Original Research Article

THE FREQUENCY AND IMPORTANCE OF HEMATOLOGICAL PARAMETERS IN REACTIVE AND CLONAL THROMBOCYTOSIS

ABSTRACT:

Objectives: To evaluate the frequency of reactive and clonal thrombocytosis based on age, sex, clinical findings, and severity of thrombocytosis. We also highlight the determination of hematological parameters for the diagnosis of these disorders required the management of thrombocytosis to reduce the morbidity and mortality rate.

Methods: This descriptive experimental study was conducted in the Diagnostic and Research laboratory, Peoples University of Medical and Health Sciences, Nawabshah and department of Pathology, from July 2017 to June 2018. Total 325 patients including 260 patients with reactive thrombocytosis and 65 patients with clonal thrombocytosis, their age ranged between 12 and 45 years and 35 to 68 years were selected. The male to female ratio were 1.5:1 and 2.5:1 while clinical history and clinical examination were noted. The blood samples were taken from all these patients for the analysis of hematological parameters by a hematological analyzer (Nihon Corden) and an iron profile performed for assessment of iron status to confirm the diagnosis of iron deficiency anemia. The examinations of peripheral blood smears and bone marrow smears in the case of clonal thrombocytosis seen in chronic myeloid leukemia essential for the diagnosis.

Results: The mean ages and male to female ratio among 325 patients with reactive and clonal thrombocytosis were 28.5 $\pm$ 16.5, 51.5 $\pm$16.5 and 1.5:1, 2.5:1 ratio were found in this study. The mild to moderate thrombocytosis were found in reactive thrombocytosis while moderate to severe thrombocytosis was detected in patients with chronic myeloid leukemia.

Conclusions: The frequency of thrombocytosis was higher in clonal thrombocytosis than the reactive type.

Key Words: Hematological Parameters, Frequency, Reactive Thrombocytosis, Clonal thrombocytosis.

INTRODUCTION:

The thrombocytosis is one of the hematological disorders characterized by increased platelet count of more than 45,0000 per cubic mm in peripheral blood can be divided into primary or essential or clonal and secondary or reactive types[1]. The platelet in secondary thrombocytosis acute phase reactant increases in response to various stimuli such as inflammatory cytokines including interleukin-6,11 and 1, tumor necrosis factor beta, colony stimulating factor and thrombopoietin more frequently seen in inflammation due to the infection or tissue injury caused by trauma or surgery, cancers and iron deficiency anemia[2]. Patients usually in secondary thrombocytosis due to acute and chronic bacterial and viral infections present with fever, tachycardia,

mild anemia, rarely hepatosplenomegaly, low hemoglobin, increase ESR, total leucocyte count less than 50,000/cm with neutrophilia and increase platelet count above 50,000 per cubic mm that can be normalized after treatment of conditions that cause thrombocytosis[3]. The increased erythropoietin level that is homologous to the thrombopoietin regulating the platelet production causes thrombocytosis in iron deficiency anemia and patients present with sign and symptoms of anemia, low hemoglobin, decrease serum iron, ferritin and increased iron binding capacity along with thrombocytosis[4]. Clonal disorders or primary thrombocytosis seen in chronic myeloid in contrast to the reactive type is caused by clonal expansion of hematopoietic progenitor cells in bone marrow due dysregulation of physiological mechanism that control the production of platelet is caused by genetic mutations including calreticulin, Basic cluster region- Abelson and thrombopoeiten receptor genes[5,6]. Clonal thrombocytosis or primary type is common in adults than children, slow in onset and patient usually present with dizziness, headache, bleeding hepatosplenomegaly and laboratory abnormalities such as increase platelet count above 10 lacs per cubic mm, leukocytosis with the presence of immature cells in peripheral blood and bone marrow smears, prolong bleeding time, prothrombin time, activated thromboplastin time and presence of large or small dysmorphic platelets, non-granular, platelet conglomerates, fragments of megakaryo-cytes[7]. Bleeding tendency and thrombotic complications are more common in clonal thrombocytosis than the secondary thrombocytosis and depends upon risk factors such as age, number of the platelet count, and genetic mutations, hence patients with advanced age, platelet count above 10,00000/cmm and genetic mutation including JAK-2/V617F in chronic myelo-proliferative disorder including CML have high risk of complications[8]. The treatment of chronic myelo-proliferative disorder required asprin and hydroxyurea, for bleeding and thrombotic complications, however in children below the age of 12 years, there is a risk of the development of Reye's, syndrome, and cancer can occur due to the use of these drugs[9]. From the above, our aim of this study is to evaluate thrombocytosis among patients with infection, iron deficiency anemia, chronic myeloid leukemia, and patients who undergo splenectomy. We also highlight the dangerous complications of this disorder and its management to reduce morbidity and mortality.

MATERIAL AND METHODS:

The current descriptive experimental study was conducted in the Diagnostic and Research laboratory, Peoples University of Medical and Health Sciences, Nawabshah and department of Pathology, from July 2017 to June 2018. We selected 325 patients, age ranged between 2 and 65 years, 225 males and 100 females coming from various cities, villages of district Shaheed Benazirabad, at reception of diagnostic and research laboratory of PUMHSW, Nawabshah. The clinical history and physical examination of all these patients were performed and blood and bone marrow biopsy samples were collected for routine laboratory testing such as complete blood count, examination of blood and bone marrow smear to detect thrombocytosis among the patients with hematological and non-hematological disorders. Iron profile was required for the diagnosis of iron deficiency

RESULTS:

A total of 325 patients with their mean age 33.5±31.5 and male to female ratio of 2.2:1 were included in this study. These patients were diagnosed with a hematological

and non-hematological disorders based on clinical manifestations such as fever with cough, burning micturition, diarrhea, body ach, head ach, pallor ness, splenomegaly, and, history of splenectomy. The mean value of Hemoglobin g/dl 11.5 ± 1.5, Total leucocyte Count/cumm 21200 ± 5000, Neutrophils % 85 ± 5, Lymphocytes % 10 ± 5, were founded in this study. Among the patients with urinary tract, gastrointestinal tract, respiratory tract infections, and iron deficiency anemia.

DISCUSSION:

The importance of comparison and risk of complication among the patients with reactive and clonal thrombocytosis were evaluated by different studies such as among the children at the age of two years, frequency of secondary thrombocytosis due to infection overall was 37 to 78% and respiratory tract infection was 60 to 80% as observed by the Ozcan et, al. and wang JL et al[10,11]. They observed that the most common cause of secondary thrombocytosis among the children are acute and chronic viral infections and clinic hematological findings among the 810 adult patients with secondary thrombocytosis were fever, tachycardia, weight loss, anemia, leukocytosis with neutrophilia, and platelet count above 50,0000 per cubic mm as detected by wang JL et al. and Rose et al[11,12]. Secondary thrombocytosis due to release of cytokines such as interleukin, IL-3, IL-6, and IL-11 which stimulate megakaryopoiesis, increasing the number of platelets as mentioned by Kulnigg-Dabsch et al[13]. In inflammation processes, the production of IL-6 in macrophage fibroblasts increases, together with a simultaneously-observed increase in the concentration of the granulocyte growth factor GM-CSF. Inflammatory factors also lead to the reduction in the level of hemoglobin, by disturbed erythrocyte production (due to disturbances in iron management and inhibition in suppression of erythropoietin), or shortening their life. There is a direct relationship between the number of platelets and the value of white blood cells, as well as an inversely-proportional relation ship between the intensity of thrombocytosis and the severity of anemia. Post splenectomy reactive thrombocytosis and uncontrolled reactive thrombocytosis among the patients with idiopathic thrombocytopenic purpura after splenectomy was treated with thrombocytopheresis were detected by Khan PN et al[14]. Das SS et al[15]. while reactive thrombocytosis due to the iron-deficiency anemia leading to rare complication such as Raynauds phenomena among the male patients was observed by khan F et al[16]& Subha R et al[17] stated that thrombocytosis among the patient with colonic cancer after surgical resection of colon developed pseudo-hyperkalemia due to the increased release of potassium during the clotting process, other causes for pseudo hyperkalemia include a tourniquet, ethanol containing antiseptics, cold temperature, time delay in sample transport, contaminants like potassium-containing intravenous fluids, potassium salts of tube additives and heparin-induced WBC lysis for reverse pseudo-hyperkalemia. The frequency of reactive thrombocytosis due to infection and tissue injury was 91.8% while clonal thrombocytosis was 8.2% among the 10 patients was founded by Syed NN et al[18]. Beatrice JM[19] stated that among the two types of thrombocytosis such as primary and secondary, the primary as myelo-proliferative disorders rare in children seen in chronic myeloid leukemia, polycythemia, and essential thrombocythemia also called clonal disease derived from a multipotent hematopoietic cell. They also described the signs and symptoms of disease occurring due to the stimulation of the megakaryocytic line, without significant granulocytic and red blood cell stimulation and in these patients, megakaryocytes production takes place due to increased sensitivity to the thrombopoietin stimulation. The average age of children in these disorders is 11 years with increased platelet count leading to bleeding and thrombotic complications observed by Chiarello P et al[20]. Chronic myeloid leukemia with extreme

thrombocytosis that is above 10,00000 /cmm leading to syncope and myocardial infarction and features of essential thrombocytosis in peripheral blood and bone marrow smears among the patients with chronic myeloid leukemia were detected by Rawa I et al[21] and Bychu YJ et al[22]. The platelet dysfunction in the form of normal platelet aggregation with ADP, collagen, and epinephrine and failure of aggregation with ristocetin among the patients with chronic myeloid leukemia was founded by Olga MA et al[23]. Reported portal vein thrombocytosis among the 32 years old male diagnosis with CML who head anemia, leukocytosis and thrombocytosis while platelet indices such as high mean platelet volume and platelet distribution width along with platelet count more than 50,0000 /cm were found in primary or clonal thrombocytosis seen in chronic myeloid leukemia and platelet count less than 50,0000 /cmm with low MPV and PDW were found in reactive thrombocytosis as reported by Saud BA et al[24].

Conclusions

The following conclusions and suggestions were made from the above study

1. The reactive thrombocytosis was more common among the children and adults with high frequency of male and female as compared to the clonal thrombocytosis common in adults with a high frequency of male The most common causes of reactive thrombocytosis are infections, after splenectomy and iron deficiency anemia while the cause of clonal thrombocytosis is chronic myeloid leukemia.
2. Mild to moderate thrombocytosis was common in reactive thrombocytosis and moderate to severe thrombocytosis was founded in clonal thrombocytosis seen in chronic myeloid leukemia. However none of our patients was present with neither extreme thrombocytosis nor any thrombocytic complication was detected in any patient.
3. Further studies are required to detect thrombocytic-complication sn among patients with two major types of thrombocytosis. Hence we advise the physician to treat these patients as soon as possible to reduce the risk of death due to the bleeding and blockage of the blood vessels of vital organs by dangerous thrombi among these patients

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Table 1

The comparison of reactive and primary or clonal thrombocytosis on the basis of age, sex and Clinical findings

N=325

Types of thrombocytosis	Reactive or secondary thrombocytosis seen in Infection, after splenectom and iron deficiency anemia	Clonal or primary thrombocytosis seen in chronic myeloid leukemia
Age	33.5±31.5 years	51.5±16.5 45±20 years
Sex	Male 180 female 120 Male to female ratio 1.5:1	Male 18 Female 7 Male to female ratio 2.5:1
Clinical findings	Fever, cough, burning micturition, dysuria, dyspnea and chest crepitation History of splenectomy Pallor ness, anorexia, weight loss dyspnea on exertion koilonychias	Fever, Pallor ness, anorexia, weight loss hepatospleenomegally
Total patients 325(100%)	300(92.5%)	25(7.7%)

N= is the number of patients

Table 2. The comparison of reactive and primary or clonal thrombocytosis on the basis of Laboratory parameters

Laboratory parameters	Reactive thrombocytosis	Primary thrombocytosis
Hemoglobin g/dl, ESR/h	8.2±1.8, 70±20	10.5±1.3 30±10
Total leucocytes count / cumm	250000±10000	1,400000±50000
Differential leucocytes count, neutrophil l%, Lymphocyte %, monocyte %, eosinophil % immature cells myelocytes meta myelocytes band cells A staining score of LAP (20 - 100 out of a maximum of 400) is considered normal.	 80±5 35±10 8±2 6±1 Nil 140±10	 20±10 40±5 5±3 10±2 18±3 8±2 10±3 10±6
Platelet count/cumm Platelet indices Mean platelet volume (femtolitter) platelet distribution width%	6,00000±1,20000 6.1±0.5 7.2±0.3	800000±10000 7.5±0.4 8.6±0.5
Iron profile in iron deficiency anemia Serum iron level mcg/dl ferritin level, mcg/l total iron binding capacity mcg/dl	 50±5 10±3 440±3	 80±10 300±30 Iron: 60-170 mcg/dL TIBC: 240-450 mcg/dL
Peripheral and bone marrow smears	PBS Peripheral blood showing microcytic hypochromic RBC in iron deficiency anemia while normocytic, normochromic RBC are seen in other conditions. WBC are hyper	PBS & BMS The normocytic, normochromic RBC, Immature WBC such as myelocytes, metamylocytes are seen in chronic myeloid leukemia while Platelets are large or small and hypolobated

	granular and hyper lobed in infections and platelets are normal in morphology	Bone marrow is hyper cellular due to the excessive myelopoiesis with presence of large number of myelocytes and hypo granular as well as hypolobated large mega karyocytes seen in chronic myeloid leukemia

Table 3. Severity of thrombocytosis in reactive and primary types on the bases of platelet count per cubic mm
N=325

Types of thrombocytosis	Severity of thrombocytosis	The Platelet count /cmm	No of patients
Reactive thrombocytosis	Mild to moderate	650000±150000	300
Primary thrombocytosis seen in Chronic myeloid leukemia	Moderate to severe	800000±100000	25

N=number of patients