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Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count

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Abstract. Griesshammer M, Bangerter M, Sauer T, Wennauer R, Bergmann L, Heimpel H (University of Ulm, Germany). Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count. *J Intern Med* 1999; **245:** 295–300.

Objective. To determine the aetiology and clinical significance of an elevated platelet count (thrombocytosis) in a large cohort of patients.

Design. A retrospective review of the medical records was performed on all patients, who had at least one platelet count $\geq 500 \times 10^9$ L^{-1}.

Setting. Departments of Medicine and Surgery, University of Ulm, Germany.

Subjects. A total of 732 patients with thrombocytosis.

Main outcome measures. Classification of thrombocytosis and thromboembolic complications, and evaluation of laboratory parameters distinguishing between primary and secondary thrombocytosis.

Results. Of the total of 732 patients, 89 (12.3%) had primary and 643 (87.7%) had secondary thrombocytosis. Essential thrombocythaemia was observed in 40 of 89 patients (45%) with primary thrombocytosis. The most frequent causes of secondary thrombocytosis were tissue damage (42%), infection (24%), malignancy (13%) and chronic inflammation (10%). Primary thrombocytosis was significantly associated with a higher platelet count and an increased incidence of both arterial and venous thromboembolic complications. In secondary thrombocytosis, thromboembolic events were restricted to the venous system and occurred only in the presence of other risk factors. Mean values of leucocyte count, haematocrit, erythrocyte sedimentation rate, fibrinogen, serum potassium and lactate dehydrogenase were significantly different in primary and secondary thrombocytosis.

Conclusions. The finding of an elevated platelet count on routine blood examination has diagnostic, prognostic and therapeutic implications. It is of clinical importance to distinguish between primary and secondary thrombocytosis, as thrombotic complications occur more frequently in primary thrombocytosis. Unless additional risk factors are present, secondary thrombocytosis is not associated with a significant risk for thromboembolic events.

Keywords: aetiology, platelets, thrombocytosis, thrombosis.

Introduction

Thrombocytosis refers to a platelet count above the normal value. Today, with the widespread use of electronic cell counters and the subsequent availability of a platelet count as part of a 'routine' 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 [1,2]. Thrombocytosis is classified according to its origin into primary and secondary forms. The term primary thrombocytosis refers to a persistent elevation of platelet count due to clonal thrombopoiesis as it occurs in chronic myeloproliferative or in some myelodysplastic disorders [1]. 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 exertion [3–6]. In contrast, secondary thrombocytosis associated with malignancy, chronic infection, iron deficiency or chronic inflammatory diseases may persist for a longer time [7–11]. To determine the aetiology and clinical

significance of an elevated platelet count, we reviewed the medical records on 732 individuals in whom a platelet count of greater than or equal to 500×10^9 L^{-1} was encountered during a 3.5-year period.

Patients and methods

The medical technologists in the laboratory of clinical chemistry were instructed to identify all patients (in-patients and outpatients) in whom a platelet count of greater than or equal to 500×10^9 L^{-1} was found between July 1991 and January 1995. During this period, 732 patients with a platelet count of greater than or equal to 500×10^9 L^{-1} were identified in the Departments of Medicine and Surgery at the University of Ulm. We retrospectively reviewed the medical records of all 732 patients to determine: (i) the aetiology of elevated platelet counts; (ii) additional laboratory parameters, i.e. full blood count, serum potassium, creatinine, lactic dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and plasma fibrinogen; (iii) the presence of thromboembolic complications; and (iv) follow-up information.

All platelet counts were performed on Coulter counter STKS (Coulter Electronics, Krefeld, Germany) using EDTA anticoagulated fresh blood. The normal range of platelet counts for this machine is $150–450 \times 10^9$ L^{-1}. High counts were confirmed by repeat examinations and/or peripheral smear examination.

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.

The SAS system was used for the statistical calculation. Descriptive statistics were calculated for patient characteristics and laboratory parameters for each aetiological group. Chi-square and Fisher's exact tests were used to assess group differences in categorical variables, and Wilcoxon's rank sum test was used to assess group differences in continuous variables. All significance levels were two-sided.

Results

A total of 732 patients with a platelet count $\geq 500 \times 10^9$ L^{-1} were observed during the study period. The various underlying conditions associated with an elevated platelet count are listed in Table 1. Primary thrombocytosis as the cause of platelet elevation was found in 89 cases (12.3%). Secondary thrombocytosis was the most frequent cause of an elevated platelet count and occurred in 643 cases (87.7%). Platelet counts ranged from 500×10^9 to 1664×10^9 L^{-1} (median 575×10^9). Eighty-five per cent of all patients ($n = 622$) had platelet counts $\leq 750 \times 10^9$ L^{-1}, 11.2% ($n = 82$) had platelet counts between 750 and 1000×10^9 L^{-1} and 3.8% ($n = 28$) had platelet counts $\geq 1000 \times 10^9$ L^{-1}.

Of the 643 patients with secondary thrombocytosis, 378 were male and 265 female. The age range was 1–90 years, with a median age of 54 years. The observed platelet counts ranged from 500×10^9 to 1346×10^9 L^{-1} (median 563×10^9).

Tissue damage was the most common cause of secondary thrombocytosis, occurring in 269 patients (36.7%). It was found that 235 cases (87%) were due to major abdominal (83 cases), cardiovascular (71 cases), orthopaedic (63 cases) and thoracic (18 cases) surgery. In 69 of 235 cases (29%), surgery was performed because of a malignant tumour, but thrombocytosis was first seen postoperatively. In the remaining patients, tissue da-

Table 1 Aetiology of thrombocytosis in 732 patients

Diagnosis	*n* (%)
Primary thrombocytosis	89 (12.3%)
Essential thrombocythaemia	40 (5.5%)
Chronic myeloid leukaemia	24 (3.3%)
Polycythaemia vera	18 (2.5%)
Osteomyelofibrosis	4 (0.6%)
Unclassified myeloproliferative disease	3 (0.4%)
Secondary thrombocytosis	643 (87.7%)
Tissue damage	269 (36.7%)
Infection	154 (21.0%)
Malignancy	85 (11.6%)
Chronic inflammatory disorders	65 (8.9%)
Multiple causes	14 (1.9%)
Renal disorders	13 (1.8%)
Post-splenectomy	12 (1.6%)
Miscellaneous	8 (1.1%)
Uncertain aetiology	23 (3.1%)

Median age (range), 54 (1–90) years; male:female ratio, 57:43.

mage was due to miscellaneous operations (25 cases), acute pancreatitis (five cases), burns (one case) or extensive myocardial infarction (three cases).

Thrombocytosis associated with infection occurred in 154 patients (21%). The majority were acute infections (86%). Patients with pneumonia constituted 30.5% (47 cases) of all infections. Other infections associated with thrombocytosis were gastrointestinal (17 cases) and hepatobiliary infections (11 cases), soft tissue infections with or without abscesses (17 cases), osteoarthritis and osteomyelitis (13 cases), septicaemia (11 cases), urinary tract infections (eight cases), tuberculosis (five cases), nervous system infections (three cases) and miscellaneous infections (22 cases).

There were 85 patients (11.6%) with thrombocytosis at the initial presentation of malignancy. The malignancies most commonly associated with thrombocytosis were carcinomas of the gastrointestinal tract (23 cases), malignant lymphomas (21 cases), lung cancers (13 cases), carcinomas of the liver, gall bladder or pancreas (six cases), ovarian or breast cancers (five cases) and soft-tissue or bone sarcomas (four cases).

Amongst chronic inflammatory disorders causing thrombocytosis, Crohn's disease (23 cases), colitis ulcerosa (15 cases), rheumatoid arthritis (11 cases) and chronic pancreatitis (nine cases) were the most common.

Multiple causes responsible for thrombocytosis were seen in 14 cases (1.9%). Infection after surgery was the most common contributing factor to thrombocytosis in this group. Six patients had both an acute infection and a rebound thrombocytosis after recovery from marrow suppression due to chemotherapy.

Amongst renal disorders giving rise to thrombocytosis, chronic renal failure was the cause in 12 cases and acute renal failure in one case. Postsplenectomy thrombocytosis was seen in 12 cases (1.6%).

The miscellaneous group consisted of patients with thrombocytosis following upper gastrointestinal bleeding in five cases, iron deficiency anaemia of unknown origin in two cases and autoimmune haemolytic anaemia in one case.

The aetiology of thrombocytosis in 23 cases (3.1%) could not be classified into one of the aetiological subgroups.

Of the 89 patients with primary thrombocytosis, 39 were male and 50 were female. The age range was 22–87 years, with a median age of 54 years. The observed platelet counts ranged from 512×10^9 to 1664×10^9 L^{-1} (median 839×10^9) and were significantly higher compared with platelet counts in secondary thrombocytosis ($P < 0.001$). Essential thrombocythaemia was the most common cause of primary thrombocytosis (40 of 89 cases, 45%). Compared with secondary thrombocytosis, primary thrombocytosis was significantly associated with a higher rate of thromboembolic complications. Eleven thromboembolic complications (12.4%) occurred in patients with primary thrombocytosis, compared with 10 complications (1.6%) in patients with secondary thrombocytosis ($P < 0.001$). Most complications (eight cases) were observed in patients with essential thrombocythaemia. There were two thrombotic episodes in two polycythaemia vera patients and another in a patient with osteomyelofibrosis. Six of these thromboembolic complications were of venous origin (two deep vein thromboses, one thrombophlebitis, one mesenterial vein thrombosis, two portal vein thromboses) and five were of arterial origin (two peripheral arterial thromboses, two ischaemic strokes, one carotis interna thrombosis). All thromboembolic complications in patients with secondary thrombocytosis were of venous origin (seven deep vein thromboses, two deep vein thromboses with pulmonary embolism and one portal vein thrombosis after splenectomy). All thromboembolic complications in secondary thrombocytosis occurred postoperatively (eight cases) or were observed in patients with an underlying malignancy (two cases).

There were 28 out of the 732 patients (3.8%), who had a platelet count $\geq 1000 \times 10^9$ L^{-1}. A platelet count $\geq 1000 \times 10^9$ L^{-1} was significantly associated with primary thrombocytosis and was observed in 23 patients with primary thrombocytosis compared with five patients with secondary thrombocytosis ($P < 0.001$). The mean duration of platelet elevation in patients with secondary thrombocytosis was short compared with untreated cases of primary thrombocytosis (1.5 vs. 47.2 months, $P < 0.001$).

We determined parameters indicated by the literature as potentially useful for differentiating between primary and secondary thrombocytosis,

Table 2 Univariate analysis of discriminatory characteristics distinguishing primary from secondary thrombocytosis

Characteristic	Primary thrombocytosis		Secondary thrombocytosis		
	n	Mean (SD)	*n*	Mean (SD)	*P*-value
Leucocytes ($\times 10^9$ L^{-1})	89	15.9 (13.8)	643	10.9 (5.2)	$P = 0.003$
Haematocrit (%)	89	39.2 (8.5)	643	33.8 (5.3)	$P < 0.001$
Platelets ($\times 10^9$ L^{-1})	89	872 (274)	643	597 (105)	$P < 0.001$
ESR (mm)	89	14 (25)	452	50 (33)	$P < 0.001$
Fibrinogen (g L^{-1})	54	2.9 (1.2)	84	5.0 (1.9)	$P < 0.001$
Potassium (mmol L^{-1})	89	5.0 (0.8)	623	4.5 (0.6)	$P < 0.001$
LDH (U L^{-1})	83	315 (189)	353	231 (115)	$P < 0.001$

SD, standard deviation; ESR, erythrocyte sedimentation rate (after 1 h).

such as erythrocyte sedimentation rate (ESR), fibrinogen, serum potassium and lactate dehydrogenase (LDH). A univariate analysis of discriminatory characteristics distinguishing primary from secondary thrombocytosis is shown in Table 2.

Discussion

Until the introduction of electronic blood cell counting instruments, platelet counts were not usually included in the routine complete blood cell count. Now that accurate platelet counts are part of the routine blood cell count, thrombocytosis is being encountered much more frequently [6]. Elevated platelet counts, except in those with known or suspected myeloproliferative disorders, have often been ignored as thrombocytosis has been considered inconsequential [13].

In the present study, 732 patients with a platelet count of $\geq 500 \times 10^9$ L^{-1} were studied: the elevations for 89 (12.3%) were a result of primary thrombocytosis, whereas the elevations for 643 (87.7%) were due to secondary thrombocytosis. Thrombocytosis after surgical or traumatic tissue damage occurred in most of our patients (36.7%). Recent surgery as a cause of thombocytosis is well established and is most frequently observed after coronary artery bypass grafting and after major abdominal surgery, especially splenectomy [3,5,6,9,14]. It has been demonstrated that postoperative thrombocytosis is mainly the result of increased platelet production, but there is concomitantly a sizeable redistribution of platelets from the splenic platelet pool to the general circulation [15].

The second most common cause of thrombocytosis in our series was infection (21.0%). A respiratory tract infection was the most common condition. In other studies, infection has also been found to be one of the most frequent causes of thrombocytosis, especially in children [6,13,16]. Wolach *et al.* [17] observed thrombocytosis in 92.5% of children with pneumonia and empyema. 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 [11].

Thrombocytosis has been described as a clue to an underlying malignancy in some patients in whom the diagnosis has not yet been suspected or established [3]. Similar to our series, carcinomas of the gastrointestinal tract, malignant lymphomas and lung cancers have been described as the most frequent malignancies associated with thrombocytosis [5–7]. In a recent study of 1115 patients with lung cancer, the overall prevalence of thrombocytosis was 32% and was found to be an independent negative prognostic factor of survival [18].

The association of thrombocytosis with chronic inflammatory disorders, such as chronic inflammatory bowel disease and rheumatoid arthritis, was similar to that reported in earlier studies [3,6]. In adults, Robbins & Barnard [5] observed autoimmune diseases in 7.8% of their patients with thrombocytosis; except for two, all of them had rheumatoid arthritis.

Our results demonstrate a significantly higher incidence of both arterial and venous thromboembolic complications in patients with primary thrombocytosis (12.4%) than in patients with secondary thrombocytosis (1.6%). All patients with secondary thrombocytosis developing thrombotic complications had additional risk factors such as preceding surgery or a coexisting malignancy. Unless there are additional risk factors, secondary thrombocytosis of

various aetiologies, including post-splenectomy thrombocytosis, seemed not to be associated with a significant risk for haemostatic complications. In one large retrospective study comprising 318 patients without myeloproliferative disorders who underwent splenectomy, no significant increase in the incidence of thromboembolic events was detected [19]. All thromboembolic events in primary thrombocytosis were observed in patients with essential thrombocythaemia, polycythaemia vera or osteomyelofibrosis, whereas in cases with chronic myeloid leukaemia no such complications occurred. Primary thrombocytosis in chronic myeloid leukaemia is known to be associated with a lower incidence of thrombotic events compared with other myeloproliferative disorders with platelet elevation [20].

In view of the aforementioned, it appears that each patient who presents with thrombocytosis should be carefully evaluated. The aim is to distinguish between reactive and clonal thrombocytosis. The discriminatory value of plasma interleukin-6, C-reactive protein, platelet distribution width, lactate dehydrogenase, fibrinogen and ESR has been shown [21–24]. We additionally identified leucocytes, platelet count, haematocrit and serum potassium as being significantly different in patients with primary and secondary thrombocytosis. Elevated serum potassium levels in thrombocytosis are due to an *in vitro* rise of potassium concentration during whole-blood coagulation, an effect known as pseudohyperkalaemia. A significant correlation was found between serum potassium concentrations and the whole-blood platelet count [25]. This might explain why serum potassium concentrations are higher in primary thrombocytosis.

The finding of an elevated platelet count on routine blood examination has diagnostic, prognostic and therapeutic implications. The problem of determining whether thrombocytosis is a primary or secondary event is sometimes difficult. There is no unique laboratory test to distinguish reliably between primary and secondary thrombocytosis. However, abnormalities of simple non-invasive tests such as ESR or CRP suggest secondary thrombocytosis. If no apparent cause can be detected, the diagnosis depends on other procedures, such as a bone marrow biopsy, or on watching the platelet count over a longer period of time. In most instances, platelet elevation is due to secondary thrombocytosis in response to tissue damage, infection, malignancy or a chronic inflammatory disorder. Unless additional risk factors are present, the risk of thrombotic complications is not increased. Primary thrombocytosis is rare and usually associated with myeloproliferative diseases. In this case, the risk of both arterial and venous thrombotic events is significantly increased, especially in essential thrombocythaemia.

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