Essential Thrombocythemia

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Abstract : This is a review of twelve cases of Essential Thrombocythemia at Suratthani Hospital. They were 6 males and 6 females aged between 39 to 87 years old. The initial clinical presentations were as follows: 2 asymptomatic cases (incidentally found on routine CBC check up), 4 cases of cerebral infarction (one of them presented with paresthesia, erythromelalgia, transient ischemic attack, and a convulsion which finally progressed to cerebral infarction), 1 case with ischemic heart disease, 1 case with deep vein thrombosis of the left leg and an intramuscular hematoma of the left calf, 1 case with an intramuscular hematoma of the right gluteus muscle, 1 case with ischemic gangrene of the toes and an upper gastrointestinal hemorrhage, 1 case with erythromelalgia with an ischemic digital ulcer, and another case with a post-operative hematoma. The average platelet count was 1,524x10^3/µl. The treatment regimens were busulfan or hydroxyurea and additional treatment with an antiplatelet aggregation agent in patients with vascular occlusive disease. The patients responded well to the treatment. Due to the long natural history of essential thrombocythemia and the leukemogenic side effects of chemotherapy, more suitable therapy should be considered especially in asymptomatic patients.

Key words : Thrombocythemia, Myeloproliferative disorder, Thrombosis, Hemorrhage

เรื่องย่อ : **เกล็ดเลือดสูงผิดปกติชนิดไม่ทราบสาเหตุ**

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ทำการศึกษาผู้ป่วยที่มีเกล็ดเลือดสูงผิดปกติชนิดไม่ทราบสาเหตุจำนวน 12 รายที่มารับการตรวจรักษาที่โรงพยาบาลสุราษฎร์ธานี ผู้ป่วยมีอายุระหว่าง 39-87 ปี เป็นชาย 6 คน หญิง 6 คน โดยมีอาการและอาการแสดงในขณะที่เริ่มต้นให้การวินิจฉัย ดังนี้ตรวจพบโดยบังเอิญจากการตรวจนับเม็ดเลือดในการตรวจร่างกายประจำปีทั่วไป 2 ราย เส้นเลือดสมองอุดตัน 4 ราย (ซึ่ง 1 รายเริ่มต้นจากความรู้สึกผิดปกติ ระบบประสาทผิดปกติชั่วครู่ ชักและสุดท้ายจึงมีอาการของสมองตาย อัมพาตขัดเจน), กล้ามเนื้อหัวใจตายจากหลอดเลือดแดงอุดตัน 1 ราย, หลอดเลือดดำขาซ้ายอุดตันและเลือดออกในกล้ามเนื้อน่องซ้าย 1 ราย, เลือดออกในกล้ามเนื้อแก้มก้นขวา 1 ราย, นิ้วเท้าเน่าจากหลอดเลือดแดงอุดตัน 1 ราย, แผลเรื้อรังที่นิ้วมือและนิ้วเท้าจากเลือดเลี้ยงไม่พอ 1 ราย, และ 1 รายมีเลือดออกมากผิดปกติหลังผ่าตัดตัดมดลูก ค่าเกล็ดเลือดเฉลี่ย 1,524x10^3/มคล. ผู้ป่วยได้รับการรักษาด้วย busulphan หรือ hydroxyurea บางรายที่มีการอุดตันของหลอดเลือดได้รับการรักษาด้วยแอสไพริน ผลการรักษาดี เนื่องจากโรคนี้มีการดำเนินโรคช้าและยาที่ใช้ในการลดเกล็ดเลือดมีผลก่อให้เกิดมะเร็งเม็ดเลือดได้ ดังนั้นแพทย์ผู้ให้การรักษาควรพิจารณาอย่างรอบคอบโดยเฉพาะอย่างยิ่งในผู้ป่วยที่ยังไม่มีอาการหรืออาการแสดง

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INTRODUCTION

Essential thrombocythemia (ET) is a rare clonal myeloproliferative disorder of unknown origin, distinct from polycythemia vera, chronic myelogenous leukemia and idiopathic myelofibrosis.[1,2] It is characterized by a persistent increase in platelet counts greater than or equal to $600x10^3/\mu l$, excessive proliferation of megakaryocyte in bone marrow, a normal erythrocyte mass, absence of the Philadelphia chromosome and the absence of permanent bone marrow fibrosis. ET was first reported in 1934 by Epstein and Goedel.[3] Clinical manifestations of ET are thrombohemorrhagic complications. Prior to the incorporation of a platelet channel in automated complete blood cell counters, platelet counts greater than or equal to 1,000 $x10^3/\mu l$ were thought to be rare. Since platelet counts have become part of routine blood counts, ET has been found more frequently in both symptomatic and asymptomatic subjects.[2,4-6] This paper reports twelve cases of ET. The purpose of this report is to remind physicians of the presenting symptoms of essential thrombocythemia.

MATERIALS AND METHODS

Patients

This report includes twelve patients with newly diagnosed ET at Suratthani Hospital between October 1993 and January 2002 who underwent periodic follow up. The criteria for establishing the diagnosis of ET was based on a modification of the definition reported by the Polycythemia Vera Study Group.[7] It included :-

1. A platelet counts persistently more than 600 x $10^3/\mu l$.
2. Atypical megakaryocytic hyperplasia in the bone marrow.
3. Absence of known causes of reactive thrombocythemia.
4. Exclusion of thrombocythemia related to other myeloproliferative disorders (normal hematocrit less than 46%, normal RBC's mean corpuscular volume, absent of collagen fibrosis of marrow, no abnormal leukoerythroblastic cells).

Method

The medical records of twelve patients in whom essential thrombocythemia was diagnosed from October 1993 to January 2002 were reviewed. Clinical signs and symptoms emphasizing the initial manifestations were evaluated. Particular attention was paid to the four major risk factors of vascular disease including hypertension, cigarette smoking, diabetes mellitus and dyslipidemia as well as a history of previous thrombotic events in patients with ischemic stroke and venoarterial occlussion.

Diagnostic evaluations were peripheral blood count by automatic cytocoulter, urine analysis, initial bone marrow examination, chest roentgenography, ultrasonography of the hepatobiliary system and affected parts. Further investigations included:-

1. Bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT) were checked in ET patients with hemorrhagic features.
2. Routine blood chemistry profile for vascular risk factors (fasting plasma glucose (FPG), BUN, creatinine, lipid profile, serology for syphilis) and brain CT in ischemic stroke patients.
3. Angiography of the left femoral artery in the ET patient with ischemic digital gangrene of the left 4th and 5th toes. The patients were followed up at intervals, peripheral blood counts and other investigations were performed as clinically necessary.

RESULTS

Clinical data:

The average age of the patients was 66 years (ranged 39-87 years).

The sex distribution showed male:female ratio of 1:1.The duration of symptoms before the diagnosis of ET varied from two days to eight years. Initial presenting symptoms were deep vein thrombosis in 1 case, spontaneous intramuscular hematoma in 2 cases (buttock, calf), upper gastrointestinal hemorrhage in 1 case, ischemic stroke in 4 cases, ischemic heart disease (inferior-anteroseptal wall myocardial infarction with first

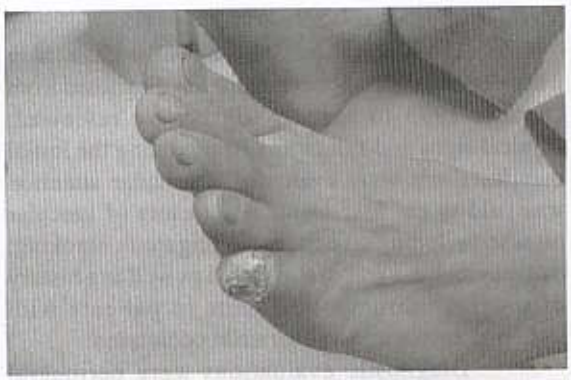

Figure 1, 2. There are acrocyanosis and ischemic gangrene of left little toe, left middle finger.

degree AV block) in 1 case, ischemic gangrene of toes in 1 case and ischemic digital ulcer in 1 case (Figure 1, 2), and post-operative hematoma in 1 case. In eight patients with arterial occlusion, only one had hypertension. Splenomegaly in 3 patients was detected by physical examination and ultrasonography. None of them had hepatomegaly. Duration of follow up ranged from 1 month to 9 years. Most of the patients with ischemic stroke were men. One case with ischemic stroke had warning signs and symptoms of microvascular occlusion, eg. erythromelalgia, paresthesia, transient ischemic attacks, convulsion, and the patient ended up with a complete stroke before the underlying ET was detected. Only 1 case developed ischemic stroke after being asymptomatic for 7 years. Hydroxyurea was given in 8 cases, 2 cases were given busulfan. An antiplatelet aggregating agent (aspirin) was given in 8 cases. The clinical data of the patients are summarized in Table 1.

Laboratory data:

The hematocrit ranged between 40 - 48% (except one of them who had an upper GI hemorrhage at the time of diagnosis whose hematocrit was 21.7%). Red cell morphology and mean corpuscular volume were normal. There was a slightly increased leukocyte count. The platelets were bizarre and markedly increased (ranged 834 - 2,200 x 10^3/µl (Figure 3). Bone marrow examination revealed normal to mild hypercellularity, marked megakaryocytic hyperplasia and abnormal bizarre megakaryocyte with platelet clumping in all patients (Figure 4-6). No bone marrow fibrosis was observed. Bleeding time, prothrombin time and activated partial thromboplastin time were normal in most patients. The laboratory data is summarized in Table 2. In the 6 cases with thrombotic complications, additional investigations included FPG, lipid profile, VDRL, TPHA, CT brain an angiogram to demonstrate the lesion. FPG ranged between 83-120 mg/dl, cholesterol ranged between 139-173 mg/dl, triglyceride ranged between 50-167 mg/dl, BUN ranged between 13-28 mg/dl, creatinine ranged between 0.7-1.2 mg/dl, all of them had VDRL and TPHA non-reactive. Only 2 cases had vascular risk factors (hypertension and cigarette smoking). The results of the CT brain in 5 of the cases with ischemic stroke were as follows:-

Case No.1- cerebral infarction involving the left temporal and left occipital lobe.

No.4- acute infarction of the right high frontal lobe involving the cortex and subcortical region.

No.5- cerebral infarction of the periventricular and subcortical region of the left parietal lobe.

No.7 - small infarction of the left internal capsule.

No.11-small infarction at the genu of the left internal capsule and brain atrophy.

Left femoral angiography in case No.6 with ischemic gangrene of the toes, showed diffuse irregular narrowing of the left femoral artery, left popliteal artery, with distal run off (anterior and posterior peroneal artery).

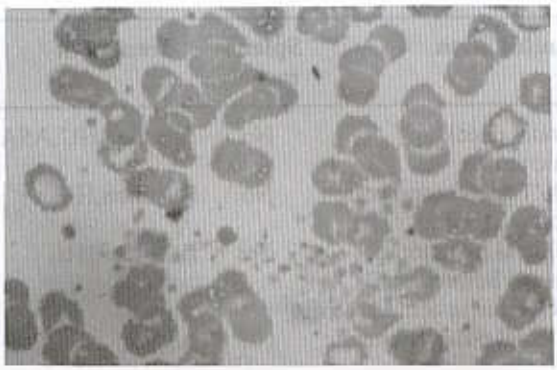

Figure 3. Peripheral blood smear shows a significant increase in platelets with irregularity in size and shape, giant platelet.

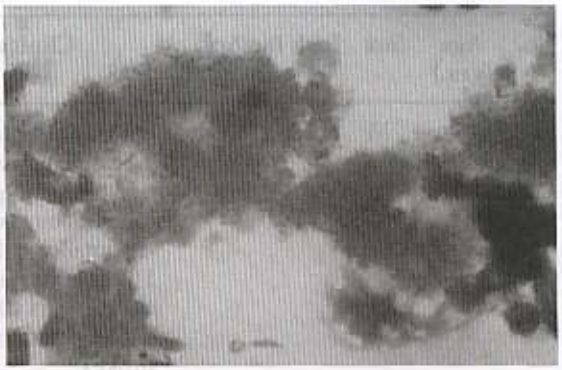

Figure 4. Shows platelet clumping in bone marrow aspiration smear.

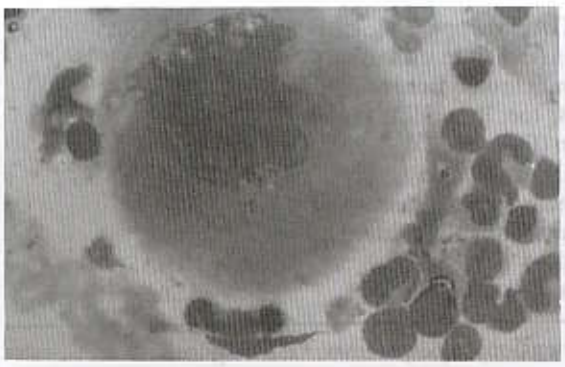

Figure 5. Shows immature megakaryocyte (no platelet budding and granularity) in bone marrow.

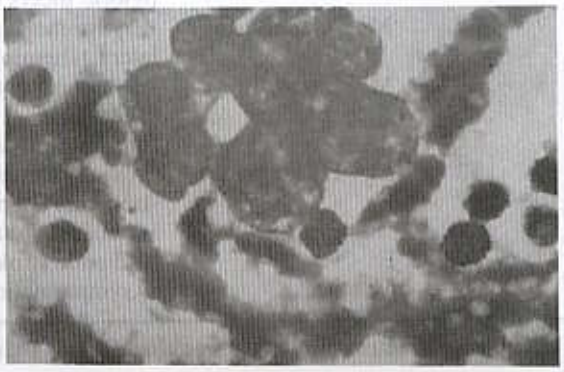

Figure 6. Shows megakaryocytic nuclear hypersegmentation in bone marrow.

DISCUSSION

This paper reports twelve patients who have extreme thrombocytosis. Ten patients presented at the time of diagnosis with thrombohemorrhagic symptoms. Only two patients were asymptomatic, the diagnosis being made incidentally on routine CBC check up. The diagnosis of ET should first avoid confusion with pseudothrombocytosis from platelet sized particles (red blood cell or white blood cell fragments) which are erroneously enumerated as platelet by automatic particle counting, so a peripheral blood smear is recommended to confirm the diagnosis of ET. Secondly, ET must be distinguished from reactive thrombocytosis (Table 3) and other myeloproliferative diseases such as polycythemia vera, agnogenic myeloid metaplasia and chronic myeloid leukemia. Of all cases with extreme thrombocytosis, 82% had reactive thrombocytosis, 14% had a myeloproliferative disease and 4% had an uncertain etiology. ET accounted for 4%.[6]

Table 1. Clinical data.

No.	Age (yrs.)	Sex	Risk factors	Clinical manifestation	Spleno-megaly	Treatment
1	61	M	HT	-Asymptomatic (annual check up)*, 7 years later ischemic stroke	No	Busulfan,HU, ASA
2	66	F	-	-Erythromelalgia, DVT Lt. femoral vein, spontaneous hematoma Lt. calf	No	Busulfan,HU
3	56	F	-	-Spontaneous Rt. Gluteal hematoma*, 1 year later spontaneous hematoma Rt. calf, 3 years later UGH due to acute gastritis	Yes	Busulfan,HU
4	87	M	-	-Lt.hemiparesis, Lt.facial pulsy (ischemic stroke)	No	ASA
5	48	M	-	-1992 erythromelalgia, TIA, 1994 convulsion, 1999 Lt.hemiparesis (ischemic stroke), 2000 progressive stroke with recognized ET*	Yes	HU,ASA
6	84	F	-	-Erythromelalgia, ischemic gangrene of Lt. 4th and 5th toes, 4 months later UGH due to multiple shallow pyloric ulcers*	No	Amputation of toes, blood transfusion, HU
7	62	M	Alcoholism	-Erythromelalgia, TIA, syncope, 3 months later Lt. hemiparesis (ischemic stroke)*	Yes	HU,ASA
8	39	M	Cigarette smoking	-Erythromelalgia and chronic ischemic digital ulcer at Lt. 4th toe, Rt. middle finger for 1 year off and on (Figure 1, 2)	No	HU,ASA
9	53	F	HT	-Post-operative (TAH) hematoma	No	HU
10	77	F	-	-Ischemic heart disease 1 year (inferior and anteroseptal wall myocardial infarction)	No	ASA
11	76	F	-	-Ischemic stroke 2 days	No	HU,ASA
12	81	M	-	-Asymptomatic, gouty arthritis	No	ASA

Vascular risk factors : cigarette smoking, DM, HT (hypertension), dyslipidemia, *ET diagnosis.

In Thailand, there have been a few reports of essential thrombocythemia.[8,9] Our data showed a male : female ratio of 1:1. Other reports showed a male preponderance, but in younger patients a female preponderance was found.[2,5,9-14] Most patients were older (mean 66 years old) which was similar to other reports but with a higher incidence of thrombohemorrhagic events.[3,5,14] Thrombosis occured more commonly than hemorrhage and particularly in those with a prior thrombotic event. Evaluation of the risk factors for thrombosis in ET patients found to include age, a previous thrombotic event and length of thrombocytosis. Smoking, DM, hyperlipidemia and hypertension were not found to be risk factors.[5,10,15] However, some reports showed cigarette smoking to be significantly associated with thrombosis.[16] Our data found that thrombotic events (both venous and arterial) were more common than hemorrhagic events which was similar to other reports which showed thrombotic events in 18-84% and hemorrhagic problems in 13-37%.[1] Venous thrombosis was less common in ET patients.[1,17] The most common presenting symptom was erythromelalgia, caused by a disturbance of the microcirculation especially in the fingers and toes which might lead to digital gangrene.[1,18] Ischemic stroke was found in 5 ET patients, 1 of them had warning symptoms of thrombosis - erythromelalgia, transient ischemic

Table 2. Laboratory data.

Case No.	Peripheral blood							Bone marrow			
	Hb/Hct (gm/dl,%)	WBC Count (x10³/μl)	P (%)	L (%)	M (%)	E (%)	Platelet (x 10³/μl)	Cellularity(%)	Ery	Mye	Megakaryocyte Amount	Megakaryocyte Abnormal (%)
1	13/40	13	56	35	6	3	1,022	55	N	N	+++	60
2	13.4/45	36.3	76	15	4	5	1,781	55	N	N	+++	70
3	13.1/41.2	37.9	88	10	2	-	1,579	60	+	+	+++	80
4	13.7/42.2	28.5	72	14	13	1	1,042	50	N	N	+++	70
5	15.4/48	18.8	84	11	4	1	834	60	N	N	+++	80
6	7.2/21.7	11.7	76	11	5	8	1,000	65	+	+	+++	70
7	15.4/48.1	22.4	85	10	-	5	1,933	60	N	N	+++	60
8	13.1/40.6	13.5	64	24	4	8	2,200	80	+	+	+++	50
9	15.6/48.3	13.8	48	48	1	3	2,000	80	+	+	+++	50
10	-/43.9	19.6	76	12	4	8	1,515	60	N	N	+++	45
11	-/42	34.7	61	26	5	8	1,660	70	N	N	+++	30
12	-/37.8	15.4	88	9	-	3	1,720	80	N	N	+++	50

N = Normal, Ery = Erythroid series, Mye = Myeloid series, P = PMN, E = Eosinophil, L = Lymphocyte, M = Monocyte, + = Slightly increase, +++ = Megakaryocyte more than 6/low power field with platelet clumping.

Table 3. Clinical and laboratory features helpful in distinguishing ET[1] from other causes of thrombocytosis.

Feature	ET	RT
Chronic platelet increase	+	-
Known causes of thrombocytosis	-	+
Thrombosis or hemorrhage	+	-
Splenomegaly	+	-
Bone marrow reticulin fibrosis	+	-
Bone marrow megakaryocytic cluster	+	-
Abnormal cytogenetic features	+	-
Increased acute phase reactant (C-reactive protein fibrinogen)	-	+
Spontaneous colony formation (erythroid colony)	+	-

RT = Reactive thrombocytosis.

attack and convulsion. One ischemic stroke patient had hypertension. Other reports showed that a hematologic disorder was a definite cause of cerebrovascular disease in 2.7% and ischemic stroke as a presenting manifestation of ET was probably under recognized.[12] Male gender was significantly associated with arterial thrombosis.[19] Ischemic heart disease was found in 1 case. Ischemic ulcer and gangrene were found in 2 cases, one of whom was a cigarette smoker. Cigarette smoking might aggravate the severity of thrombosis especially in female patients.[19] Clinical bleeding was found in 4 cases, most of which were not life-threatening similar to other reports.[4] Most of them had normal bleeding time and coagulation time. Only the case with an upper GI hemorrhage required a packed red cell transfusion of 2 units. Two patients presented with both thrombotic and hemorrhagic manifestations.

Splenomegaly was found in 3 patients (25%). Several reports have shown splenomegaly in association with ET (14-48%).[5,11,20] Hematologic findings revealed thrombocytosis with an average platelet count of $1,524 \times 10^3/\mu l$. In ET patients, thrombocytosis is probably due to excessive autonomous thrombopoiesis, as platelet survival time is found to be normal. The platelets show abnormal structure and function.[4] The natural history of ET has shown that a platelet count of more than $600 \times 10^3/\mu l$ is often associated with thrombohemorrhagic complications. So, cytoreducing therapy is administered in symptomatic patients to maintain platelet counts below $600 \times 10^3/\mu l$.[21] Some reports have suggested that the platelet count should be reduced to less than $450 \times 10^3/\mu l$.[22] In asymptomatic patients careful consideration of therapy should be given, because of the risk of leukemia secondary to chemotherapy and the long natural history of ET.[4,23] The physician has to weigh the therapeutic outcome with cost-effectiveness.[24] All patients in this report responded well to chemotherapy with busulfan or hydroxyurea within 2-4 months (platelet counts decreased to less than $400 \times 10^3/\mu l$). Both drugs were equally effective, but hydoxyurea seemed to have fewer side effects. In patients with erythromelalgia, ischemic heart disease and ischemic stroke, an antiplatelet aggregant such as ASA was given. Currently 9 patients are doing well, one patient is bed ridden but alert, one is receiving physical therapy and wheel chair training, and one patient is lost to follow up.

CONCLUSION

Although the incidence of newly diagnosed ET patient is low, there is in fact a conspicuous population of ET among outpatients and inpatients in both surgical and medical departments. Ischemic stroke, myocardial infarction, thrombotic vascular disease and hemorrhage as a presenting manifestation of ET is probably under-recognized. Therefore physicians should attempt to make as early a diagnosis as possible. Prognostic factors are ageing, previous occurrence of thrombotic events and duration of thrombocytosis. Treatment is problematic, one needs to balance between the necessity of preventing thrombosis/ hemorrhagic complications and drug toxicity. Life expectancy in essential thrombocythemia is close to normal.[1,4,25]

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