Occurrence, Etiology, and Clinical Significance of Extreme Thrombocytosis: A Study of 280 Cases

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PURPOSE: To determine the etiology and to evaluate the clinical consequences of an extremely elevated platelet count.

PATIENTS AND METHODS: A review of the medical records was performed on all patients encountered during a 5½-year period who had at least one platelet count of 1,000 × 10^9/L or greater.

RESULTS: Of the total of 280 patients with extreme thrombocytosis (EXT), 231 (82%) had reactive thrombocytosis (RT), 38 (14%) had a myeloproliferative disorder (MPD), and 11 (4%) had cases of uncertain etiology. RT was more common than MPD in all age groups except those in the eighth decade and older. Symptoms of bleeding and/or vaso-occlusive phenomena were noted in association with EXT in 21 (56%) of the MPD patients but in only 10 (4%) of the RT patients. Treatment to lower the platelet count and/or inhibit platelet function was employed in 36 MPD patients and 23 RT patients. Eight patients with MPD and 34 with RT are known to have died, but no patient in either group is known to have died of a thrombotic or bleeding event when the platelet count was greater than or equal to 1,000 × 10^9/L.

CONCLUSIONS: Platelet counts greater than or equal to 1,000 × 10^9/L should not be considered rare events in the general, acute-care hospital population, and usually represent a reactive phenomenon.

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Prior to the incorporation of a platelet channel in automated complete blood cell counters (CBC analyzers), platelet counts greater than or equal to 1,000 × 10^9/L were thought to be rare and, when encountered, were believed to be most often due to myeloproliferative disorders (MPDs) [1,2]. However, during a previous study on the clinical consequences of extreme thrombocytosis (EXT), we noted that platelet counts of this magnitude were not a particularly rare event and appeared to be more often the result of a reactive process than a MPD [3]. Since this previous study relied predominantly on bone-marrow files to identify the study population, we believed it was probably biased toward patients with MPD as opposed to those with reactive thrombocytosis (RT). Therefore, in order to further assess the occurrence, etiology, and clinical significance of EXT, we reviewed the medical records on all individuals in whom a platelet count of greater than or equal to 1,000 × 10^9/L was encountered during a recent 5½-year period.

PATIENTS AND METHODS

From January 1, 1984, through June 30, 1989, the medical technologists in the hematology laboratory of North Carolina Baptist Hospital were instructed to identify all patients (i.e., in-patients and out-patients) in whom a platelet count of greater than or equal to 1,000 × 10^9/L was found. All patients (n = 9) included in the previous series [3] were excluded from the present series. During this period, all complete blood counts (CBCs) and platelet counts were obtained with whole blood anticoagulated with ethylene diaminetetraacetic acid using Coulter S-Plus or S-Plus 4d hematology analyzers (Coulter Electronics, Hialeah, FL). All platelet counts were confirmed by visual correlation with a Wright's-stained blood smear of the corresponding sample. The hospital is a tertiary care facility that had 650 beds during the period of the study.

The medical records of all 280 patients identified were examined to determine: (1) the etiology of the thrombocytosis; (2) the peak platelet count; (3) the presence of bleeding and/or vaso-occlusive symp-

TABLE I

Clinical Findings in 280 Patients with Extreme Thrombocytosis

Etiology	No. of Patients (%)	Mean Age (y)	Sex M	Sex F	Mean Peak Platelet Counts ($\times 10^9$/L)
RT	231 (82)	31	142	89	1,195
MPD	38 (14)	57	18	20	1,808
Uncertain (RT vs MPD)	11 (4)	75	6	5	1,437

RT = reactive thrombocytosis; MPD = myeloproliferative disorder.

toms associated with EXT; (4) if treatment for EXT was instituted; and (5) follow-up information. Regarding the etiology of EXT, patients were considered to have RT if they had one or more clinical conditions well recognized as being associated with thrombocytosis [2,4] and did not have a diagnosable MPD. Patients with MPD were classified as having primary thrombocythemia (PT) or polycythemia vera (PV) according to the Polycythemia Vera Study Group (PVSG) criteria [5,6], chronic granulocytic leukemia (CGL) if the Philadelphia chromosome was present in association with granulocytosis, or idiopathic myelofibrosis (IMF) based on appropriate bone marrow and clinical findings.

Descriptive statistics were calculated for patient characteristics, peak platelet counts, and symptoms, separately for each etiologic group. χ^2 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.

RESULTS

Pertinent clinical findings are summarized in **Table I.** Of the 280 patients, 166 were male, and 114 female. The ages ranged from 12 days old to 100 years old, with a mean age of 37 years.

Etiology

The underlying primary conditions associated with EXT are shown in **Table II.** The 231 patients in the RT group ranged in age from 12 days to 92 years, with a mean age of 31 years. The most common cause of EXT was an infectious process (31%). The 43 (19%) patients in whom postsplenectomy status was considered the most likely cause of EXT included 4 adults in whom hyposplenism secondary to sickle cell disease (i.e., "autosplenectomy" status) was present. Splenectomy was performed because of traumatic injury in 18 cases and for nontraumatic reasons (e.g., staging procedures, hemolytic anemias) in 21 cases. The nine (4%) patients in whom RT was of uncertain etiology mostly involved afebrile children, six of whom were less than 1 year of age. More than 1 cause for RT was present in 90 (39%) of these patients, mostly in trauma patients in whom blood loss, infection, and inflammation were commonly encountered.

TABLE II

Etiologic Conditions Associated with Extreme Thrombocytosis

Total Cases		280
Reactive thrombocytosis		231
Infection (%)	72 (31)	
Post-splenectomy (or hyposplenism) (%)	43 (19)	
Malignancy (%)	33 (14)	
Trauma (%)	32 (14)	
Inflammation (noninfectious) (%)	21 (9)	
Blood loss (%)	13 (6)	
Uncertain etiology (%)	9 (4)	
Rebound (%)	8 (3)	
Myeloproliferative disorders		38
CGL (%)	16 (42)	
PT (%)	11 (29)	
PV (%)	5 (13)	
IMF (%)	2 (5)	
Unclassified (%)	4 (11)	
Uncertain etiology		11

CGL = chronic granulocytic leukemia; PT = primary thrombocythemia; PV = polycythemia vera; IMF = idiopathic myelofibrosis.

Of the 38 MPD cases, the most common disorder associated with EXT was CGL (42%). Three of the four MPD patients in whose cases the precise classification was unclear involved those with features of both PV and PT. The remaining patient probably had PT but had undergone splenectomy elsewhere 36 years prior to the clinical diagnosis of PT; the reasons for splenectomy and the preoperative platelet count were not known. The age range of MPD patients was 14 to 87 years, with a mean of 57 years. The platelet count was greater than 1,000 $\times 10^9$/L at the time of the initial diagnosis of MPD in 25 (66%) patients, less than 1,000 $\times 10^9$/L at diagnosis in 10 (26%) patients, and unknown at diagnosis in 3 (8%) patients.

The 11 patients with EXT of uncertain etiology ranged from 62 to 100 years of age, with a mean age of 75 years. In five of these patients, the EXT was likely due to a MPD, but all five had conditions known to cause RT and a short follow-up or incomplete work-up. The remaining six patients in this subgroup were thought to have RT, but the cause of the EXT was not well investigated.

The age distribution (**Figure 1**) of cases of EXT showed that the RT group was significantly younger ($p < 0.0001$) than the MPD group, with the highest incidence (33 patients) occurring in those under 1 year of age. MPD was slightly more common than RT only in patients over 70 years of age. When RT is considered by age groups, an infectious process was the most common cause in the first decade (39 of 60 patients); trauma was the

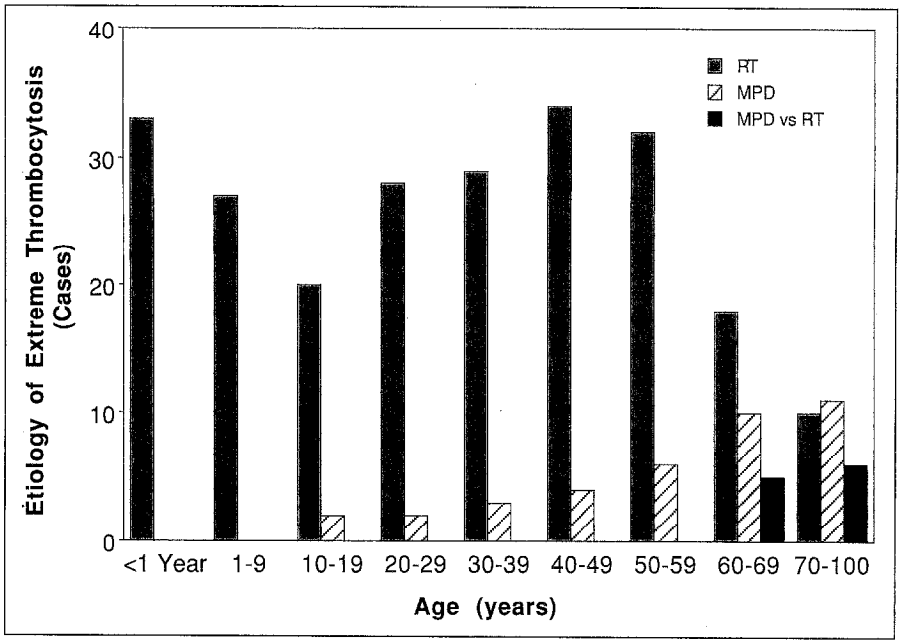

Figure 1. Incidence of extreme thrombocytosis according to patient age. RT = reactive thrombocytosis; MPD = myeloproliferative disorder; MPD vs RT indicates uncertainty if the disease process represented MPD or RT.

most common cause in the second decade (9 of 20 patients); postsplenectomy status was most common (29 of 57 patients) in both the third and fourth decades; malignancy was most common in the fifth through seventh decades (29 of 84 patients), and infectious disorders were most common in patients over 70 years of age (6 of 10 patients). Among those with MPD, there was no discernable pattern of increased or decreased frequency of the various MPD subtypes related to patient age except that three of the four youngest patients had PT.

Peak Platelet Counts

The peak platelet counts in the RT group ranged from $1,000 \times 10^9$/L to $2,092 \times 10^9$/L, with a mean peak of $1,195 \times 10^9$/L; in the MPD group, peak counts ranged from $1,047 \times 10^9$/L to $2,900 \times 10^9$/L, with a mean peak count of $1,808 \times 10^9$/L. The difference in the mean peak counts between these two groups is statistically significant ($p < 0.0001$). The group with EXT of uncertain etiology had peak counts ranging from $1,072 \times 10^9$/L to $2,194 \times 10^9$/L, with a mean peak count of $1,437 \times 10^9$/L. Thirteen of 38 (34%) MPD patients and 2 of 11 (18%) patients with EXT of uncertain etiology had peak platelet counts greater than $2,000 \times 10^9$/L, whereas only 2 of 231 (0.9%) of RT patients had platelet counts of this magnitude.

Symptoms

Symptoms of bleeding or vaso-occlusive disease associated with EXT are summarized in **Table III.**

MPD: The nine patients with bleeding ranged from 35 to 78 years of age, with a mean age of 62 years. Four of the nine patients had minor bleeding episodes, such as bleeding after shaving, or epistaxis. Two other patients had chronic bleeding, which may have been due to factors other than the MPD. In both patients, work-up of the bleeding disorder (chronic hematuria following transurethral prostate resection in one, and dysfunctional, postmenopausal uterine bleeding following long-term estrogen treatment in the other) led to the diagnosis of CGL. The remaining three patients had severe chronic gastrointestinal bleeding, one due to a gastric ulcer, and the other two without a specifically identifiable source of bleeding; all three required blood transfusions.

The nine patients with symptoms of vaso-occlusive disease included four patients with head-

TABLE III

Bleeding or Vaso-occlusive Symptoms Associated with Extreme Thrombocytosis

Disorder	Total Cases
MPD	38
Bleeding (%)	9 (24)
Vaso-occlusive (%)	9 (24)
Both (%)	3 (8)
Neither (%)	17 (44)
RT	231
Bleeding (%)	7 (3)
Vaso-occlusive (%)	3 (1)
Neither (%)	221 (96)
Uncertain etiology	11
Bleeding (%)	1 (9)
Vaso-occlusive (%)	5 (46)
Both (%)	1 (9)
Neither (%)	4 (36)

MPD = myeloproliferative disorder; RT = reactive thrombocytosis.

aches as their only symptom. All four were females, three with PT (two of whom were teenagers) and one with PV. Three patients had symptoms of cerebral transient ischemic attacks. Only two patients had documented thrombotic events: one PV patient with deep vein thrombosis and one CGL patient with a cerebrovascular infarct. These nine patients ranged in age from 15 to 87 years, with a mean age of 57 years; the four patients with headaches as their only symptom had a mean age of 37 years, considerably less than that of the other five patients in this subgroup (74 years).

None of the three patients with both bleeding and vaso-occlusive symptoms required transfusions. One of the three patients, a 31-year-old man, had documented superior mesenteric venous thrombosis, but this occurred 14 months after splenectomy elsewhere for trauma. Prior to splenectomy, his platelet count was normal, but his platelet count remained persistently elevated after the thrombotic event despite the use of chemotherapy. The other two patients had symptoms of myocardial or cerebral ischemia but no documented thrombotic events.

RT: Only 10 (4%) patients had symptoms associated with EXT: bleeding in 7 (6 of whom had iron-deficiency anemia) and vaso-occlusive symptoms in 3. Blood transfusions were required in only one patient. The difference in the number of patients experiencing symptoms of bleeding or vaso-occlusive disease between the two groups (MPD versus RT) of patients is statistically highly significant ($p < 0.0001$).

UNCERTAIN ETIOLOGY: The five patients with vaso-occlusive symptoms had a mean age of 67 years; three of the five had symptoms of cerebral or myocardial ischemia, and the remaining two had documented thrombotic events (chronic subdural hematoma in one and femoral artery thrombosis in the other). The single patient with only bleeding symptoms was an 83-year-old man with chronic gastrointestinal bleeding of uncertain etiology. The only patient with both bleeding and vaso-occlusive symptoms was a 100-year-old woman with a bleeding gastric ulcer and paresthesias.

Treatment

MPD: Of 21 symptomatic patients, 20 received hydroxyurea either alone (7 patients) or in combination with anticoagulants, plateletpheresis, and/or drugs that inhibit platelet function (e.g., aspirin, dipyridamole). The only symptomatic patient who did not receive such treatment was a PV patient with deep vein thrombosis who was treated with anticoagulants only. All but 1 of the 17 asymptomatic MPD patients also received hydroxyurea either alone or in combination with plateletpheresis/antiplatelet drugs. The single exception was a 27-year-old woman with PT who has remained asymptomatic during a follow-up period of 27 months.

RT: All three patients with vaso-occlusive symptoms received therapy to inhibit platelet function, and one of the three received anticoagulant therapy as well. One of the three patients received hydroxyurea when he was thought to have a MPD, but the drug was discontinued when it was decided that the thrombocytosis was of a reactive nature. None of the seven patients with bleeding symptoms received therapy for EXT. However, 20 asymptomatic RT patients received platelet-function-inhibiting agents. The most common condition in this group was Kawasaki's disease, in which aspirin therapy, both as an antipyretic and platelet antiaggregating agent, is standard [7].

UNCERTAIN ETIOLOGY: Two of the symptomatic patients were treated with platelet function inhibitors; the other patient was treated with a combination of hydroxyurea and aspirin. The other four symptomatic patients received no therapy to lower the platelet count or inhibit platelet function, but all four asymptomatic patients did (hydroxyurea in 2; melphalan plus aspirin in 1; dipyridamole in 1).

Follow-up

MPD: The mean follow-up in this group was 29 months. Eight patients have died (6 CGL; 2 PV); 9 were lost to follow-up (7 of whom were discharged to their local physician) after a mean follow-up of 8 months; 21 are still being followed after a mean follow-up of 41 months. Of those who died, 4 died in blast crisis of CGL, 3 died of infection, and 1 died of unknown cause(s). None were known to have died of thrombotic or bleeding events.

RT: The mean follow-up in this group was 19 months. Thirty-four patients died: 23 with malignant tumors, 6 of infectious disease, 2 with sickle cell disease, and 3 of unknown cause(s). Five other patients were discharged with advanced stage malignancies and are probably dead. One hundred four patients were lost to follow-up after a mean follow-up of only 7 months. Most of these patients had acute illnesses, such as infections or traumatic injuries, and were discharged from follow-up after the acute process had been successfully treated. None are known to have died. Eighty-eight patients are still being followed after a mean follow-up of 38 months.

UNCERTAIN ETIOLOGY: The mean follow-up was 7 months. Three died: one of chronic subdural hema-

toma, one of sepsis, and one of uncertain cause. Five have been lost to follow-up after a mean follow-up of only 3 months. Three are still being followed after a mean period of 17 months, but their platelet counts are not being monitored, and the etiology of the EXT has not been investigated.

COMMENTS

EXT, herein defined as a platelet count greater than or equal to $1,000 \times 10^9$/L, has been said to occur uncommonly or even rarely as a reactive phenomenon [1,2,8,9], but the results of the present study indicate that this is not the case. Of 280 consecutive patients with platelet counts of this magnitude encountered during the 5½ years of this study, the elevations for 231 (82%) were a result of RT, whereas the elevations for only 38 (14%) were due to MPD. Thus, our findings are in general agreement with those of Schilling [10] who found 74 cases of RT and 28 of MPD in a series of 102 "platelet millionaires" during an 18-month period and demonstrated that platelet counts greater than or equal to $1,000 \times 10^9$/L are not unusual in a general hospital population, particularly in young patients. Considering the wide variety of medical conditions associated with RT in the hospital population and the relatively low frequency of MPDs, this should not be surprising, although it is quite clear that the great majority of platelet counts associated with RT are less than $1,000 \times 10^9$/L.

Prior to the widespread use of whole blood platelet counters and the subsequent availability of a platelet count simultaneously with a CBC, platelet counts had to be ordered separately and were performed by manual, time-consuming methods. Since the danger of bleeding in association with thrombocytopenia has long been recognized, most platelet counts are ordered to ensure the platelet count is not decreased, particularly if an operation is being contemplated or if there are bleeding symptoms. Although serial platelet counts are standard procedure in patients with severe thrombocytopenia, elevated counts, except in those with known or suspected MPD, have traditionally been ignored since thrombocytosis is considered inconsequential.

The present study confirms the infrequency of clinical consequences of thrombocytosis per se in the vast majority of reactive forms of EXT. Bleeding symptoms, which were present in seven (3%) patients, were the underlying cause, rather than the result, of EXT, and the platelet count returned to normal levels as the bleeding, or its effects (i.e., iron-deficiency anemia), was treated. Of the three (1%) RT patients with vaso-occlusive symptoms coincident with EXT, two had evidence of arteriosclerotic peripheral vascular disease: a 92-year-old woman with ischemic changes of her legs and feet in whom an arteriogram demonstrated bilateral femoral artery occlusions, and a 48-year-old man with cerebral ischemia who was found to have severe bilateral carotid artery stenosis and in whom an endarterectomy specimen revealed severe atherosclerosis. The remaining patient in this group had advanced, unresectable lung carcinoma and experienced a cerebrovascular accident 2 days after her platelet count peaked at $1,058 \times 10^9$/L. These three patients, together with rare case reports documenting the occurrence of serious vaso-occlusive episodes in patients with RT [11,12], even at levels well below $1,000 \times 10^9$/L [13,14], indicate that prophylactic treatment with platelet-function-inhibiting agents might be considered reasonable in RT. But we are not aware of any reliable methods that can be used to predict which RT patients are at risk for vaso-occlusive events or to determine whether platelet function inhibitors will be effective in preventing them. In view of the great frequency with which RT occurs and the rarity of thrombotic complications, even in those with platelet counts in the EXT range, it appears that the condition can be safely ignored as it was in the majority of RT patients in this series, the exception being patients with Kawasaki's disease [7].

The situation with patients with EXT associated with MPD is more controversial. Thirty-six of the 38 MPD patients in this series of patients received therapy specifically aimed at lowering the platelet count and/or inhibiting platelet function. This is in accordance with conventional beliefs that patients with MPDs and platelet counts in the EXT range are at increased risk for thrombotic and/or hemorrhagic events [15,16], despite the lack of evidence that the thrombocytosis per se is of etiologic importance when such events occur [2,17]. Recently, the value of treating older PT patients with platelet anti-aggregating agents has been questioned [18], and follow-up only, without treatment, has been recommended for asymptomatic young patients with PT [19].

The low incidence of bleeding and/or thrombotic complications in RT patients with EXT was similar to that in our previous series [3] as was the frequency with which bleeding episodes were encountered in MPD patients (32% present series versus 36% previous series). On the other hand, signs or symptoms of vaso-occlusive disease were significantly more common in the present MPD

group, involving 12 of 38 (32%) patients compared with 3 of 72 (4%) patients in the earlier study ($p = 0.0001$). We are not certain how to explain this difference but suspect that it may be because platelet counts are now being obtained more frequently in patients with vaso-occlusive disorders than they were during the period of the previous series (1964 to 1983). Although our results demonstrate a significantly higher incidence of vaso-occlusive and/or bleeding manifestations associated with EXT in MPDs than in RT (56% versus 4%, $p < 0.0001$), like Schilling [10], we were impressed with the notable lack of documented cerebral or myocardial infarctions, thrombophlebitis, or peripheral arterial thromboses despite the presence of EXT, which, in some of these patients, persisted for weeks or months. Patients with symptoms of transient cerebral or myocardial ischemia were typically in the age range in which atherosclerotic disease is expected, and headache, which was the only symptom present in four patients, is not ordinarily thought of as being caused by thrombocytosis. No fatal hemorrhagic or thrombotic events are known to have occurred in these patients. Because of these features, we are unconvinced that continuous, long-term therapy to lower the platelet count is indicated for asymptomatic patients with isolated EXT.

Finally, the relatively high frequency with which EXT is encountered as a reactive phenomenon in a general, acute care hospital population (i.e., roughly one case per week in this study and more than two cases per week currently, following an expansion of our hospital's capacity by about 150 beds) indicates the need for caution before making a diagnosis of PT. The diagnosis of PT is largely a diagnosis of exclusion [5,20,21]. The most widely used diagnostic criteria—those of the PVSG [5]—require sustained thrombocytosis to a level of greater than or equal to $600 \times 10^9/L$ in the absence of any associated conditions known to cause RT. Although 90% of patients with PT have platelet counts greater than or equal to $1,000 \times 10^9/L$ according to the PVSG experience [5], other investigators, although they agree that it is necessary to exclude conditions associated with RT, have decreased the lower limit of thrombocytosis required for a diagnosis of PT to greater than or equal to $500 \times 10^9/L$ [22] or greater than or equal to $450 \times 10^9/L$ [23]. Not surprisingly, the frequency with which PT is being diagnosed has increased as the threshold level of thrombocytosis required for diagnosis has decreased [22]. In our experience, platelet counts in the 450 to $600 \times 10^9/L$ range are not uncommon in conditions associated with bleeding or in conditions associated with thrombosis when there is accompanying necrosis and/or inflammation. For example, during a recent 4-month period, we found that 9 of 23 (39%) patients who underwent amputation of a lower extremity because of occlusive peripheral vascular disease had a platelet count greater than $450 \times 10^9/L$ before surgery. Thus, the problem of determining whether thrombocytosis is a primary or secondary event in such patients may be quite difficult. Clearly, controlled, prospective clinical trials are needed to resolve the controversy regarding the role of thrombocytosis in causing vaso-occlusive or hemorrhagic events and to determine what type of therapy, if any, is indicated.

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