Reactive thrombocytosis in children

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The aim of this study was to evaluate the causes of thrombocytosis, which was defined as a platelet count greater than 500 x 10^9/L, and to compare the groups with mild and severe thrombocytosis. A total of 484 patients were evaluated for the etiology of thrombocytosis. Patients with a platelet count between 500-800 x 10^9/L were considered to have mild thrombocytosis, while those with a count of ≥800 x 10^9/L were considered as having severe thrombocytosis.

Of 484 patients included, 63% had thrombocytosis due to an infectious disease, 11.4% had a chronic inflammatory condition, 8.5% had anemia, and 5.2% had tissue injury. The frequency of chronic inflammation was higher in the severe thrombocytosis group compared to the mild thrombocytosis group (p=0.006). In conclusion, severe infections and chronic inflammatory conditions should be considered in the differential diagnosis of a patient with severe thrombocytosis.

Key words: childhood, chronic inflammation, infectious disease, reactive thrombocytosis.

With widespread use of automated electronic devices, platelet counts have become a routine component of complete blood count, which has led to a higher frequency of thrombocytosis being encountered during daily practice. Platelets are particles originating from the cytoplasm of megakaryocytes, and the normal range for circulating platelets is 150-450 x 10^9/L. They are the smallest cells that take part in the hemostatic process[1].

Thrombocytosis is classified as either essential (primary) or reactive (secondary). Essential thrombocytosis develops as a result of either a clonal bone marrow disorder or an abnormality in the biology of thrombopoietin. Reactive thrombocytosis, on the other hand, occurs as a result of stimulation of megakaryopoiesis due to several conditions such as infections, tissue injury or anemia. Thrombocytosis of childhood is mostly reactive, with a reported incidence of 6-15% among hospitalized children[2]. It was reported that many markers of the acute phase reaction, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are significantly elevated in patients with reactive thrombocytosis[3].

The aim of this study was to evaluate the causes of thrombocytosis, which was defined as a platelet count of greater than 500 x 10^9/L, and to compare the groups with mild and severe thrombocytosis in children up to the age of 18 years.

Material and Methods

This study was undertaken in Ankara Children's Hematology Oncology Training and Research Hospital, with the approval of the local ethics committee. The records of all patients (inpatient and outpatient) aged between 5 days and 18 years, who were evaluated between July 2006 and March 2007 for thrombocytosis, with a platelet count of more than 500 x 10^9/L, were systematically reviewed. Patients with thrombocytosis confirmed by a peripheral blood smear were also included in the analysis. Children with a platelet count of 500-800 x 10^9/L were placed in the "mild thrombocytosis" group, while the "severe thrombocytosis" group was comprised of children with a platelet count of >800 x 10^9/L.

Patients were further stratified into six groups based on the most likely underlying cause of the thrombocytosis, namely infectious diseases,

chronic inflammation, anemia, tissue damage, prematurity, and splenectomy.

Children with a history of burns, trauma or surgery one week prior to presentation were placed in the tissue injury group. Prematurity was defined as a being born with a gestational age of less than 37 weeks. Patients who underwent splenectomy more than four weeks prior to presentation were placed in the splenectomy group. Children in whom an obvious cause of thrombocytosis could not be ascertained were placed in the "cause unknown" group. Patients with a chronic inflammatory condition or who were on corticosteroids or anti-inflammatory treatment were not included in the final analysis.

All blood cell counts in our hospital are performed in the hematology laboratory using a Beckman-Coulter MAX-M autoanalyzer. ESR was determined using a Monitor 100® (Electa Lab, Italy) device, while measurements of serum CRP levels were performed by nephelometric method on a Beckman-Coulter Immage® device.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA). Values were either provided as numbers and percentages, or as mean±standard deviation, where applicable. Comparisons of the frequency of all variables between patients with mild thrombocytosis and severe thrombocytosis were made using the chi-square test, Fisher's exact test and Student's t-test. A p-value of ≤0.05 was considered indicative of statistical significance.

Results

During the nine-month study period, reactive thrombocytosis was identified in 484 patients presenting to the outpatient and inpatient clinics, which approximates 4.5% of all measured complete blood counts. The median age of the patients was 0.9 years (min: 5 days, max: 18 years), and the male-to-female ratio was 1.32. Platelet counts fell most frequently in the 500-600 x 10^9/L range (Table I), and most patients were younger than two years of age (65.9%).

Table I. Distribution of Study Population According to Thrombocyte Count

Thrombocyte count x 10^9/L	Number of patients (%)
500-599	263 (54.3)
600-699	114 (23.6)
700-799	66 (13.6)
800-899	19 (3.9)
900-999	14 (2.9)
≥ 1000	8 (1.7)

Among the recognized causes of reactive thrombocytosis, an infection was encountered in 63%, followed by chronic inflammation in 11.4%, anemia in 8.5%, tissue injury in 5.2%, prematurity in 1.9%, and a history of splenectomy in 1.2%. A cause could not be identified in 8.9% of patients. The most commonly encountered causes were infections and chronic inflammation, with respective mean ages of 26.1±38.9 months and 99.4±58.5 months ($p<0.001$).

A breakdown of infectious etiologies of thrombocytosis revealed upper respiratory infections to be responsible for 25% of the cases, followed by pneumonia in 15.7%, acute gastroenteritis in 10.5%, sepsis in 8.5%, bronchiolitis in 6.9%, meningitis in 5.2%, and deep neck abscesses in 3.9% of patients. A variety of other infections (viral hepatitis, cellulitis, septic arthritis, empyema, and lymphadenitis) made up the remaining 5.9%.

Upper respiratory infections were the most

Table II. Age Distribution of Patients with Mild and Severe Thrombocytosis

Age group	All patients n=484 (%)	Mild thrombocytosis n=443 (%)	Severe thrombocytosis n=41 (%)	p-value
0-2 years	319 (65.9)	294 (66.4)	25 (61.0)	0.486
2-6 years	72 (14.9)	66 (14.9)	6 (14.6)	0.964
6-10 years	51 (10.5)	47 (10.6)	4 (9.8)	0.865
>10 years	42 (8.7)	36 (8.1)	6 (14.6)	0.157

common cause of mild thrombocytosis (21.3%) among the infectious etiologies, while severe thrombocytosis was most commonly associated with lower respiratory tract infections (26.1%). Meningitis was a cause of mild thrombocytosis in 4.3% (12/282) of patients with infectious diseases, compared to 17.4% (4/23) in the severe thrombocytosis group (p=0.024).

The differences between the mild and severe thrombocytosis groups with regards to gender (p=0.260) and age distribution were statistically insignificant (Table II).

Most of the study group was comprised of patients younger than two years of age. The rate of infectious diseases was higher in patients under two years than in those older than two years (70.2% vs 49.1%, p<0.001). The rates of chronic inflammation (28.5% vs 2.5%, p<0.001) and splenectomy (3% vs 0.3%, p=0.019) were higher in patients older than two years. There was no statistically significant difference in the remaining groups.

The chronic inflammation rate was higher in the severe thrombocytosis group compared to the mild thrombocytosis group (10.2% vs 24.4%, p=0.006). However, when we compared them according to age (under or over 2 years), the difference was not statistically significant in patients older than two years, but was statistically significant in patients under two years. There was no difference between groups with regard to the frequencies of other disease conditions (Table III).

Nephrotic syndrome (32.7%) was the most commonly encountered condition in the chronic inflammation group, followed by juvenile rheumatoid arthritis (30.9%), Henoch-Schönlein purpura (21.8%), familial Mediterranean fever (9.1%), inflammatory bowel disease (3.6%), and Kawasaki disease (1.8%).

We could not identify the etiology of thrombocytosis in 43 patients, but numbers of thrombocytes had decreased to normal in all of them during the four-week follow-up. The majority of them might have been associated with an unidentified upper respiratory tract infection.

Overall, eight patients had a platelet count exceeding 1000 x 10^9/L (4 had an infectious disorder, 2 had chronic inflammation, 1 had undergone splenectomy, and 1 had anemia).

The mean hemoglobin concentration of the study population was 11.0±2.1 mg/dl (min: 7.4, max: 16.6), with a mean value in the severe thrombocytosis group of 10.1±1.8 mg/dl compared to 11.0±1.9 mg/dl in patients with mild thrombocytosis (p=0.004). The average white blood cell (WBC) count in the severe thrombocytosis group was significantly higher than that of the mild thrombocytosis group (17693±7448 cells/mm^3 vs. 14873±7499 cells/mm^3, p=0.018).

C-reactive protein (CRP) levels were measured in 362 of the 484 children included in the study, with 46.6% of the patients having a positive result. CRP levels were elevated in 75% of patients with severe thrombocytosis compared to 46.8% in the mild thrombocytosis

Table III. Distribution of Disease Conditions in Patients with Mild and Severe Thrombocytosis

		Two years of age or younger			Older than two years of age		
Disease/condition	All patients n=484 (%)	Mild thrombocytosis n=294 (%)	Severe thrombocytosis n=25 (%)	p-value	Mild thrombocytosis n=149	Severe thrombocytosis n=16	p-value
Infectious diseases	305(63.0)	207 (70.4)	17 (68.0)	0.800	75 (50.3)	6 (37.5)	0.329
Chronic inflammation	55(11.4)	5 (1.7)	3 (12.0)	0.018	40 (26.8)	7 (43.8)	0.155
Anemia	41 (8.5)	28 (9.5)	3 (12.0)	0.447	10 (6.7)	0 (0.0)	0.350
Tissue injury	25 (5.2)	18 (6.1)	0 (0.0)	0.221	6 (4.0)	1 (6.3)	0.517
Prematurity	9 (1.9)	9 (3.1)	0 (0.0)	0.475	0 (0.0)	0 (0.0)	
Splenectomy	6 (1.2)	0 (0.0)	1 (4.0)	0.078	4 (2.7)	1 (6.3)	0.403
Unknown	43 (8.9)	27 (9.2)	1 (4.0)	0.331	14 (9.4)	1 (6.3)	0.559

Table IV. Comparison of Laboratory Findings in Patients with Mild and Severe Thrombocytosis

Finding	Mild thrombocytosis n=443	Severe thrombocytosis n=41	*p*-value
Hemoglobin* (g/dl)	11.0±1.9	10.1±1.8	0.004
WBC* (cells/mm^3)	14873±7499	17693±7448	0.018
CRP$^\Omega$ positivity (n, %)	151 (46.6)	27 (75.0)	0.001
ESR (mm/hour)	53.6±37.5	76.0±36.6	0.005

*values provided as mean± standard deviation.
$^\Omega$values provided as number and percentage of total.
CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. WBC: White blood cell count.

group (p=0.001). Overall, ESR was measured in 188 patients, with children in the severe thrombocytosis group having a mean value of 76.0±36.6 mm/hour compared to 53.6±37.5 mm/hour in patients with mild thrombocytosis (p=0.005). Laboratory findings have been summarized in Table IV.

We did not observe any bleeding or thrombosis during the study period. Follow-up results of up to four weeks from the date of presentation were available in 448 patients, and in 83.6% of them, platelet count had returned to normal level (<500 x 10^9/L), which was statistically significant for all disease conditions, except the splenectomy group.

Discussion

Thrombocytosis is very common in children, with the reported frequency of a platelet count exceeding 500 x 10^9/L being between 5-15%[4-7]. In our study, we identified reactive thrombocytosis in 4.5% of patients admitted to our hospital. In a study by Matsubara et al.[7] on 456 children, severe thrombocytosis (platelet count >800 x 10^9/L) was observed in 5.3% of patients. In our study, 8.5% of the 484 children had severe thrombocytosis (platelet count >800 x 10^9/L).

Thrombocytosis, whether mild or severe, is quite common in childhood, particularly during the first two years of life, after which the incidence of reactive thrombocytosis decreases with age[4,7,8]. The incidence of reactive thrombocytosis is higher in newborns, especially premature infants, which has been attributed to higher levels of thrombopoietin as well as to megakaryocyte precursor cells being more sensitive to thrombopoietin[2]. Ishiguro[9] observed that levels of serum thrombopoietin decrease with age. In our study, nearly two-thirds of patients with either mild or severe thrombocytosis were younger than two years of age.

In a study by Yohannan et al.[8], it was reported that infections were the most common cause of thrombocytosis in children younger than five years of age, while in older children, chronic inflammation was more prevalent. Our study produced similar results, in that the mean age of patients in the infectious diseases group was around two years, compared to a mean age of eight years in the chronic inflammation group. This could be explained by the fact that chronic inflammatory conditions generally manifest in older ages during childhood.

The reported frequency of reactive thrombocytosis due to infections in children is between 37-78%, most commonly in association with respiratory tract infections (60-80%), followed by infections involving the gastrointestinal and urinary tracts[2]. In a study on patients with severe thrombocytosis (platelet count >800 x 109/L), infectious diseases were the most commonly encountered cause, with infections of the respiratory tract again being the most prevalent[10]. Infectious diseases were also the most common cause of reactive thrombocytosis in our patient population, with respiratory tract infections being the most frequent cause, followed by urinary tract and gastrointestinal system infections.

In a study by Matsubara et al.[7] among patients with mild thrombocytosis due to infectious diseases, upper respiratory tract infections were most commonly observed, while in patients with severe thrombocytosis, infections more frequently involved the lower respiratory tract. In another study on 94 children with a platelet count greater than 900 x 10^9/L, infectious diseases were again the most common cause

of reactive thrombocytosis, although in this case, infections of the central nervous system were the most frequently implicated cause[4]. It was reported that the rate of thrombocytosis was higher in patients with severe pulmonary tuberculosis than in healthy controls[11]. In our study population, as leading causes of severe thrombocytosis, lower respiratory tract infections were followed by meningitis. This suggests that the extent of thrombocytosis increases with the severity of infection.

The reported frequency of chronic inflammation in children with reactive thrombocytosis is 4.1%[8], with an estimated prevalence of 9% among children with severe reactive thrombocytosis[6]. In our study, the frequency of chronic inflammation was significantly higher in the severe thrombocytosis group compared to patients with mild thrombocytosis. A correlation between the degree of thrombocytosis and diseases severity is apparent.

It was reported that anemia is a common cause of reactive thrombocytosis[12]. In a study by Yadav et al.[13], investigators observed that 65% of children had thrombocytosis due to an infectious disease, of which 29% were also anemic. On the other hand, the authors reported the presence of anemia as the only likely cause of thrombocytosis in only 12.6% of patients. The prevalence of infections in our study population was 63%, and 32.3% of patients with an infectious disease also had anemia. Anemia was the only apparent cause of thrombocytosis in 8.5% of the children in our study.

We observed CRP positivity in 60.8% of patients with both an infectious disease and anemia compared to 17.6% in children with anemia alone. We also managed to demonstrate an increase in values of the acute phase reactants CRP and ESR in correlation with an increase in the extent of thrombocytosis, and significantly more patients with severe thrombocytosis had anemia compared to those with mild thrombocytosis. These findings suggest that in a case with both an infection and anemia, it is the infection that is most likely to be responsible for the reactive thrombocytosis, and the infection itself may indeed be the cause of anemia.

In a recently published study, the degree of reactive thrombocytosis was found to be positively correlated with WBC count and negatively correlated with hemoglobin concentration, with no apparent correlation with CRP levels[14]. In our study, however, both WBCs and CRP levels correlated positively with the degree of reactive thrombocytosis, while a negative correlation was observed with hemoglobin concentrations.

In a previous study, no thrombotic or hemorrhagic complications were encountered in patients with severe thrombocytosis[4]. Furthermore, in a recent study carried out in 89 newborns with thrombocytosis in the neonatal intensive care unit, no hemorrhagic complications were observed, but portal vein thrombosis developed in one newborn associated with intestinal malrotation[15]. Similar to these findings, we did not observe any hemorrhagic or thrombotic complications during the study period.

In conclusion, although infectious diseases are the most common cause of reactive thrombocytosis, the presence of another condition such as chronic inflammation, anemia or tissue injury should also be investigated. Levels of acute phase reactants correlate positively with the degree of thrombocytosis. Severe infections and chronic inflammatory conditions should be considered in the differential diagnosis of a patient with severe thrombocytosis.

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