treatment details and follow-up of patients who continued their treatment in our institution (n=37)

Treatment	PV	ET	IMF
Wait and Watch	0	0	1 (25%)
Hydroxyurea	0	5 (26.3%)	1 (25%)
Aspirin	0	2 (10.5%)	1 (25%)
Phlebotomy + Hydroxyurea + Aspirin	12 (85.7%)	0	0
Hydroxyurea + Aspirin	2 (14.3%)	12 (63.2%)	0
Hydroxyurea + RBC transfusions	0	0	1 (25%)
In follow-up	14 (50%)	19 (79%)	4 (66.6%)
Lost to follow	14 (50%)	5 (21%)	2 (33.3%)
Mean follow-up (months)	71.3±57.2	52±47	32.0±18.7

Table-4: Clinical features and haematological parameters in patients with respect to *JAK2*-(V617F) mutation status

	JAK2 V617F Positive	*JAK2* V617F Negative
Number of patients	43 (74%)	15 (26%)
Abnormal laboratory results	18 (41.8%)	9 (60%)
Constitutional symptoms	5 (11.6%)	1 (6.7%)
Symptoms of splenomegaly	1 (2.3%)	1 (6.7%)
Symptoms influencing daily activities	7 (16.3%)	2 (13.3%)
Symptoms related to myeloproliferation	8 (18.7%)	1 (6.7%)
Cerebrovascular events	2 (4.7%)	1 (6.7%)
Budd-Chiari Syndrome	1 (2.3%)	0
Gangrene	1 (2.3%)	0
Haemoglobin (g/dl)	15.5±3.2	13.3±3.0
Haematocrit (%)	48.4±10.5	41.5±8.8
Red Blood Cells (X 10^{12}/L)	7.3±4.7	4.8±0.6
White blood cells (X 10^9/L)	19.4±12.3	10.1±2.9
Platelets (X 10^9/L)	716±485	876±535

DISCUSSION

Our study ascertained several important facts in Pakistani patients with PV, ET and IMF. To the best of our knowledge, it is the first study from Pakistan detailing clinico-pathological profile of patients with PV, ET and IMF. The median age at presentation for all three conditions in our study is comparable to that described in the literature (Table-1). Sex ratios for PV, ET and IMF in this study are quite different from international data. Male to Female ratio in PV was 2.1:1 which is almost double. Female preponderance in ET (female to male ratio of 2:1) has been reported in several studies however, female to male ratio was found to be 3.8:1 in this study. All 6 patients with IMF were males. Although PV and ET are identified by chance in a proportion of patients, almost half of the patients with these conditions in our study came to medical attention due to incidental abnormal

laboratory findings (Table-2). Only three (10.7%) patients with PV had pruritus whereas, it has been reported in as high as 68% of the patients with PV.[16] Thrombotic events were present in four (14.3%) patients with PV (cerebrovascular event in 2, Budd-Chiari syndrome in 1 and gangrene in 1). These figures are comparable to international data.[17] In ET however, only one (4.2%) patient presented with cerebrovascular thrombosis. Incidence rates of thrombosis in ET varying from 9 to 22 percent have been described in various studies.[12,18]

Patients who continued their follow-up in our institute, hydroxyurea in combination with aspirin was the most common treatment modality utilized for PV and ET. Considering the follow-up period of 77.8±59.5 months in patients with PV who required phlebotomies, the requirement for it was low (5.0±6.0 units of whole blood). Patient with both PV and ET responded well to hydroxyurea with no events of thrombosis, transformation or death (except one patient). Higher risk of both disease transformation and death in hydroxyurea resistance disease has been published in literature.[19,20] In patients with MF, calculation of scores according to Dynamic International Prognostic Scoring System[21] (DIPSS) revealed following results: intermediate risk-1 (5 patients) and intermediate risk-2 (1 patient). One patient with intermediate risk-2 DIPSS score remained clinico-haematologically stable during the follow-up period of 20 months. Median survival in intermediate risk-2 category according to DIPSS is 4 years.[21]

The prevalence of *JAK2* V617F mutation in this study is comparable to available international literature (Table-1). The more aggressive clinico-pathological features in *JAK2* V617F mutation positive patients as well as lower platelet counts are in accordance with other reported studies.[7,8] Interestingly, the single patient with ET who developed AML after 9 years of initial diagnosis was negative for this mutation.

Besides being the first study from Pakistan detailing clinico-pathological features and outcomes of patients with PV, ET and IMF, other strength of this study is its long duration (19 years; from 1995–2013) and reasonable follow-up (57.2±50 months). Although the sample size is not large enough however, considering the annual incidence of 0.5-2.5 cases per 100,000 populations in western countries, the current data from a tertiary care centre provides a passable insight into behaviour of these conditions in study population. We could not provide the data on frequency of other mutations like exon 12 mutation in PV and MPL gene in ET due to unavailability of these tests at our institute. Similarly, quantification of *JAK2* V617F burden to assess risk of thrombosis could not be scrutinized.

CONCLUSIONS

This study demonstrated a relatively more benign form of PV, ET and IMF with lesser frequency of symptoms and good response to treatment. Transformation to aggressive forms like myelofibrosis and myelodysplasia were also not seen in any patient. The possible influence of genetic and environmental factors on milder phenotype of these conditions in Pakistani population needs further exploration.

AUTHOR'S CONTRIBUTION

MSS collected and analysed the data, searched literature and wrote-up the manuscript. MUS, Salman NA and MK conceptualized the study and reviewed the manuscript critically. ZAA collected data and proof-read the manuscript.

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