Essential Thrombocythaemia: A Single Institution Experience of 16 Years

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Received: 6 February 2012 / Accepted: 11 June 2012 / Published online: 26 June 2012
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Abstract This presentation is a clinical narrative and long term follow up (6–16 years) of 21 prospectively studied patients with essential thrombocythaemia (ET) in Kuwait. The median age (55.9 years) is younger than reported by others. Two patients were below the age of 40 years with one of them presenting as post-polycythaemia ET at 16 years of age. Twelve patients (57.1 %) remained asymptomatic throughout the period of follow up. Four patients complained of erythromelalgia, three (19 %) suffered from thrombotic episodes and only one (4.3 %) had excessive bleeding. Four patients presented with splenomegaly. Intensity of thrombocytosis or duration of very high platelet count had no relationship with these complications. Two patients transformed to post-ET myelofibrosis and one patient developed chronic myeloid leukaemia (CML). None transitioned to acute leukaemia. All patients are still alive after follow up for 6–16 years. Janus kinase 2 mutation was positive in eight (38 %) patients. It had no bearing on transition of our ET patients to post-ET myelofibrosis or CML. Platelet aggregation tests were performed in 14 patients. Six (42.9 %) showed defective response to ADP. Only one of these patients suffered from bleeding. All patients were given aspirin (81 mg/day). Cyto-reductive therapy with hydroxyurea was taken by six (42.9 %) subjects. Two patients

who were treated with anagrelide and one with alpha-interferon did not continue treatment for long.

Keywords Essential thrombocythaemia · Thrombocytosis · Myeloproliferative disorder · Post-ET myelofibrosis

Introduction

Essential thrombocythemia (ET) is one of the rare chronic myeloproliferative disorders (CMPD), with potential for transition to other forms of myeloproliferative diseases such as post-ET myelofibrosis and leukemia [1]. Transition to myelodysplastic syndrome (MDS) [2] has also been reported.

ET occurs largely in older age group, being extremely rare in children [3]. It may remain asymptomatic for a long period of time or may present with both thrombotic and hemorrhagic episodes that often do not leave serious sequelae unless involving myocardium or central nervous system [4].

The present study is a single institution retrospective analysis of our 16 years' experience with 21 patients with ET, vis-à-vis its clinical presentation, laboratory findings, management and long term outcome. Only adult patients are included. Over the same period we have also observed and followed up six pediatric patients with unrelenting clonal thrombocytosis. Analysis of these patients' forms the subject of a separate study awaiting publication.

Patients and Methods

A total of 21 patients with ET were observed from 1996 to 2011. The year wise distribution of cases is shown in

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Table 1. For numerical comparison, the number of patients with other causes of thrombocytosis (post-splenectomy and reactive thrombocytosis) observed during the same period also has been included. Fourteen patients continued to be followed up until the time of writing this report (2011). The remaining seven patients had ceased to report for follow up after a variable period of 2–9 years.

The criteria applied for diagnosis of ET before the year 1997 included;

- (A) Sustained platelets count of $>500 \times 10^9/L$ with normal hemoglobin and white blood cell count. Patients with iron deficiency anemia or any other primary hematological disease were excluded.
- (B) Bone marrow examination showing hyper-cellular marrow with remarkable megakaryocytic hyperplasia and/or clustering and morphological abnormalities like large size and hyperplod nuclei.
- (C) No other accountable cause of thrombocytosis.

After 1997, the criteria to diagnose ET was based on that proposed by Polycythemia Vera Study Group [5].

A- Criteria

1. Raised red blood cell mass (male >36 mL/kg and female >32 mL/kg).
2. Absence of any secondary cause of erythrocytosis.
3. Bone marrow biopsy—increased cellularity, enlarged megakaryocytes with hyperplod nuclei or clusters of megakaryocytes, increased reticulin (optional).

B- Criteria

1. Platelet count $>400 \times 10^9/L$.
2. Absolute neutrophil count $>10 \times 10^9/L$.
3. Splenomegaly by palpation or ultrasonogram.

For diagnosis of ET;

A1 + 2 + 3	Early PV
A1 + 2 + 3 + any B	Overt PV
A3 + B1	ET

Table 1 Year wise distribution of patients with essential thrombocythaemia and other causes of thrombocytosis

		2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996
Essential thrombocythemia	New patients during the year	1	2	0	1	1	1	1	2	1	3	2	1	0	2	2	1
	Patients carried from previous years	13	11	11	10	9	8	8	7	6	4	4	3	4	3	1	0
	Patients dropped out of follow up	0	0	0	0	0	0	1	1	0	1	2	0	1	1	0	0
	Total number during the year	14	13	11	11	10	9	8	8	7	6	4	4	3	4	3	1
Post-splenectomy thrombocytosis	New patients during the year	2	3	0	1	2	0	0	2	1	1	0	2	0	1	2	1
	Patients carried from previous years	7	4	6	6	5	6	8	6	5	5	7	6	6	6	4	3
	Patients ceased to follow up	2	0	2	1	1	1	2	0	0	1	2	1	0	1	0	0
	Total for the year	7	7	4	6	6	5	6	8	6	5	5	7	6	6	6	4
Reactive thrombocytosis	New patients during the year	8	9	6	9	7	9	7	4	6	7	8	7	8	6	7	4
	Patients carried from previous years	1	0	2	0	2	0	1	2	2	0	2	1	0	3	5	8
	Patients ceased to follow up	4	8	8	8	9	7	8	5	6	5	10	6	7	9	7	7
	Total for the year	4	1	0	2	0	2	0	1	2	2	0	2	1	0	5	5

Table 2 The relevant clinical data of patients with essential thrombocythaemia

Assigned name	Age	Sex	Year of diagnosis	Last year of follow up	Follow up periods in years	Clinical features					
						Erythromelalgia	Thrombosis	Haemorrhage	Splenomegaly	Treatment	Outcome
A	71	M	1996	1998	2	YES	NO	NO	NO	Asp	ET
B	59	M	1997	1999	2	NO	NO	NO	NO	Asp	ET
C	51	F	1997	2001	4	NO	NO	NO	NO	Asp + HU + INF	ET
D	49	F	1998	2001	3	YES	NO	NO	NO	Asp	ET
E	42	M	1998	2011	13	NO	NO	NO	NO	Asp	ET
F	59	F	2000	2011	11	NO	NO	NO	NO	Asp + HU	C M F
G	53	M	2001	2002	1	NO	NO	NO	NO	Asp	ET
H	26	F	2001	2011	10	YES	NO	YES	NO	Asp + HU	ET
I	63	F	2002	2011	9	NO	CNS	NO	YES	Asp	ET
J	46	F	2002	2004	2	YES	NO	NO	NO	Asp + Ang	ET
K	47	M	2002	2011	9	NO	NO	NO	NO	Asp + HU	ET
L	68	F	2003	2011	8	NO	NO	NO	YES	Asp	C M F
M	59	F	2004	2011	7	NO	NO	NO	NO	Asp	C M L
N	63	M	2004	2011	7	NO	NO	NO	YES	Asp + HU	ET
O	39	M	2005	2005	1/2	NO	NO	NO	NO	Asp + Ang	ET
P	48	F	2006	2011	5	NO	NO	NO	NO	Asp	ET
Q	69	F	2007	2011	4	NO	NO	NO	NO	Asp	ET
R	71	F	2008	2011	3	NO	CVS	NO	NO	Asp + HU	ET
S	41	M	2010	2011	1	NO	CVS	NO	YES	Asp	ET
T	53	F	2010	2011	1	NO	NO	NO	NO	Asp	ET
U	76	M	2011	2011	1/2	NO	NO	NO	A	Asp	ET

HU Hydroxyurea, Ang Anagrelide, INF α -Interferon, CMF Chronic myelofibrosis, CML Chronic myeloid leukemia, PRV Polycythemia vera, Asp Aspirin (81 mg/day)

We re-evaluated our cases for diagnostic criteria as proposed recently in 2008 revision of WHO classification [6]. All the cases were found to be conforming to these criteria too.

All patients included in the present study were subjected to the following laboratory investigations at the time of diagnosis and periodically during the course of follow up

- (A) CBC, differential WBC count and blood smear examination.
- (B) Bone marrow examination including trephine biopsy for reticulin and collagen and FISH study for bcr/abl gene fusion and 5q- and peripheral blood for Jak2 (V617F) mutation by PCR.
- (C) Ultrasonogram of abdomen for spleen size particularly in obese patients and those with doubtful splenomegaly.
- (D) Blood smear examination during the course of follow up for
 - (i) Leukoerythroblastic reaction as an alert for transition to post-ET myelofibrosis.

- (ii) Immature leukocytes (myelocytes and blast cells) as an alert for emergence of leukemia.

- (E) Routine biochemical examination including serum iron, transferrin, ferritin and LDH.

Results

The relevant clinical and laboratory data of 21 patients with ET is shown in Tables 2 and 3. The analysis of the clinical data (age and sex distribution, clinical presentation, duration of follow up, treatment given and the disease outcome) is shown in Table 4 while analysis of the laboratory data (platelet count at diagnosis, bcr/abl gene fusion, Jak2 (V617F) mutation and platelet aggregation tests) is shown in Table 5.

From the above data the following inferences are significant

The median age of our patients is 55.9 years (range 26–76). Nearly half of the patients (52 %) were between 50

Table 3 The relevant laboratory findings of the patients with essential thrombocythaemia

Assigned name	Range of plt. count ($\times 10^9/L$)	Period (in years) for which platelet count remained				Post-cyto reductive therapy minimum plt count	Platelets aggregation test	BCR/ABL gene fusion	JAK2 (V617F) mutation	Preceded by PRV
		Up to $800 \times 10^9/L$	$800-1,000 \times 10^9/L$	$1,000-1,200 \times 10^9/L$	$>1,200 \times 10^9/L$					
A	693–897	1.5	0.5	0	0	NA	Not Done	Negative	Negative	No
B	641–920	1	1	0	0	NA	Not Done	Negative	Negative	No
C	751–1190	2	1	1	0	437	Not Done	Negative	Negative	No
D	693–711	14	0	0	0	NA	Not Done	Negative	Negative	No
E	630–989	2	1	0	0	NA	Normal	Negative	Positive	No
F	701–993	9	3	0	0	412	Not Done	Negative	Positive	Yes
G	633–811	0.5	0.5	0	0	NA	Not Done	Negative	Negative	No
H	840–1310	6	3	1	1	489	Abnormal	Negative	Positive	Yes
I	795–899	6	4	0	0	NA	Normal	Negative	Negative	No
J	810–1315	0.5	0.5	0.5	0.5	432	Abnormal	Negative	Positive	No
K	923–1510	6	1.5	1.5	0.5	415	Normal	Negative	Negative	No
L	818–980	4	5	0	0	NA	Normal	Negative	Positive	Yes
M	601–713	8	0	0	0	NA	Not Done	Positive*	Negative	No
N	983–1309	3	3	2	1	538	Normal	Negative	Positive	Yes
O	583–910	0.5	0.5	0	0	310	Abnormal	Negative	Negative	No
P	701–890	2	4	0	0	NA	Normal	Negative	Negative	No
Q	611–748	5	0	0	0	NA	Normal	Negative	Negative	No
R	653–1193	0.5	3	1.5	0	512	Normal	Negative	Positive	No
S	539–820	1	1	0	0	NA	Normal	Negative	Negative	No
T	601–721	2	0	0	0	NA	Normal	Negative	Negative	No
U	723–998	0.5	0.5	0	0	NA	Normal	Negative	Positive	No

NA Not applicable, since cytoreductive therapy not given

* bcr/abl gene fusion positive when transformed into CML

Table 4 The analysis of laboratory data of patients with ET

	Number	Percentage
Platelets count $\times 10^9/L$ at diagnosis and during follow up		
Up to $500 \times 10^9/L$	0	0
501–800	13	61
801–1,000	7	33
1001–1,200	1	5
$>1,200$	0	0
BCR/ABL gene fusion*		
+ve	1	4.7
–ve	20	96.3
JAK2 (v617f) mutation		
+ve	8	38
–ve	13	62
Platelet aggregation test**		
Abnormal	3	14.2
Normal	11	52.3
Not done	7	33.3

* bcr/abl gene fusion was detected on follow up at the point of diagnosis of CML

** For platelet aggregation tests ADP, collagen, epinephrine, arachidonic acid and ristocetin were used as agonists

and 70 years of age. The gender ratio (M:F) was 2:1.5. Two patients were below the age of 40 years, one of them being only 16 years of age at the time of diagnosis.

Most of the patients (85.7 %) have continued to remain in a steady state in ET. Only three patients (14.3 %) progressed to the other forms of CMPD (two to post-ET myelofibrosis and one to CML). The criteria for diagnosis of post-ET Myelofibrosis was reviewed and applied according to the criteria of the International Working Group on myelofibrosis (IWG-MRT) [7]. Time to transition was 7–10 years. No patient transitioned to acute leukemia.

The intensity of thrombocytosis in the three patients who transformed to other CMPD did not show a consistent pattern. None of them showed platelet count of $>1,000 \times 10^9/L$ at any time before or after transition and progression to other form of CMPD. One of the patients who progressed to post-ET myelofibrosis developed massive splenomegaly and has recently undergone splenectomy because of transfusion dependant anemia and physical effects associated with massive size of spleen.

In respect of the clinical features, four patients (19 %) complained of erythromelalgia (that is, warm erythematous

Table 5 Analysis of the relevant clinical data of patients with ET

Age (yrs)	Sex	Number	%
1-Age and sex			
<40	M	1	4.7
	F	1	4.7
41–50	M	3	14.2
	F	3	14.2
51–60	M	2	9.5
	F	3	14.2
61–70	M	2	9.5
	F	4	19
>70	M	1	4.7
	F	1	4.7
Years of follow up	Continuing till date		Ceased to follow up
	Number	%	Number %
2-Duration of follow up			
1–2	3	14.2	5 23.5
3–5	2	9.5	2 9.5
6–8	3	14.2	
9-11	4	18.5	
12–14	2	9.5	
Clinical features		Number	%
3-Clinical presentation			
Splenomegaly		4	19
Erythromelalgia		4	19
Thrombosis		3	14.2
Hemorrhage		1	4.7
4- Disease outcome			
Continued as ET		18	85.7
Transition to CMF		2	9.5
Transition to CML		1	4.7
Transition to AL		0	0
PV to ET		4	19
PV to ET to CMF		1	4.7
5- Treatment given			
ASPIRIN alone		12	57
ASPIRIN + HU		6	28.5
ASP + Ang		2	9.5
ASP + α -INF		1	4.7

distal extremities with painful burning sensation of one or more toes and/or fingers), three patients (14.3 %) suffered from arterial thrombotic events (brain infarction and coronary thrombosis) and one patient (4.7 %) had an episode of excessive bleeding after oral surgery. Four patients (19 %) had splenomegaly. None had the history of thrombotic disease or excessive hemorrhage at the time of diagnosis of ET.

Eight patients who received cytoreductive treatment included two patients with thrombotic events, one patient

with hemorrhagic episode and five patients who insisted to take cytoreductive therapy for psycho-emotional reasons with the belief that their dizziness and heaviness of head was related to the high platelet count. Of these eight patients, six patients were given hydroxyurea, two patients were given anagrelide (both of whom dropped out of compliance). One patient additionally required interferon, but could not continue this treatment for long.

The patients were followed up for 1–14 years (mean = 4.9 years). Nine out of 21 patients (42 %) were

followed up for more than 6 years (one patient for 14 years, one for 12 years, one for 11 years, two for 10 years, one for 9 years, two for 8 years and one for 6 years). The two patients who transitioned into post-ET myelofibrosis were followed up for 8 and 11 years, while the one who developed CML has been followed up for 7 years. All the patients are still alive. The disease of these patients remained unchanged in the steady state of ET for at least 5 years after the diagnosis. The patient who transitioned into CML, did so after 5 years, while the two patients who transitioned into post-ET myelofibrosis started transforming after 7 and 9 years.

Discussion

Although first described in 1934, the earliest series of the cases of ET was reported only in 1960 [8]. It is a rather uncommon disease, the prevalence of which in different parts of the world is unclear because the criteria for its diagnosis have not been uniform all along. Moreover, the diagnosis requires bone marrow examination as one of the essential investigations that is not consistently performed in many countries. No certain data exists about the prevalence of this disease in the Middle-East countries. However, from a population study in USA, its incidence has been reported as 24/100,000 in Connecticut [9]. We, in our institution, could observe only 21 cases in 16 years, with no more than 0–3 new cases being observed in any given year (see Table 1). The number of patients with other causes of thrombocytosis, that is post-splenectomy and transient reactive thrombocytosis that came to our observation during the same period was 136. Patients with ET thus constituted 14.7 % of all cases of thrombocytosis. Schilling [10] reported that out of their 158 cases of thrombocytosis, 28 conformed to myeloproliferative disease. Similar findings are reported by Santosh-Kumar et al. [11].

ET is a disease of the older age group, being extremely uncommon in children. Cortellazo et al. [4] have reported the median age as 68 years (range 40–85 years) and Fenaux et al. [3] as 60 years (range 48–81 years). In our patients the median age was 55.9 years (range 16–76 years), with ten patients (45.2 %) under the age of 50 years and two patients were below 40 years of age. It is difficult to ascertain the possible reason for the occurrence of ET at younger age in our patients. No specific genetic factors are known to be associated with this disease. However, it may be mentioned that six out of our eight patients who were below the age of 50 years are the product of consanguineous marriage as compared with four of the remaining 13 patients who were older. Consanguinity has, however, not been noted in the studies reported by other workers.

ET usually presents with four major clinical features that is vasomotor symptoms (erythromelalgia), thrombotic episodes, bleeding and splenomegaly. Twelve of our 21 patients (57.1 %) remained asymptomatic throughout the period of follow up. Four patients (19 %) presented with erythromelalgia, three patients (14.1 %) had thrombotic episodes, only a solitary patient (4.5 %) developed bleeding and four patients (19 %) showed splenomegaly. Three patients had overlapping clinical features. The single patient who had excessive bleeding also complained of erythromelalgia and two patients who developed thrombotic episodes also had splenomegaly. From a large series of 147 ET patients, Fenaux et al. [3] reported that only 53 (36 %) were asymptomatic. Fifty of their patients (34.6 %) complained of vasomotor symptoms (erythromelalgia), 27 (18.3 %) had thrombotic episodes and 27 (18.3 %) had haemorrhagic events. Cortellazo et al. [4] reported a much higher incidence of thrombotic episodes (6.6 % per patient-year) than haemorrhagic manifestation (0.33 % per-patient year). Splenomegaly has been reported in 25–50 % patients with ET [12]. Although our patients were followed up for a longer period (9–16 years), yet the proportion of patients who remained asymptomatic is significantly higher.

There is no consistent pattern of platelet count in the three of our patients who developed thrombotic events. The mean maximum platelet count recorded in these patients was $937 \times 10^9/L$ (range 595–1,193). The median age was 58.3 years with one patient being 41 years of age. Among the risk factors cited for thrombosis and bleeding in ET patients, age more than 60 years, previous history of thrombotic events, and long duration of thrombocytosis, smoking, diabetes mellitus and obesity are mentioned as prominent [4, 5, 13]. Intensity of thrombocytosis is said to be unrelated to thrombosis, though patients who present with haemorrhagic events have higher platelet count [14, 15]. In our solitary patient who showed excessive bleeding, the maximum platelet count recorded was $1,310 \times 10^9/L$.

Platelet aggregation test was performed in 14 of our 21 patients. Six of them (42.9 %) showed abnormal results. But only one patient had excessive bleeding. The random bleeding time in this patient was normal. All our six patients showed hypo aggregation to ADP. Two patients showed reduced aggregation to ADP and collagen and one patient to ADP, collagen and epinephrine. Fenaux et al. [3] reported that 61 out of their 147 patients were subjected to platelet aggregation tests. Forty-five (73.3 %) showed abnormal results, and 27 (18.3 %) suffered from haemorrhagic events. A variety of platelet functional defects have been reported by Baker et al. [16]. It may be noted that we did not perform von Willebrand Factor (vWF) antigen assay and Ristocetin co factor (vWF:RCo) assay in our patients.

Jak2 (V617F) mutation was tested in all of our 21 ET patients. Eight of them (38 %) showed positive results. One

of these patients diagnosed at the age of 16 years was a patient with post-polycythaemia ET. The two patients who finally transitioned into post-ET myelofibrosis were also positive for Jak2 mutation, while the one who developed CML was negative. Baxter et al. [17] reported Jak2 mutation in more than half of their patients with ET. They also mentioned that no correlation exists between Jak2 mutation and either thrombotic or bleeding complications or transition to other forms of CMPD. Our study also shows similar findings.

Only three of our 21 (14.3 %) patients transitioned to other forms of CMPD. Two patients, 59 and 68 years females developed post-ET myelofibrosis and one, 59 years female developed CML. No patient transitioned to acute leukemia. The maximum platelet count recorded in these three patients was 993, 980, $713 \times 10^9/L$. One of the two patients who transitioned to post-ET myelofibrosis had splenomegaly at the time of diagnosis of ET. They had remained in asymptomatic state for 8 and 10 years and none had received cytoreductive therapy. Both were positive for Jak2 (V617F) mutation. The patient who developed CML did so after 7 years of having remained as ET. She was negative for bcr/abl gene rearrangement at the time of diagnosis of ET, but showed positive when she developed CML. Fenaux et al. [3] encountered a single instance of transition to acute leukaemia among their 147 patients with ET while Gangat et al. [13] reported acute leukaemia in 3.3 % of their ET patients. Transition to CML has not been reported by them or any other worker. It is difficult to ascertain whether the development of CML in our patient is a transition from ET or is related to a coincidentally occurring additional random mutation.

Life expectancy is described as nearly normal in ET [18]. Five year survival of 81 % has been reported by Hehlmann et al. [19] and 10 year survival as 64 % by Fenaux et al. [3]. Cortezzo et al. [20] showed overall survival at the end of 7 years as 73.3 %. Gangat et al. [13] have proposed survival rates on the basis of prognostic risk factors. The higher risk factors being age >60 years, WBC count $>15 \times 1,069/L$, smoking, diabetes mellitus and long duration of thrombocytosis. They reported average survival for 278 months for low risk patients, 200 months for intermediate risk and 111 months for high risk patients. According to their observations, Jak2 mutation had no impact on survival. So far, all of our 21 patients with follow up for 9–16 years are alive.

Several studies have been reported concerning the benefit or otherwise of cytoreductive therapy in ET. Among our patients cytoreductive therapy with hydroxyurea was taken by six (42.9 %) subjects. Two patients who were treated with anagrelide and one patient with alpha-interferon did not continue treatment for long.

Cortellazzo et al. [20], from a study of 114 cases, reported only two cases of thrombotic events among 56 patients who

were treated with hydroxyurea compared with 13 out of 58 subjects who were given only antiplatelet medications. Fenaux et al. [3] treated 129 patients with cytoreductive therapy (22 with P^{32} , 35 with busulphan and 72 with hydroxyurea) and 60 patients with only antiplatelet drugs. They concluded that hydroxyurea is most effective in reducing the occurrence of thrombotic events with minimum risk of major haemorrhage or transition to AML. Harrison et al. [21] from a study of 809 patients followed up for 39 months reported significant risk of serious haemorrhage, arterial thrombotic episodes and transformation into AML, with combination of anagrelide and aspirin therapy. Experience with alfa interferon therapy has been elaborated by Gilart et al. [22] and treatment related risk of leukemic transition from ET has been emphasized by Murphy et al. [23]. Among our three patients who developed thrombotic episodes (arterial thrombosis in all of them) and one patient who had excessive bleeding, none had taken any cytoreductive therapy before the occurrence of these events. Thirteen more patients who had not been given cytoreductive therapy also remained free from thrombotic or haemorrhagic episodes. None of our patients transitioned to acute leukemia. However, the number of patients in our study who took cytoreductive therapy is too small for any valid comparisons and conclusions in this regard.

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