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Thrombocytosis: A Disease or a Response?

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Abstract

Objective: The aim of our study is to investigate the etiologic causes of thrombocytosis and check the presence of JAK2 mutation in these cases of thrombocytosis, retrospectively.
Methodology: This is a cross-sectional study conducted at Chughtai Institute of Pathology, Lahore from January to July 2025. A total of 100 patients with persistent thrombocytosis were included in the study. Both male and female patients above 18 years of age were included in the study. Already diagnosed cases were excluded along with patients on any sort of chemotherapy. A detailed history of the patient was taken, and all aspects of their present illness and previous medical history were analyzed. CBC counts and JAK2 mutation were analyzed and data were analyzed using SPSS.
Results: In our study a total of 100 patients were recruited which consisted of 46 females and 54 males. The average age was 53.4 years (range 24 to 76 years). The presence of JAK2 V617F mutation was detected in the total of 44 patients indicating primary thrombocytosis whereas 56 patients had secondary thrombocytosis.
Conclusion: It is essential to investigate thrombocytosis especially in old age, as it might be the only sign indicating a hidden MPN. Thereby, it is imperative that thrombocytosis should not be overlooked and must be thoroughly investigated
Key words: Thrombocytosis, Janus kinase, Essential thrombocythemia.

Introduction

Thrombocytosis, defined as a sustained elevation in platelet count above the normal upper limit(450x109/L), is a frequently encountered laboratory abnormality in clinical practice. It represents a heterogeneous condition that may arise either as a reactive physiological response to an underlying disorder or as a manifestation of a primary clonal hematologic disease, particularly myeloproliferative neoplasms (MPNs).[1,3,8] Distinguishing between these entities is of critical importance, as their prognostic implications, therapeutic strategies, and associated risks—especially thrombotic and hemorrhagic complications—differ substantially.

Reactive (secondary) thrombocytosis accounts for the majority of cases and is commonly associated with infection, inflammation, tissue injury, iron deficiency, and malignancy.[2,4,7] Several population-based and hospital-based studies have demonstrated that infectious and inflammatory conditions remain the predominant causes of thrombocytosis in general medical settings.[4] Additionally, non-malignant chronic diseases have been shown to have a significant association with elevated platelet counts, underscoring thrombocytosis as a nonspecific but clinically relevant biomarker of systemic disease [5]

In contrast, primary thrombocytosis occurs in the context of clonal bone marrow disorders, most notably essential thrombocythemia (ET), a classical Philadelphia chromosome–negative MPN.[3,10] Although less common than reactive causes, clonal thrombocytosis carries a substantial risk of vascular events and disease progression. Recent advances in molecular diagnostics, including the identification of driver mutations such as *JAK2*, *CALR*, and *MPL*, have enhanced diagnostic accuracy; however, clinical suspicion remains pivotal, particularly in elderly patients where thrombocytosis may be the sole presenting abnormality of an underlying MPN.[9,10]

According to the World Health Organization (WHO), the diagnosis of essential thrombocythemia (ET) requires fulfillment of specific clinical, laboratory, molecular, and bone marrow criteria. The WHO criteria include a sustained platelet count ≥450 × 10⁹/L, bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei and minimal or no increase in granulopoiesis or erythropoiesis, exclusion of other myeloid neoplasms (such as polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndromes), and the presence of a clonal marker, most commonly mutations in JAK2, CALR, **or** MPL; in the

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absence of these mutations, evidence of clonality and exclusion of reactive thrombocytosis are required. Bone marrow morphology plays a central role in distinguishing ET from prefibrotic primary myelofibrosis, as emphasized by Gisslinger et al., who demonstrated that WHO-based histopathologic assessment—characterized by loose clusters of large megakaryocytes with abundant cytoplasm and hyperlobulated nuclei and little to no reticulin fibrosis (grade 0–1)—has significant diagnostic and prognostic value compared with older criteria. Tefferi and Pardanani further highlight that these bone marrow findings are critical not only for accurate diagnosis but also for risk stratification and management, as misclassification can lead to differences in thrombotic risk assessment and long-term outcomes. [11, 12]

Emerging evidence has also highlighted thrombocytosis as an important marker for occult malignancy, particularly in primary care and geriatric populations.[6] Studies have demonstrated a strong association between unexplained thrombocytosis and subsequent cancer diagnosis, reinforcing the need for systematic evaluation rather than dismissing thrombocytosis as an incidental or benign finding.[5,6] This is especially relevant in older adults, where age-related comorbidities may obscure early signs of clonal hematologic disease.

Despite its clinical significance, thrombocytosis is often under-investigated, leading to delayed or missed diagnoses of serious underlying conditions, including MPNs. Given the broad etiological spectrum and potential for significant morbidity, a structured and thorough diagnostic approach is essential.

The present study, *"Thrombocytosis: Disease or a Response"*, was undertaken to analyze the etiological profile of thrombocytosis in 100 patients, with particular emphasis on identifying cases of occult MPNs and differentiating them from reactive causes. By systematically evaluating patients with thrombocytosis, this study aims to reinforce the importance of not overlooking this hematological abnormality especially in the elderly where it may serve as the only clue to a hidden myeloproliferative disorder.

Methodology

This is a cross-sectional study conducted at Chughtai institute of pathology, Lahore from January to July 2025 after taking approval from Institutional Review Board (IRB), IRB # 1283. A total of 100 patients with persistent thrombocytosis (for more than 3 months) were included in the study after taking their informed consent. Both male and female patients above 18 years of age were included in the study. Already diagnosed cases were excluded along with patients on any sort of chemotherapy. A detailed history of the patient was taken by a resident hematologist. All aspects of their present illness and previous medical history were analyzed. A physical examination was also performed with special consideration given to lymphadenopathy and hepatosplenomegaly. All previous reports were analyzed and new were ordered where required. The basic aim of the study was to find the cause for thrombocytosis. Most patients had already undergone tests like blood culture, CRP levels, serum erythropoietin levels, iron study profile, autoimmune disorder profile and viral screening, so these results were noted.

Then 2 vials of venous blood sample (3ml each) were taken from each patient in Ethylenediamine tetra acetic acid (EDTA) tube under aseptic conditions following standard sampling procedures for phlebotomy. After which the samples were run on Sysmex XN-1000 automated hematology analyzer and complete blood counts including platelet count, total leucocyte count, hemoglobin, hematocrit and blood indices were extracted. The peripheral smears were examined microscopically to confirm the presence of thrombocytosis and rule out pseudo-thrombocytosis and any other abnormality.

The other vial was used to detect the JAK2 V617F mutation. The sample was sent to the molecular department as soon as possible at 2-8°C. The "JAK2 V617F Mutation Detection "is a qualitative Real-Time (RT) PCR based test. This test utilizes two different probes to discriminate the wild type allele from the mutant allele due to a very specific matching. During the extension phase of the PCR, the perfectly matched probe is cleaved by the 5' →3' exonuclease activity of Taq DNA polymerase separating the reporter dye from the quencher and thus releasing a detectable fluorescence. The probe not perfectly matched will disappear rather than cleaved by the Taq DNA polymerase and no reported dye is released. The fluorescence signal generated is collected at the end of the PCR and

immediately indicate the presence of targeted sequences in the sample.

Simultaneously, all suspected MPNs cases were also tested for BCR ABL1 fusion gene to rule out CML. Fluorescence in situ hybridization (FISH) was used to detect the characteristic Philadelphia chromosome translocation, t(9;22)(q34;q11).

All patients who had positive JAK2 V617F mutation, underwent bone marrow biopsy. Bone marrow biopsy was performed using trephine needle under aseptic conditions. Xylocaine analgesic was used to minimize the pain and patient's comfort was ensured. The bone marrow aspirate slides were stained using Giemsa stain and Leica Pylorius tissue processor was used to prepare the trephine. The aspirate and trephine were thoroughly examined and immunohistochemical stains were applied where required.

All the results obtained were noted and the data were entered in the excel work sheets, checked manually and logically corrected where needed. The data was analyzed using Statistical Package for the Social Sciences (SPSS 20.0) and frequency and percentages were calculated for categorical variables.

Results

In our study a total of 100 patients were recruited which consisted of 46 females and 54 males. The average age was 53.4 years (range 24 to 76 years). The means age of males was 51.2 years and of females was 56.9 years, respectively. The patients diagnosed with MPN had an average age of 54.4 years.

The platelet count observed in all the patients recruited in this study had platelet count of more than 450 x 10^9/L. Patients with MPN specially ET had significantly higher platelet count as compared to those labelled with infective/inflammatory etiology.

Out of the total 100 patients with thrombocytosis, 4 had an autoimmune disorder, 19 had inflammatory/ infective etiology, 2 patients had history of thrombosis, 31 were diagnosed to be having iron deficiency anemia and 44 were diagnosed as MPN with 32 among them as ET. 2 patients had CML, 8 had PV and 2 had MF. Infection-related thrombocytosis was included in "inflammatory" group and diseases such as rheumatoid arthritis and systemic lupus were referred as autoimmune diseases. Most patients with MPNs had significant splenomegaly which were confirmed through abdominal ultrasonography. Patients with inflammatory causes had significant history of joint pains and some had lymphadenopathy.

The presence of JAK2 V617F mutation was detected in the total 44 patients. 56 patients had negative results. All the patients that had positive JAK2 V617F mutation underwent bone marrow biopsy to confirm their diagnosis. 32 patients were diagnosed to have ET on bone marrow biopsy which showed megakaryocytic hyperplasia. 2 patients had bone marrow findings consistent with CML with positive BCR ABL fusion gene, 8 patients had bone marrow findings of PV and 2 had marked fibrosis on bone marrow thus were labelled as PMF.

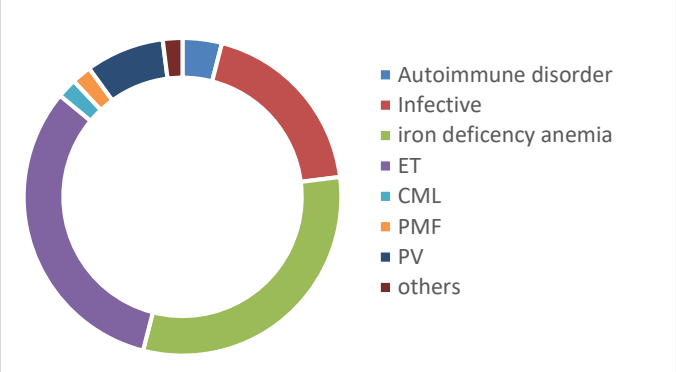

Figure 1: Etiogocial causes for thrombocytopenia

Table I: JAK2 V617F mutation detected.

		JAK2V617F		*Total*
		Detected	Not detected	
	Autoimmune disease	0	4	4
	Inflammatory/Infective causes	3	16	19
	Iron deficiency anemia	1	30	31
	Essential thrombasthenia	32	0	32
	Other MPNs (CML)	2	0	2
	Other MPNs (PMF)	2	0	2
	Other MPNs (PV)	4	4	8
	Thrombosis	0	2	2
Total		44	56	100

Discussion

Diagnostic work-up for thrombocytosis is an essential step for accurate diagnosis for the patient. Therefore, it is crucial that cost effective and pain free testing should be

done to achieve a diagnosis and for this purpose this study was conducted.

According to study conducted by Yokus et al, JAK2 mutation was found to be positive in 42%of cases with thrombocytosis. They observed that primary thrombocytosis was present in 75% of the cases in the etiology. The distribution of the diagnosis groups was ET in 59 (43%) cases, polycythemia vera in 19 (14%) cases, inflammation in 13% cases, primary myelofibrosis in 6% cases, myeloproliferative neoplasms (MPNs) in 6% cases, iron deficiency anemia in 5% cases, CML in 2% cases, myelodysplastic syndrome (MDS) +MPN in 1% cases, malignancy in 1% cases, MDS in 1% cases, and autoimmune disease in 1% case.[13] These findings are quite similar to our findings as well.

According to Edahiro et al among 1,202 patients with thrombocytosis that they studied, 150 (12.5%) had primary and 999 (83.1%) had secondary thrombocytosis. Of these patients with primary thrombocytosis, 129 (86%) had at least 1 molecular marker indicative of MPNs. The major causes of secondary thrombocytosis were tissue injury (32.2%), infection (17.1%), chronic inflammatory disorders (11.7%) and iron deficiency anemia (11.1%). The median platelet count and the incidence of thrombosis were significantly higher in patients with primary thrombocytosis than in those with secondary thrombocytosis.[14] Whereas, in our study 44% patients had primary thrombocytosis with significantly higher platelet count as compared to patients with secondary thrombocytosis which constituted 56% of our study population.

The most common cause of secondary thrombocytosis in our study was iron deficiency anemia. According to Bhatta et al, thrombocytosis is very commonly seen in patients with iron deficiency. According to them, thrombocytosis with iron deficiency is seen in elderly females and this is secondary thrombocytosis which resolves after replacement of iron stores.[15]

Research conducted by Deng et al, observed that a total of 145 patients with spondylarthritis which is autoimmune disorder; thrombocytosis was found in 69 patients of these patients and had more severe disease as compared to those without thrombocytosis.[16] In our study also patients with autoimmune disorders were observed to have thrombocytosis. Another case reported by Soto et al, states that a 52 years old female with celiac disease which is again an autoimmune disorder presented with extreme thrombocytosis.[17] This extreme thrombocytosis was secondary to severe anemia.

Conclusion

We conclude in our study that almost 44% of patients in our study were diagnosed with an MPN. However, 55% of patients with thrombocytosis had a reactive cause for increased platelet counts. Iron deficiency anemia is the most common cause for reactive thrombocytosis followed by infective/inflammatory causes.

Thrombocytosis may not always indicate a disease itself; it may also be a response to some underlying another disorder. Therefore, it is essential to investigate thrombocytosis, especially in the old age as it might be the only sign indicating a hidden MPN. Thereby, it is imperative that thrombocytosis should not be overlooked and must be thoroughly investigated and JAK2 V167F mutation detection through PCR is an easy and patient friendly investigation which can ease the diagnosis of MPN.

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