Secondary erythrocytosis, a predominant cause of polycythemia- Clinical and laboratory evaluation of polycythemia in a tertiary care center

ABSTRACT

Aims: Polycythemia refers to an increased production of red blood cells from bone marrow. It is one of the frequent reasons for a hematology consultation. The present work aimed to examine the causes, clinical manifestations, prevalence, and diverse patterns in laboratory and clinical parameters among patients with polycythemia attending our outpatient clinics at the Indus Hospital and Health Network.

Study Design: The present work is retrospective observational study which included all cases of polycythemia.
Place and Duration of the Study: The study was conducted at a tertiary health care center in Karachi, Pakistan during October 2019 to July 2021.

Methodology: The data from the patient diagnosed with polycythemia was entered and analyzed by using SPSS version 24.0. Descriptive statistics as per the Gaussian Normality distribution (Sapiro-Wilk) were computed along with frequencies. The association where applicable was calculated via standard statistical methods with the chi square test for categorical while independent sample t-test for the continuous variables. The level of statistical significance will be set at $P< 0.05$.

Results: During the investigated period, a total of 33 patients were diagnosed with polycythemia demonstrating a notable male predominance (82%). The majority of the patients exhibited secondary erythrocytosis (85%) with only a minority (15%)diagnosed with polycythemia vera. Of the identified cases of secondary erythrocytosis a significant proportion (46%) was observed in individuals who were smokers while other were found with hypoxic pulmonary disease, hepatitis, and chronic kidney disease. In secondary erythrocytosis 21 patients (75%) required venesection for symptom reduction, while 7 (25%) were closely monitored due to their asymptomatic status. On the contrary all cases of polycythemia vera required a comprehensive treatment approach including venesections, cytoreduction with hydroxyurea and low dose aspirin.

Key words:Erythrocytosis, Polycythemia vera, Smoking, Venesection.

1. INTRODUCTION

Polycythemia is a hematological disorder manifested mostly as an increase in red blood cell counts (RBC), hematocrit and red cell mass. To a lesser extent thrombocytosis and/orleukocytosis is accompanied by rise in RBC counts if there is an underlying clonal cause for polycythemia [1]. For normal physiological conditions, the RBC mass is 26 to 32 mL/kg and 23 to 29 mL/kg for males and females respectively [2]. According to the latest classification scheme devised by the World Health Organization (WHO), the hematocrit and hemoglobin diagnostic thresholds are set to, >48% and 16.0 g/dL for women and >49% and 16.5 g/dL for men, respectively [3, 4].

Polycythemia is generally categorized into two subtypes i.e., Primary polycythemia or Polycythemia vera (PV) and secondary erythrocytosis. The PV constitutes clonal myeloproliferation driven by stem cells characterized by the driver mutation JAK2 distributed in almost 99% of the cases. The mutations in the exon 14 JAK2V617F are responsible for 97% of the total mutations harbored by the patients of PV while the remaining are associated with exons 12, 13, and 14 [5, 6]. The PV mainly affects women with the annual frequency of 0.68–2.60 for every 100,000 individuals. The PV patients after diagnosis usually achieve life expectancy of 14 years or more and enjoy good quality of life on cytoreduction or venesections. Thrombotic episodes and less commonly leukemic transformation are the major risk factors for mortality in PV [1, 7].

Secondary erythrocytosis (SE), is usually a result of an exogenous stimulation leading to increase production of red blood cells from bone marrow due to hypoxia or high erythropoietin drive. The overproduction of the erythrocytes in SE could be congenital i.e., driven by the mutation in the erythropoietin (EPO) receptor or may be induced or acquired whereby physiological alterations raise oxygen demand as mentioned earlier. The acquired SE results mainly in response to smoking, cardiopulmonary disorders, obesity hypoventilation, renal and hepatic disorders [2, 8, 9].

The hemoglobin(Hb)/ Hematocrit (Hct) levels are influenced not only by red cells, but also by mean corpuscular volume (MCV) [10]. Further, Red cell distribution width (RDW) serves as a readily available inflammatory biomarker, offering a simple yet effective tool [11]. Thus, RDW is a helpful parameter in differentiating the SE from the PV [12].The neutrophil-to-lymphocyte ratio (NLR) is another emerging and reliable surrogate marker for polymorphonuclear leukocytes (PMNL), serving as a predictive marker of thrombosis in PV [13, 14]. Notably, transforming growth factor beta (TGF-β1) and interleukin-10 (IL-10) play pivotal roles as key regulators of immune homeostasis, exerting anti-tumor effects [15, 16]. A well-established complication of PV such as Budd-Chiari syndrome (BCS), results from the obstruction of hepatic vein outflow or the suprahepatic portion of the inferior vena cava [17]. Markedly, isolated factor C deficiency stands out as the prime etiology of BCS in middle-aged male. The proliferation of bone marrow fibroblasts in PV is induced by abnormal megakaryocytes, which synthesize and locally release fibrogenic cytokines, including platelet-derived growth factor, basic fibroblast growth factor, and transforming growth factor (TGF-β1) [18].

There is a paucity of data on secondary erythrocytosis as most studies are carried out on polycythemia vera or myeloproliferative neoplasms in literature. This study has assessed the frequency and underlying causes for secondary erythrocytosis for the first time in our country. This study brings forward the whole spectrum of polycythemia from our tertiary health care setup rather than just a focus on PV in most of the regional studies.

2. Material and Methods

2.1Study Plan: This is a retrospective observational study which has included all cases of polycythemia (n=33) diagnosed at a tertiary health care center in Karachi, Pakistan during October 2019 to July 2021. Institutional Review Board approval was taken before initiation of study. The diagnosis for the polycythemia was made according to the WHO 2016 criteria for PV vera where polycythemia was defined as persistent rise in Hct of >49% males, >48% females and Hb of >16.5 g/dl in males and >16.0 g/dL in females. Levels above these defined threshold, presence of splenomegaly, panmyelosis (elevated hematocrit and red cell counts along with raised white cells and platelet counts) and a positive result for the JAK2V617F mutation led us to differentiate polycythemia vera from SE. The venesection thresholds were followed as per British Committee for Standards in Haematology (BCSH) guidelines for the

management of polycythemia and secondary eryhtrocyosis[19, 20].The demographics, clinical and laboratory data from the time of the diagnosis were retrieved from the electronic medical records of the hospital. The variables i.e., physical examination, body mass index, co-morbidities, status of smoking, thrombosis and therapeutic intervention/treatment employed corresponds to the clinical data while for the laboratory data complete blood count, erythropoietin levels, JAK2V617F mutation, blood gas analysis, creatinine, liver function test, hepatitis B and C screening, left ventricular ejection fraction on echocardiography and radiological scans were considered.

2.2 Statistical Analysis: The SPSS version 24 for windows was used for the statistical analysis with percentages and frequencies calculated for categorical variables like gender, smoking, comorbids, along with others. The Mean±standard deviations (SD) were calculated for continuous variables like age, BMI, blood count as per normality distribution calculated via Shapiro-Wilk assumption. The association where applicable was calculated via standard statistical methods with the chi square test for categorical while independent sample t-test for the continuous variables. The *P* values of < 0.05 were considered statistically significant.

3. RESULTS

A total of 33 patients presenting with mean age of49.48±15.08years were diagnosed with polycythemia during the studied period and were included in the present study. Of them 27 were males while six females with relative percentage of 81.82 and 18.18% respectively. Among the patients, only five (15.15%) were diagnosed with polycythemia vera (PV) while the majority, 28 (84.85%) had secondary erythrocytosis (SE). The PV group had three (60.0%) females and two (40.0%) male patients with the mean age at the time of presentation being 49.8±6.42 years. A clear male preponderance (85.71%) was evident in SE cases with recorded mean age of 49.43±16.23 years. The gender distribution of both groups is presented in Table 1.

Table 1. The distribution of gender alongside the association with diseases etiology or association among the groups based on diagnosis.*P* value computed using Fisher's Exact test.

Diagnosis	Male n (%)	Female n (%)	Total n (%)	*P*value
Polycythemia Vera	3 (60.00)	2 (40.00)	5 (18.18)	0.22
Secondary Erythrocytosis	24 (85.71)	4 (14.29)	28 (84.85)	
Total	27 (81.82)	6 (18.18)	33	

The mean body mass index (BMI) was found to be 22.77±4.85 and 25.95±5.42 for PV and SE respectively featuring non-significant association with *P* value of 0.24. However, 6 patients (18%) had BMI more than 30 kg/m^2 all belonging to SE group.The parameters included in the complete blood profile include hemoglobin (Hb g/dl), hematocrit level (HCT %), red blood cells (RBCs x 10^9/L), white blood cells (WBCs x 10^9/L) and platelets count x 10^9/L. The mean Hb level and HCT at presentation was higher in the secondary erythrocytosis group 17.17±1.89 g/dl and 51.47±5.97% as compared to the primary erythrocytosis group which had Hb of 15.60±1.20 g/dl and HCT of 51.5±3.66 %. Contrarily the mean RBCs (7.07±1.13) WBCs(23.09±8.04) and platelet counts (1020.00±588.01) was found significantly higher in primary polycythemia group in comparison to the secondary erythrocytosis with recorded mean values of 5.87±0.94, 8.51±2.37, and 239.54±79.14respectively. The percentage of deranged observations

for the discussed parameters in the studied groups along with the statistical association is presented in figure 1.

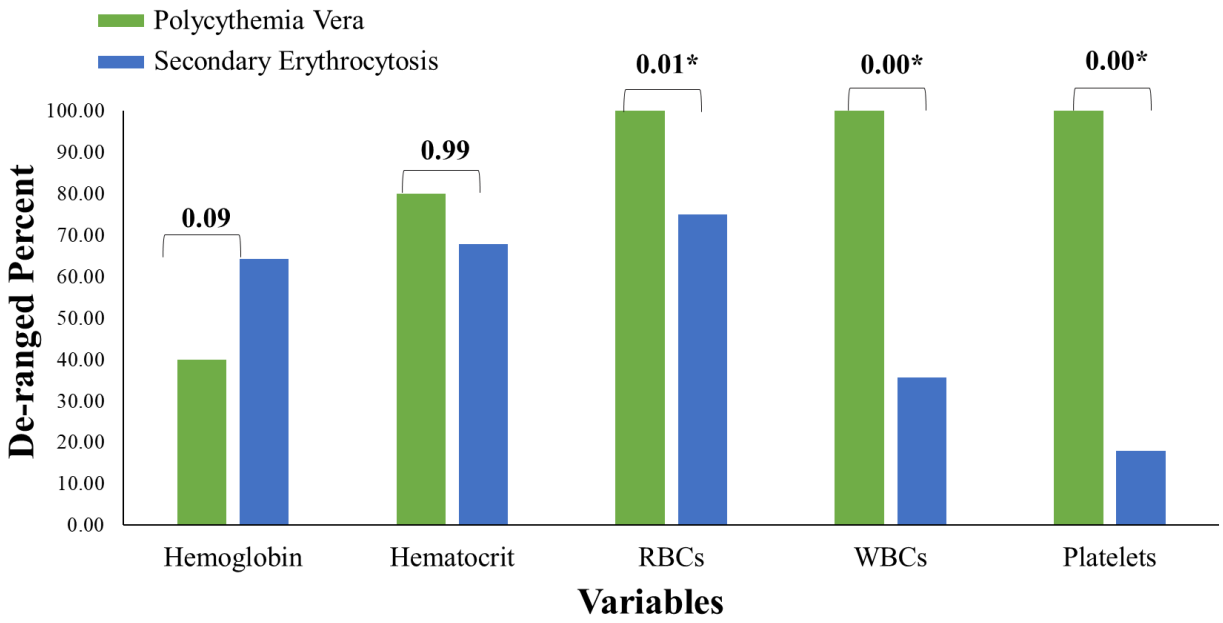

Fig. 1.The deranged observations among the patients alongside the statistical association presented on the top of the bars where * denotes the significant association. The *P* values were calculated using an independent sample t-test.

A considerable portion of the participants in our study, accounting for 42% (14 out of 33 cases), had a background in smoking. All smokers had SE except one patient who had PV. Among the cases with SE, 21.43% (six cases) were solely attributed to smoking, while 78.57% (22 cases) had additional contributing factor(s) such chronic obstructive pulmonary disease (COPD), obstructive sleep Apnea (OSA), chronic kidney disease (CKD), hepatitis, and ischemic heart disease (IHD).

Hypoxia driven erythrocytosis was observed in five cases of SE as indicated by low pO2 levels (pO2 less than 75mmHg). Detailed analysis indicated that one patient with hypoxia and SE had heart failure, one had COPD, and another had OSA. An isolated case of hypoxia presented with JAK 2 positive PV. In contrast hypercapnia which is associated with high pCO2 levels (pCO2 > 45mmHg), was observed intwo patients of SE one of them was identified as smoker and another suffered from cardiac dysfunction. Upon OSA screen (STOP-BANG scoring), four patients (14%) were found to have high suspicion of OSA that might be a cause of SE in these candidates hence were referred to pulmonology clinic for further evaluation. 3 patients with SE had COPD.The cardiac function was assessed via reviewing the left ventricular ejection fraction (LVEF), where 3 (9%) of the cases exhibit left ventricular dysfunction (EF less than 50%) 2 of them had SE and one had PV.

The renal function was assessed by considering the creatinine levels. There was no significant difference (P = 0.29) in mean values observed for both the disease groups (PV=0.83±0.18; SE=1.01±0.32) but the high level of creatinine where reported was mainly associated with SE associated withrenal dysfunction- 3 (9%) cases. Isolated SE was seen in 3 (9%) patients having a co-existing CKD, two of these patients were smokers as well. The imaging performed for these cases did not reveal any renal cysts

We observed eight (25%) patients in SE group with hepatitis, five were hepatitis B positive, two were hepatitis C positive and one had suspected nonalcoholic fatty liver disease. Additionally, two patients with PV were also had with hepatitis C.

The various other etiologies of secondary erythrocytosis are mentioned in Table 2.

Erythropoietin levels were found to be low in 42.86% of the cases including primary as well as secondary erythrocytosis. However, only a single (7.14%) case of SE was associated with elevated levels of EPO. Thrombosis was more common in PV patients where 2 (40%) patients reported thrombosis. Notably patient experienced a transient ischemic attack, while another suffered a Non-ST elevation myocardial infarction. In comparison, among the cases SE, two out of 28 (7%) cases of SE exhibited underlying thrombosis. Specifically, one patient had a history of stroke, and another had IHD.

Majority of the patients with SE (21/28:75%) underwent venesection, done due to reported headache and/or dizziness episodes in these cases. None of these patients exhibited additional symptoms of hyperviscosity, such as shortness of breath, chest pain, changes in vision, or mucosal bleeding. As part of routine clinical care, asymptomatic cases within SE domain were counseled to quit smoking, were referred to assorted specialties aimed at addressing the underlying causes. As a routine practice these cases were closely monitored for trends in Hb and HCT even before data retrieval as part of standard clinical follow-up protocols. The mean HCT threshold for venesection in most patients with SE was above 52.4%. Contrarily, the patients with PV had undergone venesections and required cytoreduction with hydroxyurea. As per the BSCH guidelines, the goal was to keep the HCT levels below 45% for all patients in the PV group [10].

Table 2. Various etiologies of secondary erythrocytosis in studied population.

Etiologies	Identified Cases in secondary Erythrocytosis n=28	Frequency %	Identified cases in Polycythemia vera n=5	Frequency %
Smoking	13	46.4	1	20.0
Hypoxia (PO2< 75mmHg)	4	14.28	1	20.00
Hypercapnea (pCO2>45 mmHg)	2	7.14	0	0.00
Obstructive sleep apnea	4	14.28	0	0.00
Hepatitis B	4	14.28	0	0.00
Hepatitis C	2	7.14	2	40.00
Kidney dysfunction	3	10.71	0	0.00
Ischemic heart disease	2	7.14	1	20.00
Non-Obstructive coronary artery disease	1	3.57	0	0.00
High erythropoietin drive	1			
Pseudopolycythemia	1	3.57	0	0.00
Cholecystoduodenalfistua	1	3.57	0	0.00
Ovarian Malignancy	1	3.57	0	0.00
Uterine fibroid	1	3.57	0	0.00

4. DISCUSSION

The current investigation explores the prevalence of secondary erythrocytosis in a tertiary care hospital setting. Markedly, a significant majority of subjects (84.85%) exhibited polycythemia specifically originating from secondary erythrocytosis. Among the patients studied, only 15.15% were diagnosed with polycythemia vera. Wouter's and colleagues conducted a comprehensive assessment of erythrocytosis prevalence in the general population. In consistent with these findings, the results from their work revealed that secondary erythrocytosis was the predominant cause, constituting 62% of cases, while polycythemia vera represented only 15% of cases within a substantial cohort of 147,167 patients[21]. In a separate South Asian study 56.8 % patients presented with secondary erythrocytosis with rest being afflicted from polycythemia vera [22]. A distinct male predominance within the secondary erythrocytosis

group was observed in the present work which agrees the study of wouters and coworkers and Nevrekar and colleagues [21, 23].

Age of patients as in this study the mean age of 49.48±15.08 was observed which is much less than the reported age for both type of erythrocytosis perhaps due to high prevalent smoking in our young population. In our study 42% of patients were smokers who had mean age of 53.21±15.23 correlating with the mean age of smokers in our general population. Presence of young smokers in our study has likely shifted the age statistics in secondary erythrocytosis to the lower side as compared to age statistics in the global data.

The mean hemoglobin and hematocrit were found elevated in secondary erythrocytosis group while primary polycythemia group featured the higher mean red blood cells, white blood cells, and platelets count. The increased count is attributed to clonal expansion driven by myeloproliferationwhich is a characteristic feature of primary polycythemia. Of the investigated factors, smoking was identified in 42% of the cases of secondary erythrocytosis.However, a small fraction (8%) of the patients presented with additional comorbidity alongside smoking, contributing to erythroid proliferation. In agreement with this the research conducted by Chin-Yee and colleagues revealed thatout of 785 cases of secondary erythrocytosis 319 (40.06%) were identified as smokers [22]. Further the prevalent comorbid associations with secondary polycythemia observed herein included chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and hepatitis. Regarding this ample amount of literature supports the association of hypoxic pulmonary disease, COPD, and OSA with secondary erythrocytosis [15-18].The incidence of erythrocytosis in presence of COPD and OSA ranges from 6.0 to 8.0 [24, 25]and 1·7–8.0 % respectively [26, 27].

Chronic viral hepatitis was seen in seven patients, with five suffering from hepatitis B and two hepatitis C. The association of hepatitis with secondary erythrocytosis has also been documented previously [19].A study conducted by Saifan and collaborators revealed the patients with HCV infection exhibited higher levels of hematocrit and hemoglobin[28].Similarly, Varma and Chan et al.,have mentioned 2 cases of ESKD who after infection with hepatitis C developed idiopathic erythrocytosis[29, 30]Erythrocytosis is also noted in patients with liver malignancies, as well as in post liver transplant setting but none of our patients with hepatitis had liver malignancy or undergone a liver transplant[31, 32]. Since we did not have genetic testing available to look for congenital causes of erythrocytosis or clonal causes other than Jak 2 V617 F mutation analysis it is quite possible, the presence of viral hepatitis as a bystander phenomenon in our reported patients. Never the less in cases of isolated JAK2 V617F-negative erythrocytosis with unclear etiology, it is recommended to conduct a hepatitis screen[19]

Erythrocytosis is generally rare in kidney diseases and there are cases of adult polycystic kidney disease and non-adult polycystic disease presenting with erythrocytosis [33]. The present study involving the patients with isolated erythrocytosis, revealed three patients with CKD with no evidence of renal cysts on imaging[34].In literature search CKD is most commonly associated with anemia, however there are multiple reported cases of erythrocytosis linked with chronic kidney disease by Shih et al, Basuet al, and Dong et al[35-37]. Similar association has been documented by others[38, 39]has also demonstrated similar association. The tissue hypoxia or an abnormal overproduction of erythropoietin are proposed as driving factors for erythrocytosis in CKD [34].

Due to the limitation of resources we were unable to carry out genetic testing for congenital and uncommon clonal causes of polycythemia in our patient population.Hence associations with erythocytosis in the above data can be easily questioned by readers in the absence of genetic testing. This seems to be a major drawback of the study, none the less our study conveys a message to delve deeper into the search for the underlying cause of polycythemia if Jak2V617F is negative, as correction of an underlying cause often resolves secondary erythrocytosis contrary to clonal or congenital polycythemia.

In our study, four patients with polycythemia experienced ischemic arterial events, while no observed case of venous thrombosis. Two patients displaying thrombosis were identified as JAK2 V617F positive, while an additional two individuals presented with an underlying secondary erythrocytosis Previously,

Corse and Kurtis reported ischemic stroke in the patient suffering from secondary polycythemia [40]. Further, the increased incidence rate of thrombosis was observed in patients with PV [41].

Management in secondary erythrocytosis is mainly controlling hematocrit with venesection if patients are symptomatic, tailoring the target on the basis of thrombotic risk. [11] Most of our patients (75%) with secondary erthrocytosisrequired venesections to control the hematocrit coupled with the management of associated underlyingrisks. These patients either had head ache or microvascular symptoms prompting us to consider venesection to reduce the symptoms.The mean HCT threshold for venesection in most patients with SE was 52.4% or above. Where needed cardiovascular risk factors were addressed and managed simultaneously to reduce the thrombotic risk in symptomatic patients with secondary erythrocytosis. The remaining fraction received reassurance,close monitoring, and counselling to control the underlying cause(s) associated with polycythemia.All smokers were encouraged to attend pulmonary rehabilitation services to seek help for smoking cessation.
All patients with PV required venesection and low dose aspirin. All patients with PV required additional cytoreduction with hydroxycarbamidegiven the high-risk nature of the disease.

5. CONCLUSION

Secondary erythrocytosis is by far the most common cause of high hemoglobin and hematocrit in our hematology clinic. All patients who turn out to be negative for JAK2 V617 F mutation require exhaustive investigation and workup to look for an underlying secondary cause. The majority of cases with secondary erythrocytosis in our clinic had a causal association with smoking and/or an underline systemic disorder.

ETHICAL APPROVAL

The Indus Hospital Institutional Review Board issued approval no: IHHN_IRB_2021_07_008 dated 6-Aug-2021.

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