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R. Jantunen · E. Juvonen · E. Ikkala · K. Oksanen
P. Anttila · T. Ruutu

Development of erythrocytosis in the course of essential thrombocythemia

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Abstract Erythrocytosis is not a feature of essential thrombocythemia (ET); this is the most important difference between ET and polycythemia vera (PV). Transformation of ET to PV has only rarely been described. We have reviewed the blood cell counts of 170 ET patients with a median follow-up of 63 months (range 11–313). Eleven of 170 patients (6.5%) developed erythrocytosis at a median of 29 months (range 12–138) after the diagnosis of ET. According to the present results, the development of erythrocytosis in patients with ET is not a rare phenomenon.

Key words Essential thrombocythemia · Thrombocytosis · Erythrocytosis · Erythroid progenitor

Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are closely related myeloproliferative disorders (MPD). Absolute erythrocytosis is a prerequisite for the diagnosis of PV, thrombocytosis for that of ET. Thrombocytosis is a common finding also in PV, but erythrocytosis is not a feature of ET. Erythrocytosis seen at diagnosis in a patient with thrombocytosis is an indicator of PV. There have been very few reports on the development of erythrocytosis or classical PV during the course of ET. Here we report the development of constant erythrocytosis in 11 of 170 ET patients with a median follow-up of 5 years.

R. Jantunen · E. Juvonen · E. Ikkala · T. Ruutu
Department of Medicine, Helsinki University Central Hospital, P.O.Box 340, FIN-00029 HYKS Helsinki, Finland

K. Oksanen
Kanta-Häme Central Hospital, FIN-13530 Hämeenlinna, Finland

P. Anttila
Helsinki Municipal Hospital, Lapinlahdenkatu 16, FIN-00180 Helsinki, Finland

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Patients

The clinical and laboratory findings at diagnosis of the present patient material, 170 patients with ET, have been evaluated and described elsewhere [9]. The median follow-up of the patients was 63 months, range 11–313 months. The diagnosis of ET was established using the following criteria: platelet count above 600×10^9/l for at least 6 months (shorter follow-up time was accepted if treatment was initiated due to complications related to thrombocythemia), no erythrocytosis and exclusion of iron deficiency, no Philadelphia chromosome, no leukoerythroblastic blood picture or morphological abnormalities of erythrocytes compatible with myelofibrosis, and no known cause of reactive thrombocytosis. Adequate iron stores were verified by stainable iron in the bone marrow or normal serum iron, transferrin, and ferritin concentrations. Patients with inadequate documentation of iron stores at diagnosis were excluded.

The data of the 170 patients during the follow-up period have been reviewed to record the development of erythrocytosis. The findings at diagnosis of the patients who later developed erythrocytosis were compared with those of the patients not showing such development.

Results

Eleven of the 170 patients with ET (6.5%), three men and eight women, developed constant erythrocytosis at a median of 29 months (range 12–138 months) after the diagnosis (Table 1). The time from the discovery of thrombocytosis to erythrocytosis ranged from 15 to 146 months (median 48 months). Despite erythrocytosis, in one man (no. 3) and in one woman (no. 4) the hemoglobin and hematocrit values remained within the normal range. In the other patients hemoglobin and hematocrit exceeded the upper limit of the normal range. In addition, four patients (nos. 7–9, 11) also developed neutrophilia.

At the time of diagnosis of ET the erythrocyte count, hemoglobin concentration, and hematocrit of

Table 1 Patients with ET who developed erythrocytosis

	At the diagnosis of ET							At erythrocytosis						Time from the diagnosis of ET to erythrocytosis, months[1]
	Sex	Age	Er	Hb	Hcr	MCV	Leuk	Plt	Er	Hb	Hcr	MCV	Leuk	Plt	
1.	M	73	5.57	170	0.51	92	8.4	600	6.24	187	0.55	88	9.8	489	21 (41)
2.	M	59	5.82	174	0.51	87	10.7	670	7.05	181	0.56	80	6.8	395	54 (54)
3.	M	52	5.66	156	0.49	86	12.0	833	6.22	167	0.52	83	11.2	838	38 (48)
4.	F	43	4.89	144	0.42	87	6.5	715	5.57	157	0.49	88	5.2	681	132 (132)
5.	F	42	5.20	159	0.46	89	8.6	794	6.30	162	0.50	86	10.2	780	40 (46)
6.	F	74	4.72	139	0.44	93	13.0	757	6.16	172	0.53	88	12.3	685	12 (15)
7.	F	58	4.52	133	0.41	91	10.0	722	5.69	162	0.51	87	20.6	813	25 (53)
8.	F	81	5.14	138	0.40	79	11.2	840	6.40	163	0.48	76	15.7	1182	29 (29)
9.	F	40	4.13	142	0.44	106	10.1	976	6.03	176	0.57	95	16.3	871	29 (71)
10.	F	46	5.07	154	0.47	93	12.4	830	5.40	165	0.49	90	12.1	1119	15 (15)
11.	F	72	3.82	140	0.41	108	10.9	1225	5.91	196	0.58	99	18.0	659	138 (146)

Normal range:
Hemoglobin (Hb) male 135–180 g/l, female 125–160 g/l
Erythrocytes (Er) male $4.50–6.10 \times 10^{12}$/l, female $4.00–5.30 \times 10^{12}$/l
Mean corpuscular volume (MCV) 80–96 fl
Hematocrit (Hcr) male 0.40–0.54, female 0.36–0.47
Leukocytes (Leuk) $4.0–10.0 \times 10^{9}$/l
Platelets (Plt) $140–320 \times 10^{9}$/l
[1] Time from discovery of thrombocytosis to erythrocytosis is shown in parentheses

the patients with later erythrocytosis showed a trend towards higher values than those of the patients with stable ET (no erythrocytosis), but the differences were not significant (Table 2). Neither were there any significant differences in the leukocyte or platelet counts. In two patients MCV was elevated at presentation. In one of them (no. 11) it was caused by vitamin B_{12} deficiency and normalized after substitution treatment. In the other patient (no. 9) MCV was elevated due to a liver disorder. In the initial bone marrow aspirate the cellularity was assessed as normal in nine patients and increased in one patient with later erythrocytosis. In one patient the cellularity could not be estimated for technical reasons. Erythropoiesis was estimated to be normal in all 11 aspirates. The spleen was not palpable in any of the 11 patients, and it was enlarged in only one of the seven patients (14%) studied with ultrasonography. Among the 159 patients without later erythrocytosis, five had palpable splenomegaly, and ultrasonography showed splenomegaly in 29 of the 114 patients (25%) studied.

Erythroid (BFU-E, CFU-E), megakaryocytic (CFU-Meg), and granulocyte-macrophage (CFU-GM) progenitors of the bone marrow were cultured using a methylcellulose assay, as described previously [10]. In nine patients the cultures were performed at the time of diagnosis of ET and in one patient (no. 4) 92 months after the initial evaluation, but 40 months prior to the appearance of erythrocytosis. In one patient (no. 9) the progenitors were cultured only at the time of development of erythrocytosis. All ten patients who later developed erythrocytosis and whose progenitors were cultured in the nonerythrocytic phase showed spontaneous erythroid colony formation, i.e., colony growth without the addition of erythropoietin to the culture plates. Spontaneous erythroid growth was seen in 54% of the patients with stable ET. Spontaneous megakaryocytic growth was seen in eight of the ten patients with later erythrocytosis and in 57% of the patients with stable ET.

At the time of diagnosis of ET, seven of the 11 patients with later erythrocytosis (64%) suffered from

Table 2 Laboratory findings at the diagnosis of ET in patients with later erythrocytosis and in patients with stable ET

	Sex	Later erythrocytosis		No erythrocytosis		Normal range
		median	range	median	range	
Hemoglobin g/l	M	170	156–174	147	92–169	135–180
	F	141	133–159	134	83–158	125–160
Erythrocytes $\times 10^{12}$/l	M	5.66	5.57–5.82	4.90	3.00–6.10	4.50–6.10
	F	4.81	3.82–5.20	4.55	3.00–5.27	4.00–5.30
Hematocrit	M	51	49–51	43	28–52	40–54
	F	43	40–47	40	27–47	36–47
MCV fl		91	79–108	88	74–105	80–96
Leukocytes $\times 10^{9}$/l		10.7	6.5–12.4	8.7	3.9–25.1	4.0–10.0
Platelets $\times 10^{9}$/l		794	600–1225	908	496–2175	140–320

symptoms related to ET, such as peripheral symptoms (erythromelalgia, Raynaud's phenomenon), disturbances of cerebral circulation, easy bruising, gingival bleeding, and urinary tract bleeding. The patients with stable disease showed symptoms at diagnosis as frequently as those with later erythrocytosis. After the development of erythrocytosis the symptoms became more common. Nine of 11 patients (82%) suffered from complications and five had several types of them. Peripheral symptoms, such as erythromelalgia, Raynaud's phenomenon, and paresthesia, were experienced by five of the 11 patients. Four patients suffered from easy bruising. Two patients had dizziness and itching. Transient ischemic attack, visual disturbances, angina pectoris, and epistaxis were experienced by one patient each. One patient died of a cerebral infarction at the age of 84 years. Fifty-nine percent of the patients with stable disease showed symptoms of ET during the course of the disease. The difference between the groups was not significant.

Prior to the development of erythrocytosis, three patients had received cytotoxic treatment, two (nos. 2 and 4) for symptoms related to thrombocytosis and one patient (no. 11) due to a high platelet count. Patients 2 and 4 were treated with busulfan for 8 and 9 weeks, respectively. Patient 11 had received a total dose of 16 mCi radiophosphorus over a period of 7 years.

Discussion

Myeloproliferative disorders can transform into another disease of the same group. Among patients with PV, 8–30% progress to myelofibrosis (MF) [8, 14, 15]. Transformation from MF into PV has also been described in a few rare cases [3, 5, 6, 16]. In ET an increase of the reticulin network in bone marrow is a common finding, but evolution to MF with its typical diagnostic features, i.e., collagen fibrosis in bone marrow, red cell anisocytosis, and tear-drop poikilocytosis, has been reported only rarely [11. 12]. Evolution of ET to PV has been described infrequently. In a recent report of the Polycythemia Vera Study Group (PVSG), three of the 91 patients with ET (3%) were mentioned to have transformed to PV during the follow-up [12]. In other previous large studies of ET, transformation into PV has not been reported [1, 4, 7].

In the present study, 6.5% of the patients with typical ET at diagnosis developed erythrocytosis. The possibility of polycythemia vera at diagnosis was eliminated by including in the study only patients with normal iron stores, erythrocyte count, hemoglobin concentration, and hematocrit. With the exception of two patients, the time from the diagnosis of ET to the manifestation of erythrocytosis was relatively long, more than 2 years, the longest times exceeding 10 years.

There were no significant differences in the findings at diagnosis between the patients who later developed erythrocytosis and those who did not. The erythrocyte count, hemoglobin concentration, and hematocrit of the patients with later erythrocytosis were slightly but not significantly higher than those of the other patients. Spontaneous erythroid colony formation was seen in all patients who later developed erythrocytosis but in only 60% of those with stable ET. Thus, spontaneous erythroid colony formation is not predictive of the development of erythrocytosis in individual patients with newly diagnosed ET, but normal erythroid colony growth may indicate a stable disorder.

A full diagnostic workup to establish the diagnosis of PV was not carried out for any of the 11 patients at the time of erythrocytosis. Later, either the patients were not available for further studies or they had been treated with cytotoxic drugs. Therefore, it was not formally shown in this study that any of the patients would have transformed from ET into PV. It is likely, however, that in at least some of the patients, e.g., no. 11, the diagnostic criteria of PV [2, 13] would have been fulfilled. The present study shows that the development of erythrocytosis in patients with ET is not a rare phenomenon, and this reflects the close relationship between these disorders.

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