Serum thrombopoietin levels in patients with reactive thrombocytosis due to lung cancer and in patients with essential thrombocythemia

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In patients with thrombocytosis normal to increased serum thrombopoietin (TPO) levels have been reported. The aim of this study was to investigate the relationship between serum TPO concentration, platelet number and plasma levels of fibrinogen in patients with reactive thrombocytosis (RT) due to lung cancer and in patients with essential (primary) thrombocythemia (ET). A total of 70 newly diagnosed patients with RT or ET (platelet counts >600 G/l) were studied: 45 with RT due to lung cancer (25 with non-small cell lung cancer, NSCLC and 20 with small cell lung cancer, SCLC), and 25 with ET. Twenty normal volunteers were used as controls.

TPO was measured by immunoassay technique (ELISA). Mean serum TPO values in patients with RT due to lung cancer were statistically significantly higher than those in patients with ET or in controls. The highest platelet count was seen in patients with ET, and mean plasma fibrinogen levels were the highest in RT patients. In NSCLC patients mean serum TPO concentrations were higher (not statistically significant) than in SCLC, and a statistically significant relationship between TPO serum concentration and fibrinogen level was observed. No correlations between platelet counts and TPO serum concentrations were found. Our results indicate increased serum TPO levels in patients with thrombocytosis in lung cancer which may be related to the activity of neoplasms. In addition, it is postulated that the relatively low TPO values in patients with ET may result from a dysregulation of the feedback loop involved in platelet production.

Key words: Thrombocytosis, lung cancer, essential thrombocythemia, thrombopoietin, fibrinogen.

Reactive thrombocytosis (RT) occurs in various diseases including inflammatory states [19], neoplastic diseases [17], iron deficiency anemia, and may appear after splenectomy [7]. Essential thrombocythemia (ET) is a primary bone marrow disease that causes thrombocytosis. In both ET and RT patients increased serum thrombopoietin (TPO) levels have been reported by some authors [2, 14, 26], whereas other investigators found slightly elevated or normal TPO serum levels in ET patients when compared with healthy controls [18, 22, 31]. A clinically relevant observation is that more thrombotic complications are seen in patients with ET than in patients with RT [3, 4], and that these complications are probably related to abnormal platelet function in ET.

In some cancer patients the addition of thrombocytosis to the present hypercoagulability may markedly increase the risk of thrombosis. Among the most thrombogenic are primary carcinomas of the pancreas, stomach, lung, colon and metastatic disease. The purpose of this study was to investigate the relationship between serum TPO concentration, platelet number and plasma levels of fibrinogen in patients with RT due to lung cancer and in patients with essential (primary) thrombocythemia.

Material and methods

Patients. The relevant Hospital Ethics Commitees approved this study. A total of 70 newly diagnosed patients with RT and clonal thrombocytosis (ET) with platelet count

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greater than 600 G/l were included in the study. Patients with lung cancer accompanied with RT were diagnosed at the Department of the Pulmonology Medical University of Wroclaw and at the Oncology Department of the Regional Lung Diseases Center in Poznan and patients with ET were diagnosed at the Department of Hematology, Hematooncology and Bone Marrow Transplantation Medical University of Wrocław since January 1999 till August 2001.

Group I consisted of 45 patients with RT due to lung cancer, 30 males and 15 females, aged from 34 to 78 years (mean $\pm$SD, 55.7 $\pm$ 9.9 years). This group was divided into two subgroups according to histological diagnosis: Subgroup IA (non-small cell lung cancer, NSCLC) – 25 patients, 17 males and 8 females, aged from 34 to 78 years (mean $\pm$SD, 56.3 $\pm$ 10.6 years) and Subgroup IB (small cell lung cancer, SCLC) – 20 patients, 13 males and 7 females, aged from 44 to 76 years (mean $\pm$SD, 55.7 $\pm$ 9.6 years).

Group II consisted of 25 patients with ET, 3 males and 22 females, aged from 34 to 72 years (mean $\pm$SD, 54.3 $\pm$ 13.4 years). Conventional criteria were used for the diagnosis of ET, no Philadelphia chromosome, negative primary myelofibrosis and the Polycythemia Vera Study Group criteria [20, 21].

Twenty normal volunteers were used as controls, 13 males and 7 females, aged from 34 to 56 (mean $\pm$SD, 40.9 $\pm$ 7.3 years).

TPO Assay. For all patients blood samples were collected to serum separator tubes in the morning before breakfast, and centrifuged at 1000 x g within 30 minutes of collection for the measurement of serum TPO.

TPO assay employs the quantitative sandwich immunoassay technique [26]. Thrombopoietin ELISA reagents were provided by R&D Systems, Inc. (Minneapolis, USA). Briefly, a monoclonal antibody specific for TPO was precoated onto 96 well ELISA plates. Serum samples and standards (recombinant human thrombopoietin, rHUTPO) were pipetted into the wells in duplicate and any TPO present was bound by immobilized antibody.

After washing, to remove unbound material, an enzyme-linked monoclonal antibody specific for TPO was added to each well. Following washing to excess antibody-enzyme reagent a substrate solution was added to the wells and color developed in proportion to the amount of TPO bound in the initial step. The reaction was stopped and the intensity of color measured at 450 nm.

The number platelets in each collected blood sample was measured automatically, using a commercially available, validated technique (Sysmex K-4500, Kobe, Japan).

The normal range was established at 150–400 x 10^9/l.

The concentration of fibrinogen was measured in citrated plasma using a second commercially available, validated technique (Behring Coagulation System, Germany). The measurement was done in duplicate. Reagent and controls were supplied by Behring (MultifibrenU, Germany). The normal range was established at 2–4.5 g/l.

Statistical Analysis. Continuous values are expressed as mean $\pm$S.D. The Student t-test and the Pearson correlation coefficient test were applied for the statistical analysis of the data.

Results

The clinical characteristics of Group I are shown in Table 1, and of Group II in Table 2, respectively.

Figure 1 shows that the serum thrombopoietin (TPO) values in patients with RT (group I) due to lung cancer (231.9 $\pm$ 117.8 pg/ml, range 104.7 to 498.9 pg/ml) were statistically significantly higher than those in patients with ET (130.6 $\pm$ 59.5 pg/ml, range 78.9 to 297.3 pg/ml; $p<0.05$) and when compared with controls (86.7 $\pm$ 17.1 pg/ml, range from 62.3 to 124.2; $p<0.05$). Serum TPO values in patients with ET were higher than in controls, but the mean values were not statistically significantly different.

TPO serum concentration in patients with RT due to NSCLC (Subgroup IA) (234.1 $\pm$ 157.7 pg/ml, range 104.7 to 498.9 pg/ml) were slightly higher than those seen in patients with SCLC (Subgroup IB) (228.7 $\pm$ 77.7 pg/ml, range 111.8 to 387.9 pg/ml), but this difference was not statistically significant.

The platelet count in ET patients (Group II) (986.7 $\pm$ 261.3 x 10^9/l, range 738.0 to 1700.0 x 10^9/l) was statistically significantly higher than that in patients with RT (Group I) (751.2 $\pm$ 141.5 x 10^9/l, range 613.0 to 1276.0 x 10^9/l, $p<0.05$) and in controls (262.3 $\pm$ 50.4 x 10^9/l, range 166.0 to 345.0 x 10^9/l, $p<0.05$).

Plasma levels of fibrinogen in RT patients (Group I) (5.76 $\pm$ 1.59 g/l, range 2.90 to 8.20 g/l) as well as in Subgroup IA (6.39 $\pm$ 1.21 g/l, range 2.90 to 8.00 g/l) and in Subgroup IB (4.90 $\pm$ 1.63 g/l, range 3.00 to 8.20 g/l) were statistically significantly higher than those in Group II (2.65 $\pm$ 0.57 g/l, range 1.90 to 4.00 g/l) and in controls (2.90 $\pm$ 0.32 g/l, range 2.11 to 3.50 g/l). Plasma fibrinogen level in subgroup IA was markedly higher than in subgroup IB.

In neither group a correlation between platelet count and TPO serum concentration was found.

Significant relationship between TPO serum concentration and fibrinogen level was present in subgroup IA only ($r=0.63$, $p<0.05$) (Fig. 2), but not in subgroup IB ($r=0.53$) nor in whole group I ($r=0.43$), group II ($r=-0.12$) and in controls ($r=-0.18$).

In the 8 patients (2 with RT and 6 with ET) who presented with thrombosis prior to diagnosis of thrombocytosis there were a total of 10 clotting events (2 events in the RT patients and 8 in ET patients). Both RT patients had NSCLC, and the thrombosis had resulted in a myocardial infarction. For the ET patients deep venous thrombosis had

Table 1. Characteristic of 45 patients with lung cancer associated with thrombocytosis (RT, Group I)

No	Age	Gender	Diagnosis	Platelet count (x 10^9/l)	TPO (pg/ml)	Fibrinogen (g/l)
1	44	M	Non-small cell lung cancer	750.0	154.56	5.78
2	65	M	Small cell lung cancer	613.0	343.18	4.70
3	70	M	Non-small cell lung cancer	655.0	299.15	5.90
4	78	M	Non-small cell lung cancer	657.0	123.67	4.75
5	70	F	Small cell lung cancer	644.0	207.80	3.00
6	50	F	Small cell lung cancer	755.0	746.70	6.90
7	51	M	Small cell lung cancer	847.0	342.52	3.20
8	68	M	Non-small cell lung cancer	704.0	129.59	2.90
9	73	F	Non-small cell lung cancer	982.0	213.00	5.90
10	59	M	Non-small cell lung cancer	1002.0	219.86	7.00
11	47	F	Small cell lung cancer	607.0	115.79	4.40
12	71	M	Small cell lung cancer	671.0	158.51	4.50
13	50	F	Small cell lung cancer	814.0	113.50	6.80
14	53	M	Small cell lung cancer	758.0	225.50	6.80
15	58	F	Small cell lung cancer	837.0	164.42	5.00
16	53	F	Non-small cell lung cancer	705.0	184.50	3.00
17	76	M	Small cell lung cancer	801.0	159.82	3.50
18	54	F	Small cell lung cancer	684.0	123.67	4.50
19	49	M	Non-small cell lung cancer	706.0	318.21	7.00
20	50	F	Non-small cell lung cancer	691.0	242.00	7.80
21	34	F	Non-small cell lung cancer	647.0	309.00	7.50
22	46	M	Small cell lung cancer	623.0	154.56	3.70
23	49	M	Non-small cell lung cancer	740.0	176.00	5.90
24	54	M	Non-small cell lung cancer	677.0	282.06	6.50
25	47	M	Non-small cell lung cancer	843.00	265.00	7.40
26	64	M	Non-small cell lung cancer	697.0	151.28	7.00
27	58	M	Non-small cell lung cancer	668.0	387.87	8.00
28	54	F	Small cell lung cancer	649.0	272.20	7.20
29	50	F	Small cell lung cancer	744.0	307.03	6.85
30	46	M	Non-small cell lung cancer	676.0	305.72	7.50
31	44	M	Small cell lung cancer	658.0	228.83	6.30
32	45	F	Non-small cell lung cancer	702.0	226.86	7.25
33	51	M	Small cell lung cancer	983.0	104.67	6.00
34	53	M	Non-small cell lung cancer	823.0	182.17	5.00
35	48	M	Non-small cell lung cancer	785.0	192.50	5.80
36	54	M	Small cell lung cancer	717.0	128.93	5.90
37	52	F	Non-small cell lung cancer	676.0	384.58	7.00
38	45	M	Small cell lung cancer	1276.0	498.94	8.20
39	66	M	Small cell lung cancer	720.0	213.71	4.70
40	52	M	Small cell lung cancer	692.0	164.42	5.50
41	69	F	Non-small cell lung cancer	666.0	145.50	6.88
42	60	M	Non-small cell lung cancer	1204.0	236.00	8.02
43	57	F	Non-small cell lung cancer	703.0	145.50	6.88
44	66	M	Small cell lung cancer	664.0	113.16	3.00
45	69	M	Non-small cell lung cancer	687.0	272.20	6.00

occurred in 2 patients, superficial thrombophlebitis in 3 patients, and pelvic and mesenteric vein thrombosis in 1 patient, respectively.

Discussion

In our study, TPO serum levels were significantly higher in RT patients (Group I) when compared with ET patients (Group II) and with normal control subjects. In ET patients TPO serum levels were only slightly higher than in normal controls. There was no correlation between platelet count and TPO serum levels in any group. Our data are in agreement with results obtained by previous authors [2, 13, 22, 28, 29].

Table 2. Characteristic of 25 patients with essential thrombocythaemia (ET, Group II)

No	Age	Sex	Diagnosis	Platelet count (x 10^9/l)	TPO (pg/ml)	Fibrinogen (g/l)
1	46	F	Essential thrombocythaemia	944.0	78.9	2.30
2	41	F	Essential thrombocythaemia	700.0	97.2	2.11
3	56	F	Essential thrombocythaemia	1700.0	297.3	2.08
4	33	F	Essential thrombocythaemia	774.0	104.8	2.60
5	66	F	Essential thrombocythaemia	770.0	116.1	1.98
6	40	M	Essential thrombocythaemia	738.0	94.1	2.72
7	35	F	Essential thrombocythaemia	1167.0	107.3	2.60
8	43	F	Essential thrombocythaemia	1564.0	96.5	2.15
9	61	F	Essential thrombocythaemia	1091.0	280.5	2.50
10	69	F	Essential thrombocythaemia	1197.0	193.2	3.80
11	66	F	Essential thrombocythaemia	665.0	118.5	2.60
12	63	F	Essential thrombocythaemia	840.0	132.2	1.90
13	54	F	Essential thrombocythaemia	830.0	119.5	3.00
14	72	F	Essential thrombocythaemia	787.0	91.3	4.00
15	66	M	Essential thrombocythaemia	900.0	116.7	2.14
16	38	F	Essential thrombocythaemia	1278.0	236.4	2.16
17	67	M	Essential thrombocythaemia	776.0	124.5	2.20
18	70	F	Essential thrombocythaemia	1200.0	89.0	2.44
19	68	F	Essential thrombocythaemia	900.0	175.5	3.36
20	34	F	Essential thrombocythaemia	1300.0	102.0	2.31
21	50	F	Essential thrombocythaemia	940.0	99.0	3.50
22	65	F	Essential thrombocythaemia	789.0	84.0	2.80
23	63	F	Essential thrombocythaemia	846.0	96.0	3.02
24	55	F	Essential thrombocythaemia	911.0	107.0	3.07
25	36	F	Essential thrombocythaemia	861.0	108.0	2.95

Currently, conflicting data concerning serum TPO levels in ET and in RT patients have been published. Griesshammer et al [9] have found significantly elevated mean TPO serum levels in 15 untreated and 10 treated patients with ET when compared with healthy controls. Wang et al [30] reported significantly higher TPO levels in patients with clonal thrombocytosis than in patients with RT (17/34 with malignant tumors).

In addition, some authors observed increased serum TPO levels in both ET and RT [2, 14, 26], whereas others found that TPO levels in ET did not differ significantly from those in RT [1, 6].

The presence of normal (our study) or elevated [9, 30] TPO serum levels in patients with ET is contrary to expectations derived from a model, in which platelets directly regulate serum concentration by adsorbing free TPO [16]. The level of TPO is mainly determined by regulation of cytokine production and change in the binding to the c-Mpl receptors and clearance of the factor from circulation.

In some ET patients the platelet c-Mpl expression was found to be significantly decreased [10], which may partly explain previous findings.

Though thrombocytosis due to myeloproliferative disorders was recognised as of clonal origin, recent laboratory studies of X- chromosome inactivation patterns in women with ET have shown that monoclonal hematopoiesis could be demonstrated in only half of the subjects, and the remainder were found to have polyclonal hematopoiesis [11]. This

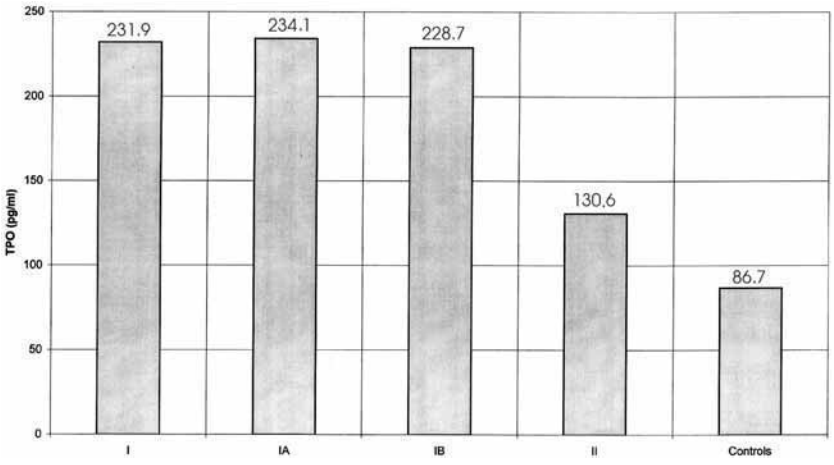

Figure 1. Serum thrombopoietin (TPO) concentration in patients with thrombocytosis due to lung cancer (Group I), non-small cell lung cancer, NSCLC (Subgroup IA), small cell lung cancer, SCLC (Subgroup IB), essential thrombocythaemia, ET (Group II), and in controls. Data are presented as means ± SD.

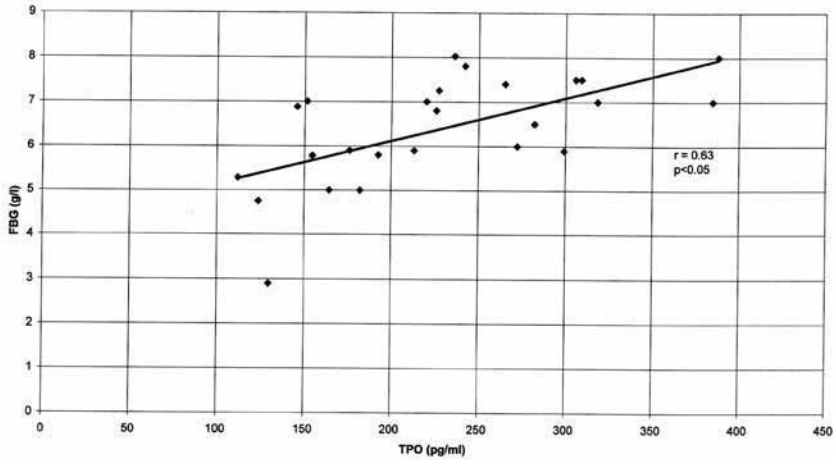

Figure 2. Correlation between serum thrombopoietin (TPO) levels and fibrinogen plasma concentration a) in patients with non-small cell lung cancer (NSCLC) associated with thrombocytosis (IA).

may partly explain the presence of the wide range of TPO levels in ET. One of possible explanation for high levels of TPO seen in patients with secondary thrombocytosis could be a defect in TPO clearance from the serum, as has been shown in thrombocytosis of clonal origin, but no data are available to confirm this theory in RT patients.

Another explanation for elevated TPO levels in RT due to malignancy could be a greatly enhanced TPO production.

The expression of TPO mRNA was found in solid tumor cells derived from colon, endometrium, kidney, liver, ovary, retinoblastoma and urinary cancers, and in leukaemia-lymphoma cell lines. TPO mRNA was also detected in most plasma cell, myeloid, megakaryocytic and erythroid cell lines, but not in pre B-cell, B-cell or T-/NK-cell lines [5].

The expression of TPO mRNA was observed in the majority of 27 carcinoma cell lines as determined by reverse transcriptase-polymerase chain reaction (RT-PCR). High blood TPO levels were observed in patients with advanced carcinomas associated with thrombocytosis. These results indicate that thrombocytosis in patients with carcinomas might be caused, at least in part, by TPO produced by carcinoma cells [25]. Marked thrombocytosis has frequently been seen in patients with hepatoblastoma, in one study, all seven untreated patients with hepatoblastoma accompanied with thrombocytosis had high serum TPO levels, and the expression of c-Mpl mRNA was found in hepatoblastoma tissues [15].

As TPO levels have been found to be elevated or normal in both RT and in thrombocytosis due to myeloproliferative disorders, e.g. ET, its potential role can not be differentiated between these two conditions.

In 60% to 80% of patients with RT, plasma or serum IL-6 levels are elevated [8, 12, 14, 23, 24, 27, 29], however levels of the sIL-6 receptor, cytokines IL-3, IL-8 and IL-11 were not statistically different [14]. An increased IL-6 level and levels of C-reactive protein (CRP) as an indicator of acute inflammatory processes have been reported by Tefferi et al in RT [27]. Uppenkamp et al [29] found elevated CRP levels correlating with high IL-6 concentrations in patients with RT, but there was no correlation between IL-6 serum levels and increased TPO concentrations in these patients.

We have found that in patients with RT due to NSCLS an elevated plasma fibrinogen levels correlate well with high serum TPO concentrations.

In conclusion our results indicate increased serum TPO levels in patients with RT due to lung cancer, which may be related to the activity of neoplasms, and relatively high values for TPO in patients with ET, which may represent a dysregulation of the feedback loop involved in platelet production.

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