Etiology and Incidence of Thrombotic and Hemorrhagic Disorders in Thai Patients with Extreme Thrombocytosis

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Abstract

A retrospective study of 126 patients with extreme thrombocytosis (defined as a platelet count $\geq$1,000 x 10^9/L) was performed during a five-year period (June 1994 - June 1999). The aim of this study was to determine the etiology and to evaluate the clinical consequences of extreme thrombocytosis. Seventy patients (55.5%) had reactive thrombocytosis (RT) with an age range of 43 $\pm$ 2.2 years, 56 (44.5%) had chronic myeloproliferative disorders (MPD) with an age range of 53 $\pm$ 2.4 years. Underlying causes of RT were malignancy (25/70 or 35.7%), infection (16/70 or 22.9%), postsplenectomized ß-thalassemia/Hb E (11/70 or 15.7%), inflammation (12/70 or 17.1%), iron deficiency anemia (6/70 or 8.6%). Duration post splenectomy in our ß-thalassemia/Hb E patients ranged from 4 months to 21 years, with a median of 10 years. Subtypes of our MPD cases were chronic myeloid leukemia (30/56 or 53.6%), essential thrombocytosis (18/56 or 32.1%), polycythemia vera (4/56 or 7.1%), agnogenic myeloid metaplasia (3/56 or 5.4%) and unclassified MPD (1/56 or 1.8%). Bleeding and thrombotic tendency were respectively noted in 7 (12.5%) and 2 (3.6%) of MPD patients. Two patients of the MPD group (3.6%) experienced both bleeding and thrombotic episodes. One patient (1.4%) of the RT group developed vasculitis-associated thrombosis. However, none of the patients in the RT group had bleeding complications. Extreme thrombocytosis was not a rare condition in a university hospital population, and bleeding and/or thrombotic complication was more common in the MPD group.

Key word : Extreme Thrombocytosis, Chronic Myeloproliferative Disorder (MPD), Postsplenectomized ß-thalassemia/Hb E, Reactive Thrombocytosis (RT), Thrombotic, Hemorrhagic.

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Extreme thrombocytosis, defined as a platelet count greater than or equal to 1,000 x 10^9/L has been attributed to various reactive thrombocytosis and chronic myeloproliferative disorders. In chronic myeloproliferative disorders (MPD), such as chronic myelogenous leukemia (CML), polycythemia vera (PV), agnogenic myeloid metaplasia (AMM), essential thrombocythemia (ET), platelet counts may be greater than 1,000 x 10^9/L. Conditions with a known cause of associated reactive thrombocytosis, such as chronic inflammatory process, infection, iron deficiency anemia, and malignancy were thought to be less likely to produce extreme thrombocytosis[1]. However, previous studies from Western countries have demonstrated that extreme thrombocytosis with a platelet count of this magnitude was not a rare event in a hospital population and even appeared to be more prevalent in thrombocytosis secondary to reactive processes[2-5]. Incidence of bleeding and/or thrombosis symptoms were more common in MPD than in reactive thrombocytosis (RT)[6-9]. The incidence and natural history of extreme thrombocytosis have not been studied in Thailand. With the widespread use of automated platelet counting nowadays, extreme thrombocytosis is being discovered in both symptomatic and asymptomatic patients. The purpose of this study was to determine the etiology and to evaluate the clinical consequences of extreme thrombocytosis in Thai patients at a university hospital in Bangkok whose platelet counts were 1,000 x 10^9/L or higher.

PATIENTS AND METHOD

Patients who attended our hospital from June 1994 to June 1999 with platelet counts of 1,000 x 10^9/L or higher were studied. Complete blood counts were done in whole blood anticoagulated with ethylene diaminetetraacetic acid using automatic cell counter (Technicon H*1,U.S.A.). All platelet counts were reassessed by a hematology medical technician in a Wright stained blood smear of the corresponding samples.

Hospital records of all 126 patients were reviewed to determine the etiology, evidence of haemorrhagic and/or thrombotic events and clinical symptoms associated with extreme thrombocytosis, medication and follow-up information of these patients.

Statistical Analysis

All data were expressed as mean ± the standard error of mean (mean ± SEM). Descriptive statistics were calculated for patient characteristics, platelet counts and symptoms, separately for each etiologic group.

RESULTS

Patients' characteristics and underlying etiology of our patients are shown in Tables 1. As can be seen, malignancy was the most common underlying cause of reactive thrombocytosis in our patients. In postsplenectomized ß thalassemia/hemoglobin E patients, duration post splenectomy ranged from 4 months to 21 years, with a median of

Table 1. Etiologic conditions associated with extreme thrombocytosis.

Diseases	No of Patients	%	Age (yrs.) Mean±SEM	Platelet Count (x10^9/L) Mean ± SEM
A. Reactive thrombocytosis	**70**	**55.5**	**43±2.2**	**1,230±43**
Malignancy	25	35.7	50±3.2	1,185±50
Infection	16	22.9	43±3	1,290±143
Inflammation	12	17.1	52±6.4	1,188±46
Postsplenectomized ß thalassemia/hemoglobin E	11	15.7	22±1.5	1,239±118
Iron deficiency anaemia	6	8.6	32±6	1,207±122
B. Myeloproliferative disorder	**56**	**44.5**	**53±2.4**	**1,336±49**
Chronic myelogenous leukemia	30	53.6	45±2.5	1,499±155
Essential thrombocythemia	18	32.1	62±4.7	1,373±93
Polycythemia Vera	4	7.1	68±2.5	1,224±104
Agnogenic myeloid metaplasia	3	5.4	59±13.3	1,372±226
Unclassified	1	1.8	75	1,291

10 years. CML was the most common (53.6%) subgroup of our MPD cases.

The peak platelet counts are summarized in Table 1. The peak platelet counts in the RT group ranged from 1,001x10^9/L to 3,187x10^9/L with a mean of 1,230x10^9/L. In the MPD group, peak counts ranged from 1,000x10^9/L to 3,000x10^9/L with a mean of 1,336x10^9/L. The difference in the mean peak platelet counts between these two groups was statistically significant ($p < 0.0034$) (Fig. 1).

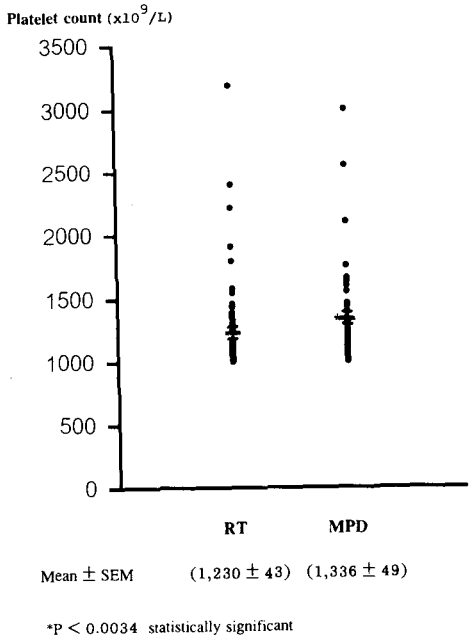

Fig. 1. Distribution of platelet count in 70 patients with reactive thrombocytosis (RT), and 56 patients with chronic myeloproliferative disorders (MPD).

The incidence of hemorrhagic and thrombotic complications are shown in Tables 2 and 3. Bleeding manifestations were more common in MPD, where 12.7 per cent of patients were affected on one or more occasion *versus* none of those with RT. However, bleeding was generally not severe. The highest incidence of bleeding was found in CML. The symptoms of bleeding were gastrointestinal bleeding, epistaxis, bleeding per gum or ecchymoses. The highest incidence of thrombosis was found in ET patients. Thrombotic events involved cerebrovascular, pulmonary and peripheral blood vessels. Two ET patients with symptoms of vaso-occlusive diseases had lacunar cerebral infarction and pulmonary embolism, in each patient. Hemorrhagic and thrombotic phenomenon were found in two ET patients : one presented with ecchymoses and peripheral arteries occlusion, the other had bleeding of a surgical wound and cerebral thrombosis resulting in multiple lacunar cerebral infarctions.

DISCUSSION

It is evident that extreme thrombocytosis is being recognized more frequently with the use of automated instruments as part of the routine complete blood count. Of 126 patients reviewed in our study during the five year period, seventy (55.5%) had reactive thrombocytosis (RT), while 56 (44.5%) had chronic myeloproliferative disorder. Platelet count of more than 1,000x10^9/L is generally thought to be uncommon for RT. However and surprisingly, our series showed more patients in this subgroup. Thus, our findings are in aggreement with that of Buss[4], which showed that of all 280 patients with extreme thrombocytosis, 231 (82%) had reactive thrombocytosis, and 38 (14%) had chronic myeloproliferative disorders. The most common under-

Table 2. Thrombohemorrhagic complications in patients with extreme thrombocytosis.

Disease	Age (yrs.) Mean±SEM	Sex		No. of complications		
		Male	Female	Bleeding No. %	Thrombosis No. %	Both No. %
MPD	53±2.4	25	31	7 12.5	2/56 3.6	2/56 3.6
ET	68.7±3.6	3	3	2 3.6	2/56 3.6	2/56 3.6
CML	40±6.4	2	1	3 5.4	-	-
PV	69.5±4.5	1	1	2 3.6	-	-
RT	43±2.2	32	38	-	1 1.4	-
RA	59	-	1	-	1 1.4	-

Table 3. Haemorrhagic and thrombotic events in patients with extreme thrombocytosis.

Case	Sex	Age	Diagnosis	Sites of		Medication	Platelet count (10^9/L)
				Bleeding	Thrombosis		
1	F	59	RA	-	Finger	Cyclophosphamide	1,064
2	M	74	PV	Epistaxis	-	Busulfan, ASA	1,058
3	F	65	PV	Gum	-	Interferon α	1,183
4	F	42	CML	Skin	-	-	1,308
5	M	28	CML	GI	-	Hydroxyurea, Busulfan, ASA	1,438
6	M	50	CML	GI	-	Hydroxyurea, Interferon α	1,660
7	M	59	ET	GI	-	Busulfan	2,552
8	F	80	ET	Skin	Foot, skin	Hydroxyurea, ASA	1,119
9	M	60	ET	Surgical wound	Brain	Hydroxyurea, ASA	1,344
10	M	72	ET	-	Brain	ASA	1,110
11	F	65	ET	-	Pulmonary	Hydroxyurea, ASA	1,100
12	F	76	ET	Skin	-	Hydroxyurea, Interferon α	1,402

lying cause of RT and MPD in this group was infection and CML respectively.

Eleven patients (15.7%) in the RT group were postsplenectomized. All of them had ß-thalassemia/hemoglobin E disease, and duration post splenectomy ranged from 4 months to 21 years, with a median of 10 years. Persistent extreme thrombocytosis in postsplenectomized non-thalassemic patients is rarely observed. The mechanism underlying persistent thrombocytosis in postsplenectomized thalassemic patients has not been fully elucidated[10-12]. However, elevated serum levels of thrombopoietic growth factors and inflammatory cytokines may play an important role in the pathogenesis in these patients[13].

Of the 126 patients, 114 (90.4%) had no thrombohemorrhagic symptoms. Contrary to previous studies from Western countries[6-8], the incidence of thrombosis in our MPD patients was only 7.2 per cent, and only one patient in the RT group developed vasculitis-associated thrombosis. Bleeding manifestations were observed in 9 patients (16%) of the MPD group, four of which were associated with acetyl salicylic acid (ASA) intake. Most of the bleeding episodes were minor, and did not require transfusion support. Our study confirmed the infrequency of thrombohemorrhagic complications in reactive thrombocytosis.

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REFERENCES

1. Zucker S, Mielke CH. Classification of thrombocytosis based on platelet function test: Correlation with hemorrhagic and thrombotic complications. J Lab Clin Med 1972;80:383.
2. Buss DH, Stuart JJ, Lipscomb GE. The incidence of thrombotic and hemorrhagic disorders in association with extreme thrombocytosis: an analysis of 129 cases. Am J Hematol 1985;20:365-72.
3. Randi WL, Stocco F, Rossi C, et al. Thrombosis and hemorrhage in thrombosis : evaluation of a large cohort of patients (357 cases). J Med 1991; 22:213-23.
4. Buss DH, Cashell AW, O'Connor ML, et al. Occurrence, etiology, and clinical significance of extreme thrombocytosis: A study of 280 cases. Am J Med 1994;96:247-53.
5. Santhosh-Kumar CR, Yohannan MD, Higgy KE, Al-Mashhadani SA: Thrombocytosis in adults: analysis of 777 patients. J Int Med 1991;229: 493-95.
6. Schafer AI. Bleeding and thrombosis in the myeloproliferative disorders. Blood 1984;64:1-12.
7. Kessler CM, Klein HG, Havlik RJ. Uncontrolled thrombocytosis in chronic myeloproliferative disorders. Br J Haematol 1982;50:157-67.
8. Cortelazzo S, Viero P, Finaazzi G, et al. Incidence and risks factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Onco 1990;8:556-62.
9. Tefferi A. Introduction : Overview of chronic myeloproliferative disorders. Sem Hematol 1999; 36:suppl 2, 1-2.
10. Sonakul D, Pacharee P, Laohapand T, et al. Pulmonary artery obstruction in thalassemia. Southeast Asian J Trop Med Pub Heth 1980;11:516-23.
11. Visudhiphan S, Ketsa-Ard K, Tumliang S, et al. Significance of blood coagulation and platelet profiles in relation to pulmonary thrombosis in ß-thalasemia/HbE. Southeast Asian J Trop Med Pub Heth 1994;25:449-55.
12. Chuansumrit A, Isarangkura P, Mahapan W, et al. Thrombotic risk of children with thalassemia. J Med Assoc Thai 1993;2:80-2.
13. Chuncharunee S, Archararit N, Hathirat P, et al. Levels of serum interleukin-6 and tumor necrosis factor in postsplenectomized thalassemic patients. J Med Assoc Thai 1997;80:S86-S91.

สาเหตุและอุบัติการณ์ของการเกิดภาวะหลอดเลือดอุดตันและการมีภาวะเลือดออกในผู้ป่วยไทยที่มีภาวะเกร็ดเลือดสูงมาก

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คณะผู้ทำการวิจัยได้ศึกษาผู้ป่วยที่มีภาวะเกร็ดเลือดสูงมาก (เกร็ดเลือด ≥ 1,000 x 10^3/ล.) ที่มารับการรักษาที่โรงพยาบาลรามาธิบดีตั้งแต่เดือนมิถุนายน 2537 ถึงเดือนมิถุนายน 2542 เป็นเวลา 5 ปี เพื่อหาสาเหตุของภาวะเกร็ดเลือดสูงและประเมินอาการทางคลินิกของผู้ป่วยที่มีภาวะนี้ พบว่าผู้ป่วยที่มีภาวะเกร็ดเลือดสูงมากทั้งหมด 126 ราย ผู้ป่วย 70 คน (55.5%) มีอายุเฉลี่ย 43 ± 2.2 ปี มีภาวะเกร็ดเลือดสูงจากสาเหตุต่าง ๆ ที่ไม่ใช่ความผิดปกติของไขกระดูก (reactive thrombocytosis, RT) สาเหตุเหล่านี้คือ การเป็นโรคมะเร็ง (25/70, 35.7%) การติดเชื้อ (16/70, 22.9%) ภาวะการอักเสบ (12/70, 17.1%) ภาวะหลังตัดม้ามในผู้ป่วยเบต้าธาลัสซีเมียฮีโมโกลบินอี ซึ่งมีอายุการตัดม้ามอยู่ระหว่าง 4 เดือน ถึง 21 ปี เฉลี่ยระยะเวลาการตัดม้าม 10 ปี (11/70, 15.7%) ภาวะขาดเหล็ก (6/70, 8.6%) สำหรับผู้ป่วยที่มีภาวะเกร็ดเลือดสูงมากอีก 56 ราย (44.5%), มีสาเหตุมาจากความผิดปกติในไขกระดูกของผู้ป่วย (MPD) ซึ่งประกอบด้วยผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเรื้อรัง (30/56, 53.6%) essential thrombocytosis (18/56, 32.1%) polycythemia vera (4/56, 7.1%), agnogenic myeloid metaplasia (3/56, 5.4%) และ unclassified MPD (1/56, 1.8%) ภาวะเลือดออกและภาวะหลอดเลือดอุดตันพบในผู้ป่วย MPD 7 (12.5%) และ 2 (3.6%) รายตามลำดับ ส่วนผู้ป่วย MPD ที่พบภาวะทั้งสองร่วมกันมีเพียง 2 ราย (3.6%) สำหรับผู้ป่วยกลุ่ม RT พบว่ามีผู้ป่วยเพียงรายเดียว (1.4%) เท่านั้นที่มีอาการอักเสบของหลอดเลือดร่วมกับการมีภาวะหลอดเลือดอุดตัน การศึกษานี้แสดงให้เห็นว่าผู้ป่วยที่มีภาวะเกร็ดเลือดสูงมากพอจะหาได้ไม่ยากนักในผู้ป่วยที่มารับการรักษาในโรงพยาบาลของมหาวิทยาลัยของรัฐ และพบว่ากลุ่มผู้ป่วยที่มีภาวะเกร็ดเลือดสูงมากที่มีความผิดปกติของไขกระดูกจะเกิดภาวะการมีเลือดออกและการมีหลอดเลือดอุดตันได้บ่อยกว่าในผู้ป่วยที่มีภาวะเกร็ดเลือดสูงมากจากสาเหตุอื่น

คำสำคัญ : Extreme Thrombocytosis, Chronic Myeloproliferative Disorder (MPD), Postsplenectomized ß–Thalassemia/HbE, Reactive Thrombocytosis (RT), Thrombotic, Hemorrhagic

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