

Etiology of Thrombocytosis and the Use of Platelet Parameters to Distinguish Between Clonal and Reactive Thrombocytosis

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ABSTRACT

We aimed to determine the etiology and changes of platelet parameters of elevated platelet counts. A prospective study was performed to evaluate all patients, who had at least one platelet count more than $450 \times 10^9/L$. 146 patients with thrombocytosis were studied.

Out of 146 patients, 16 (10.9%) had primary and 130 (89.1%) had secondary thrombocytosis. Among 16 patients with primary thrombocytosis: 6 (37.5%) patients with essential thrombocythaemia, 5 (31.25%) patients with chronic myeloid leukemia, 4 (25%) patients with polycythemia vera and 1 (6.25%) patient with myelofibrosis and myeloid metaplasia.

The most frequent causes of secondary thrombocytosis were infection (50.7%), burn (20%), malignancy (11.5%), bleeding (6.9%) and chronic inflammation (6.1%). Primary thrombocytosis was significantly associated with a higher platelet count, mean platelet volume (MPV) and platelet distribution width (PDW).

Compared with secondary thrombocytosis, primary thrombocytosis was significantly associated with platelet counts of more than $1000 \times 10^9/L$ (1.5% compared to 50%).

When a patient has an unexplained high platelet count, the combined interpretation platelet count, MPV and PDW appears to be highly useful in the differential diagnosis of thrombocytosis. Most cases of thrombocytosis are reactive and only a small percentage of patients has primary thrombocytosis.

Key Words: Thrombocytosis, Primary, Secondary, Mean platelet volume (MPV), Platelet distribution width (PDW)

ÖZET

Trombositozis Etiyolojisi, Klonal ve Reaktif Trombositozis Ayırıcı Tanısında Trombosit Parametrelerinin Kullanımı

Bu çalışmamızda trombositozda trombosit parametre değişiklikleri ve etiyolojisinin belirlenmesi amaçlanmıştır. Trombosit sayısı 450.000 üzerinde olan tüm hastalar prospektif olarak değerlendirilmiştir.

Toplam 146 hasta değerlendirmeye alındı. Onaltı hastada primer trombositoz belirlendi; 6 (%37.5) vakada esansiyel trombositoz, 5 (%31.3) vakada KML (kronik myelositer lösemi), 4 (%25) hastada polisitemia vera, bir (% 6.3) hastada myelofibrozis ve myeloid metaplazi.

Sekonder trombositozun en sık nedenleri, enfeksiyon (%50.7), yanık (%20), malignansi (%11.5), kanama (%6.9) ve kronik inflamasyon (%6.1) idi. Primer trombositozda anlamlı olarak trombosit sayıları daha yüksekti, ayrıca ortalama trombosit hacmi (MPV) ve trombosit dağılım genişliği (PDW) daha fazlaydı. Sekonder trombositozla kıyaslandığında primer trombositozda trombosit sayıları $1000 \times 10^9/L$ 'nin üzerinde olanların sayısı anlamlı olarak daha yüksekti (%1.5 vs %50).

Yüksek trombosit sayısı tesbit edildiği durumlarda, trombosit sayısı ile birlikte, MPV ve PDW dikkate alınarak trombositoz ayırıcı tanısı araştırılmalıdır. Trombositozların büyük kısmı reaktiftir, oldukça küçük bir kısmı primerdir.

Anahtar Kelimeler: Trombositoz, Primer, Sekonder, Ortalama platelet hacmi (MPV), Platelet dağılım genişliği (PDW)

INTRODUCTION

Thrombocytosis refers to a platelet count above the normal value in the circulating blood. Recently, with the widespread use of the electronic cell counters and the subsequent availability of a platelet count as part of a routine complete blood count, thrombocytosis is more often observed as an unexpected finding. Thus, an elevated platelet count has become an important clinical problem for differential diagnosis (1).

Thrombocytosis is classified according to its origin into primary and secondary types. The term primary thrombocytosis refers to a persistent elevation of platelet count due to clonal thrombocytosis as it may occur in chronic myeloproliferative or in some myelodysplastic disorders (2). Secondary thrombocytosis is due to a variety of underlying conditions. Short-lived secondary thrombocytosis is observed in conditions such as acute bleeding, trauma, major surgical procedures or after severe physical exertions (3-7).

In contrast, secondary thrombocytosis, which is associated with malignancy, chronic infection, iron deficiency, chronic inflammatory diseases or after splenectomy may persist longer (4,5,8-11).

The main interest of distinction between reactive and primary thrombocytosis resides in the increased incidence of thrombohemorrhagic complications and progress to acute leukemia in the latter group (4).

We aimed to determine the etiology of thrombocytosis and the use of platelet parameters (a useful simple non-invasive test) to distinguish between primary and secondary thrombocytosis.

PATIENTS and METHODS

The medical technologist in the hematology laboratory were instructed to identify all cases with platelet counts greater than $450 \times 10^9/L$. Among the cases who were admitted in Imam Reza Hoshoital during a 6 month period, 146 patients who presented with a platelet count $> 450 \times 10^9/L$ were investigated.

Fresh blood with EDTA-K2 anticoagulated were analyzed to determine platelet parameters between one to three hours after sampling using Sysmex KX-21.

The normal range of platelet counts for this machines is $150-450 \times 10^9/L$. High platelet counts were confirmed by repeating the tests and peripheral smear examinations.

The term primary thrombocytosis was applied to conditions with an established diagnosis of a myeloproliferative disorder according to standardized criteria (12). The term secondary thrombocytosis was applied to conditions associated with a reactive elevation of platelet count and no evidence for an underlying chronic myeloproliferative disorder. Platelet counts normalized or decreased after resolution of the acute phase. Data entry and analysis were performed with SPSS-11.5. Student's t-test was used for statistical analysis and the differences were considered significant at $p < 0.05$.

RESULTS

A total of 146 patients with a platelet count more than $450 \times 10^9/L$ were studied. The various underlying conditions associated with an elevated platelet counts were listed in Table 1.

Table 1. Etiology of thrombocytosis (n=146)

Diagnosis	N (%)
Primary thrombocytosis	16 (10.9%)
Essential thrombocythaemia	6 (4.1%)
Chronic myeloid leukemia	5 (3.4%)
Polycythemia vera	4 (2.7%)
Myelofibrosis with myeloid metaplasia	1 (0.6%)
Secondary thrombocytosis	130 (89.1%)
Infection	66 (45.2%)
Tissue damage	29 (19.8%)
Malignancy	15 (10.2%)
After hemorrhage	9 (6.1%)
Inflammatory diseases	8 (5.4%)
Renal failure	3 (2%)

Primary thrombocytosis as the cause of platelet elevation was found in 16 cases (10.9%). Secondary thrombocytosis was the most frequent cause of elevated platelet counts, which occurred in 130 cases (89.1%).

Platelet counts ranged from $463 \times 10^9/L$ to $1889 \times 10^9/L$ (median $675 \times 10^9/L$).

6.25% of all patients (n=10) had platelet count more than $1000 \times 10^9/L$.

Among 130 patients with secondary thrombocytosis, 68 were male and 62 were female. The age range was 7 months to 80 years, with a median age of 33 years (SD= 22.36).

The observed platelet counts were from 463×10^9 to $1348 \times 10^9/L$ (median $634 \times 10^9/L$).

Infection was the most common cause of secondary thrombocytosis, which occurred in 66 patients (45.2%). It was found that in 17 cases infections (25.7%) were due to tuberculosis (16 cases due to pulmonary tuberculosis and one case due to renal tuberculosis).

In the remaining patients, infection was related soft tissue infection with or without abscess (14 cases), pneumonia (11 cases), urinary tract infections (7 cases), septic arthritis (7 cases), endocarditis (4 cases), nervous system infection (3 cases) and peritonitis (3 cases).

Thrombocytosis associated with tissue damage occurred in 29 patients (19.8%). The majority were due to burns (26 cases). In the remaining patients, tissue damage was due to trauma (3 cases).

Out of 16 patients with primary thrombocytosis, 7 were male and 9 were female. The age range was 33-79 years with a median age of 59 years. Essential thrombocythaemia was the most common cause of primary thrombocytosis (6 of 16 cases, 37.5%).

The observed platelet counts ranged from $460 \times 10^9/L$ to $1889 \times 10^9/L$ (median $1010 \times 10^9/L$) and were significantly higher in comparison to platelet counts in secondary thrombocytosis (p= 0.013) (Tables 2, 3).

Eight patients (50%) with primary thrombocytosis had a platelet count of greater than $1000 \times 10^9/L$, compared with 2 patients (1.5%) with secondary thrombocytosis.

Median platelet count were significantly higher in E. T and P. V than in CML and M. M. M. (Table 3).

Compared with secondary thrombocytosis, primary thrombocytosis was significantly associated with a higher mean platelet volume (MPV) (p=0.007) (Table 2).

Significant differences were also found in PDW between patients with primary and secondary thrombocytosis (p<0.001) (Table 2).

DISCUSSION

Thrombocytosis is the presence of an abnormally high number of platelets in the circulating blood (4).

Accurate platelet counts are now part of the routine blood cell count, and thrombocytosis is being encountered much more frequently (3).

Table 2. Analysis of PLT and M. P. V and P. D. W for distinguishing primary from secondary thrombocytosis

S.D.	Maximum	Minimum	Median	Diagnosis
536.92	$1889 \times 10^9/L$	$460 \times 10^9/L$	$1010 \times 10^9/L$	PLT in primary T
138.59	$1348 \times 10^9/L$	$463 \times 10^9/L$	$634 \times 10^9/L$	PLT in secondary T
1.54	12.7 fl	7.1 fl	9.2 fl	M. P. V in Primary T
1.5	13.8 fl	4.9 fl	8.04 fl	M. P. V in secondary T
2.9	19.8 fl	9.9 fl	12.85 fl	P. D. W in primary T
9	13.1 fl	6.5 fl	9.6 fl	P. D. W in secondary T

Table 3. Median, minimum and maximum count in primary thrombocytosis.

M. M. M	P. V	CML	E. T	Diagnosis
520 x 10 ⁹ /L	1105 x 10 ⁹ /L	813 x 10 ⁹ /L	1194 x 10 ⁹ /L	Median platelet count
520 x 10 ⁹ /L	460 x 10 ⁹ /L	501 x 10 ⁹ /L	531 x 10 ⁹ /L	Minimum
520 x 10 ⁹ /L	1883 x 10 ⁹ /L	1889 x 10 ⁹ /L	1740 x 10 ⁹ /L	Maximum
520	562	602.85	499.49	S.D

Most cases of thrombocytosis are reactive and only a small percentage of patients have MPD (1).

In the present study, 146 patients with a platelet count of more than 450 x 10⁹/L were studied. The increased platelet count for 16 subjects (10.9%) was a result of primary thrombocytosis, whereas the elevations for 130 subjects (89.1%) were due to secondary thrombocytosis. The most common cause of thrombocytosis in our series was related to infection (45.2%). Tissue damage was the second most common cause. In other studies, infection has also been found to be one of the most frequent cause of thrombocytosis, especially in children (3,13,14).

In a one-year prospective study of sequential Saudi Arabian patients with platelet counts greater than 500 x 10⁹/L, 21% of cases were found to be caused by infection, 18% tissue damage, 13% chronic inflammation, and 19% rebound after bleeding, iron deficiency or cancer chemotherapy. Thrombocytosis occurring in patients with malignancy, splenectomy or M. P. D accounted for less than 5% in each instance (3).

Wolach et al. observed thrombocytosis in 92.5% of children with pneumonia and empyema (15). Reactive thrombocytosis was common in a group of 122 patients with active pulmonary tuberculosis, and the degree of platelet elevation correlated significantly with the degree of inflammation (8).

The association of thrombocytosis with malignancy and chronic inflammatory disorders, was similar to that reported in earlier studies (1,3,6). Carcinomas of the gastrointestinal tract, malignant lymphomas and lung cancers have also been described as the most frequent malignancy associated with thrombocytosis (1,3,16,17).

Chronic inflammatory bowel disease and rheumatoid arthritis were shown to be the common causes of thrombocytosis (1,3,6,17).

Similar to our series, essential thrombocythaemia and chronic myeloid leukemia have been described as the most frequent M. P. D with thrombocytosis (13).

There is a nonlinear inverse relationship between the MPV and the PLT within normal individual. Therefore, reference values for the MPV appear to vary with the PLT. The MPV is generally increased the myeloproliferative disease (5).

Our data corroborate previous studies that concern PLT and P. D. W. In MPD, the value of these parameters tend to be higher than in reactive thrombocytosis. On the other hand, our findings on MPV results, which were higher in MPD than in R.T were in opposition to Sehayek and Small studies but in accordance to Osselaer study (18,16,20).

It has been stated that reactive process typically do not produce platelet counts over 1000 x 10⁹/L but that myeloproliferative process frequently do; nonetheless, this criterion is reliable neither for diagnosis nor for the decision whether to institute antiplatelet therapy (5). In a study of sequential patients presenting with platelet counts above 1000 x 10⁹/L, reactive thrombocytosis accounted for 82% of patients, M. P. D accounted for 14%, and 4% were of uncertain etiology (13).

In our series, 50% of cases (8 out of 16) with primary thrombocytosis had a platelet count greater than 1000 x 10⁹/L, compared with 1.5% of cases (2 out of 130) with secondary thrombocytosis.

The finding of an elevated platelet count on routine blood examination has diagnostic, prognostic and therapeutic implications (1).

The problem of determining whether thrombocytosis is a primary or secondary event is sometimes difficult. There is no unique laboratory test to reliably distinguish between primary and secondary thrombocytosis. Criteria of the PVSG for diagnosis of ET are as follows: PLT exceeding $600 \times 10^9/L$, hemoglobin less than 13g/dL or normal red cell mass, stainable iron in marrow or failure of one month of iron therapy to raise hemoglobin by 1 g/dL, no Philadelphia chromosome, collagen fibrosis absent or less than 1/3 of biopsy area without both splenomegaly and leukoerythroblastic reaction and no known causes for reactive thrombocytosis (21). Using of other simple non-invasive tests such as preperal blood smear, ESR, C-reactive protein, fibrinogen, Interleukin-6, lactate dehydrogenase, hematocrit and serum potassium are useful for differential diagnosis of thrombocytosis (1,22-25). IF no apparent cause can be detected, the diagnosis depends on other procedures, such as bone marrow biopsy (4,5).

CONCLUSIONS

In most instances thrombocytosis is due to reactive process, and primary thrombocytosis is rare. Although platelet parameters including the PLT, MPV and PDW have been routinely available to clinicians for some times, their role in the diagnosis and management of patients remains unclear. Platelet parameters come along with other simple and non-invasive laboratory tests such as preperal blood smear, ESR, C-reactive protein, fibrinogen, serum potassium and LDH are useful test to distinguish between primary and secondry thrombocytosis.

Footnotes:

Nonstandard abbreviations:

RT, reactive thrombocytosis; MPD, myeloproliferative diseases; ET, essential thrombocythemia; PV, polycythemia vera; CML, chronic myeloid leukemia; PLT, platelet count; MPV, mean platelet volume; PDW, platelet distribution width, MF, myelofibrosis and PVSG, Polycythemia Vera Study Group.

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