RESEARCH ARTICLE

Clinico-Epidemiological Profile of Patients with Polycythaemia Rubra Vera - a Five Year Experience from a Tertiary Care Center

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Abstract

Background: Polycythaemia rubra vera (PV) is a Philadelphia chromosome negative myeloproliferative neoplasm characterized by increased red cell production, independent of the mechanisms that regulate normal erythropoiesis. The aim of this study was to analyze the clinico-epidemiological profile of Pakistani patients with PV. Materials and Methods: In this retrospective cross sectional study, 26 patients with PV were enrolled from January 2010 to December 2014. They were diagnosed based on WHO criteria. Results: The mean age was 53.4±9.31 years (range 36-72) and the male to female ratio was 2:1. Overall 30.7% of patients were asymptomatic. In symptomatic patients, major complaints were headache (30.8%), abdominal discomfort (23.1%), blurred vision (15.3%), pruritus (11.5%) and vascular incidents (11.5%). Physical examination revealed plethoric face and splenomegaly as predominant findings, detected in 34.6% and 30.7%, respectively, with the mean splenic span of 15.9±2.04cm. The mean hemoglobin was 18.1±1.9 g/dl with the mean hematocrit of 55.6±8.3%. The mean total leukocyte count was 12.8±7.1x10^9/l and the platelet count 511±341.9x10^9/l. Mean erythrocyte sedimentation rate was 3.5±1.22mm/hr. Serum lactate dehydrogenase, serum creatinine and uric acid were 552.7±309.2, 0.8±0.17 and 6.60±1.89 respectively. Conclusions: PV in Pakistani patients, unlike in the West, is seen in a moderately young population. The disease is frequently seen in male gender and primarily patients present with symptoms related to hyperviscosity.

Keywords: Clinico-epidemiological profile - polycythaemia rubra vera - Pakistan

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Introduction

Myeloproliferative neoplasms (MPN) are clonal hematopoietic stem cell disorders characterized by excessive proliferation of one or more myeloid lineage cells (Sag et al., 2015; Yang et al., 2015). Polycythaemia rubra vera (PV) is a chronic MPN characterized by increased red blood cell proliferation; independent of normal regulatory mechanisms. It is a Philadelphia chromosome (Ph)-negative myeloproliferative neoplasm which could be evolving to myelofibrosis or may have leukemic transformation (Ma et al., 2008; Zhang et al., 2014).

In the literature annual incidence for PV is 1-3 cases per 100,000 individuals (Sag et al., 2015; Johansson et al., 2006). It occurs most commonly in the sixth decade of life with the median age at diagnosis is ~60 years; however, disease may occur at any age (Thiele et al., 2008; Tefferi et al., 2013). Most reports indicate a slight male predominance with the male to female ratio is about 2:1 (Thiele et al., 2008).

Disease manifestations are often insidious in onset, and they are frequently related to increased blood hyperviscosity owing to a marked increase in the cellular component of blood. Succeeding sluggish blood flow lead to deprived oxygen delivery, cause symptoms that include headache, blurred vision, dizziness, vertigo and tinnitus. In nearly 20% of patients may have an episode of arterial or venous thrombosis which at times is the first manifestation of disease (Thiele et al., 2008). Physical findings are indistinctive, but may include visceromegaly, facial plethora or gouty nodules.

Several risk factors and genetic predisposition have been identified, but the specific underlying cause is not clear. The diagnosis is often reliant on the laboratory tests. Frequent findings include an elevated hemoglobin level and hematocrit; usually accompanied by leukocytosis and thrombocytosis. Virtually all patients carry the acquired somatic gain of function mutation of the Janus associated kinase genes (Agarwal et al., 2015; Yonal-Hindilerden et al., 2015).

Published local epidemiology data are scarce. There are 2-3 studies are available from Pakistan (Usman et al., 2004; Khattak et al., 2012). The present study is a single

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institution retrospective analysis of our patients with PV over five years; its demographics, clinical presentation and laboratory profile.

Materials and Methods

This descriptive cross sectional study, extended from January 2010 to December 2014, conducted at Liaquat National Hospital and Medical College. During the study period, 26 patients diagnosed to have Polycythaemia Rubra Vera were enrolled in the present study. All patients were registered in hematology clinic where patient's records were maintained along with regular follow ups.

Patients were diagnosed to have PV according to the World Health Organization (WHO) criteria (Thiele et al., 2008). Diagnosis required meeting both major criteria and one minor criteria or the presence of first major criteria together with two minor criteria.

Major criteria includes: *i*). Hemoglobin >18.5 gm/dl in male or >16.5 gm/dl in women; *ii*). Demonstration of JAK2 V617F or other similar mutation such as JAK2 exon 12 mutation; Minor criteria; *iii*). Bone marrow biopsy showing hypercellularity for age with panmyelosis; *iv*). Serum erythropoietin levels below the reference range from normal.

In-vitro culture of erythroid colonies was not done as this facility is only available in our country.

Socio-demographical data including age, gender and medical history were recorded. Clinical symptoms, signs and laboratory data of all these patients at the time of presentation were noted.

Hematological parameters were determined by Automated Cell Dyne Ruby Counter (Abott, Diagnostics). Serum creatinine, lactate dehydrogenase (LDH) and serum uric acid were detected by HITACHI 912 (Japan) by photometric assay. JAK2 V617F mutational analyses were done by Polymerase chain reaction (PCR). Bone marrow aspirate and trephine biopsy specimen were taken with Jamshidi needle, were reviewed by expert hematopathologists. Serum erythropoietin was measured by ELISA technique through automated analyzer.

Ethical approval for the study protocol was obtained by research and ethical committee LNH taken prior to the study.

Statistical analysis

Data was collected on computerized database and analyzed using SPSS windows version 22 statistical package (SPSS Inc, Chicago, IL, USA). The results were expressed as mean (SD) for quantitative variables and qualitative variables are presented as frequency and percentages.

Results

Demographical outline

A total of 26 confirmed Polycythaemia vera patients using the non probability consecutive sampling were included in this study. Out of 26 patients, 17 were males (65.3%) and 9 were females (34.7%) with male to female ratio of 2:1. The mean age was 53.42±9.31 years (range 36-72). Mostly (n=16) patients were >50 years (61.5%) of age; while 10 (38.4%) patients were ≤50 years of age.

Clinical findings

Overall 18 (69.3%) patients were symptomatic and remaining 8 (30.7%) were diagnosed incidentally. In symptomatic patients, major complaints were headache in 8 (30.8%) patients; abdominal discomfort in 6 (23.07%) patients; blurred vision in 4 (15.3%); pruritus in 3 (11.5%) patients and vascular accident were also noted in 3 (11.5%) patients. The most common vascular event was transient ischemic attack (7.69%). While one patient (3.84%) presented with Budd-chiari syndrome.

Physical examination revealed plethoric face and splenomegaly as predominant findings detected in 9 (34.6%) and 8 (30.7%) patients respectively, with the mean splenic span of 15.9±2.04cm.

Laboratory profile

The mean hemoglobin was 18.14±1.9 g/dl (range 16.5-22.1) with the mean hematocrit of 55.6±8.3%. Mean cell volume was 76.88±12.5 fl. The mean total leukocyte count was $12.8\pm7.1 \times 10^9$/l (range 4.3-28.6) and platelets counts of 511±341.9x109/l (range 132-1462). Serum erythropoietin was 6.86±5.4 u/mI. JAK2 V617 F mutation was positive in 24 (92.3%) patients out of total 26 study subjects.

Mean erythrocyte sedimentation rate was 3.5±1.22mm/1hr. Serum lactate dehydrogenase, serum creatinine and uric acid were 552.7±309.2, 0.8±0.17 and 6.60±1.89 respectively.

Discussion

Polycythaemia rubra vera belongs to clonal myeloproliferative neoplasms (MPN), characterized by unexplained red cell expansion, hyperviscosity, thromboembolism and infrequent overt bleed, could culminates into myelofibrosis (Zhang et al., 2014; Tefferi et al., 2015). PV is associated with a good prognosis with the reported median survival of 10-16 years (Cervantes et al., 2008; Hoffbrand and Moss., 2011).

This hematological disease is relatively uncommon world widely. There are a few handful studies reported from Pakistan on this hematopoietic malignancy (Usman et al., 2004; Khattak et al., 2012; Sadiq et al., 2013). The present study has demonstrated clinical features, hematological markers and biochemical profile in Pakistani PV patients.

PV usually develops insidiously and is mainly observed in people over the age of 60 years. Most of the patients in the present study presented in the 5th decade of life, with the mean age of 53 years. It was noted that the mean age in our patients was more or less similar with that was reported (51.3 years) in the previous local study (Usman et al., 2004). Similarly a large regional study reported from India, showed the mean age of 52 years in their PV patients (Sazawal et al., 2010). Recent one Thai study reported the median age of 58 years, in concurrence to our findings (Sag et al., 2015). When compared with earlier international reports, herein disease being manifested in relatively younger age as compared

with developed countries, where the median age is around 61 years (Tefferi et al., 2013). The plausible explanations are varied genetic makeup and also the higher mean age in western countries compared with South Asian locality.

The male gender preponderance was seen in the present study with the gender ratio of 2:1; which is in concurrence with the prior Indian and Thailand studies (Sazawal et al., 2010; Duangnapasatit et al., 2015).

The clinical manifestations of PV are heterogeneous, patients are usually symptomatic. Patients often have symptoms related to hyperviscosity and hypermetabolism including vascular events, headaches, night sweats, abdominal discomfort or pruritus. As most of our patients had disease symptoms (69.3%), this is more or less similar to earlier studies reported from Pakistan (77%) and Thailand (69.2%) (Usman et al., 2004; Duangnapasatit et al., 2015).

Main presenting complaints were headache (30.8%) and abdominal discomfort (23%) in a significant proportion of our patients. Previously one study reported from India disclosed thrombotic events in 2.9% of their patients (Sazawal et al., 2010). W hile thrombotic manifestation is very dominantly seen in Thai patients with PV (29%) (Duangnapasatit et al., 2015).

In the present study thrombotic events were noted in 11.5%, in which transit ischemic attack (stroke) was frequent (7.6%). All the three patients with thrombotic events had hemoglobin ≥20 gm/dl. Vascular stasis and an increased viscosity contributes to thrombotic complication in PV patients (Hoffbrand and Moss., 2011). Surprisingly, no patient in our series had bleeding manifestation. Though mean platelets counts is 511 x 109/l. A higher platelet count is frequently associated with bleeding in PV.

Splenomegaly has been reported in 11.8–70 % of patients with PV (Thiele et al., 2008; Duangnapasatit et al., 2015). However in our series it is intermediate (30.7%). In parallel to our findings, previous local study reported 30.7% of patients had splenomegaly (Usman et al., 2004). Another recent large series from Thailand, also reported splenomegaly and facial plethora in 11.8% and 10.3% respectively (Duangnapasatit et al., 2015).

The mean hemoglobin in our series was 18.14±1.9 g/dl. In concurrence to our results local studies from Rawalpindi (17.8±2.0 g/dl) and an another Karachi based (18.2 ±1.8 g/dl) study revealed similar findings (Usman et al., 2004; Khattak et al., 2012).

Lastly limitations need to be mentioned. The study sample size is small. A large sample would be a better indicator of clinical and laboratory characteristic in our population. Secondly the follow up data for disease clinical course is not available.

In conclusion, the study provides local informative facts, revealed that PV is predominantly a disease seen in moderately younger population and most patients presented with hyperviscosity. Presenting clinical features are similar as reported in available literature. Prospective studies should be pursueded on large patient cohort to investigate further disease spectrum and should incorporate follow up to determine the median survival and disease evolving trends in our local setting.

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