

Original article

Thrombosis and Thrombocytosis in a Thousand Rheumatologic Cases

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ÖZET

Bin romatolojik vakada tromboz ve trombositoz

Bu çalışmanın amacı romatolojik hastalıklarda tromboz ve tromboz insidansının belirlenmesidir.

2001-2008 yılları arasında romatolojik hastalık tanısı ile izlenmiş 1000 vaka (771 kadın, 229 erkek) retrospektif olarak tarandı. Herbir hastalık için tromboz ve trombositoz insidansı belirlendi.

Trombositoz (platelet sayısı >400 000/mm³) vakaların 89'unda (%8,9) mevcuttu. Pulmoner emboli ve derin venöz tromboz sırası ile 8 (%0,8) ve 14 (%1,4) vakada mevcuttu. Pulmoner embolisi olan hastaların 2'sinde trombositoz vardı. Trombositoz romatoid artrit, Sjögren sendromu, Sistemik lupus eritematozis, Behçet hastalığı ve sklerodermada daha sıkı. Tromboz ise Behçet hastalığında daha sıkı. Romatolojik hastalıklarda trombositoz ile tromboz arasında ilişki saptanmadı.

Ciddi komplikasyonların gelişmesini önlemek için romatolojik hastalığı olan hastalar tromboz varlığı açısından değerlendirilmelidir.

Anahtar Kelimeler: Tromboz, trombositoz, romatolojik hastalık

ABSTRACT

The aim of the study is to identify the incidence of thrombocytosis and thrombosis in patients with rheumatologic diseases. Thousand cases (771 female, 229 male) who had the diagnosis of any rheumatological disease and who were evaluated between 2001-2008 were included in this retrospective study. The incidence of thrombosis and thrombocytosis in each rheumatologic disease was investigated. Thrombocytosis (platelet >400 000/mm³) was found in 89 cases (8.9%). Pulmonary embolism and deep-vein thrombosis were found in 8 cases (0.8%) and 14 cases (1.4%) respectively. Thrombocytosis was identified in 2 of 8 patients with pulmonary embolism. Thrombocytosis was found to be relatively common in rheumatoid arthritis, Sjögren's syndrome, Systemic lupus erythematosus, Behçet's disease and scleroderma. Thrombosis was found to be relatively common in Behçet's disease. Incidence of thrombosis in our study was found to be lower than the previous studies and thrombocytosis incidence was similar to the literature. We did not find and relation between thrombocytosis and thrombosis in rheumatologic diseases. The patients with rheumatologic diseases have to be evaluated for presence of thrombosis to prevent possible serious complications.

Key Words: Thrombosis, thrombocytosis, rheumatologic diseases

INTRODUCTION

Platelets are the most important components in maintaining homeostasis. They also play a role in development of arterial thrombosis and atherosclerosis¹⁻³. Thrombocytosis is defined as platelet count more than normal limit which is accepted as 400.000/mm³.

Thrombocytosis can occur due to either a reactive process or a manifestation of a clonal hematopoietic disorder⁴⁻⁶. Usually thrombocytosis is secondary to a disease process, such as inflammation or trauma, which is named as reactive thrombocytosis, and the platelet count increases temporarily during active phase of the disease, rarely exceeding 800.000/mm^{3-5,7}. Thrombosis is described as obstruction of an artery or vein by a blood clot (thrombus). Thrombosis occurs in the blood flow by the interaction and co-existence of all vascular, cellular and humoral factors^{6,8-10}. The factors important in pathophysiology of thrombosis are endothelial damage (atherosclerotic lesions),

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vascular stasis (hyperviscosity), and alterations in the relevant blood components, such as platelets, which are also known as Virchow triad. In rheumatologic disorders, both thrombocytosis and thrombosis can be observed and may lead important complications.

In this study, we analyzed thrombosis and thrombocytosis frequency and mean platelet volume (MPV) levels at 1000 subjects with a rheumatologic disease and evaluated the clinical significance to produce a guideline for clinical evaluation of these diseases.

MATERIALS AND METHODS

A retrospective review of the patients admitted to our clinic between January 2001 and December 2008 was done. A thousand patients in the active stage of the disease were identified and included in this study. The patients are grouped according to the previous diagnosis which were obtained according to the clinical, radiological, genetical and laboratory findings. The list of the diseases is shown at Table 1.

From the medical records, a particular attention was directed to any previous occasion of pulmonary embolism and deep vein thrombosis. Any possible history of thrombotic event such as breath shortness, tachycardia, leg ache and swollen condition was recorded. The physical examination of the patients at the clinical admittance was reviewed and presence of arthritis, malar rash, uveitis, erythema nodosum, thrombophlebitis was noted.

From the laboratory examinations, platelet level, erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) level and mean platelet volume (MPV) were recorded for each patient. EDTA (ethylenediaminetetraacetic acid), which is mixed with the peripheral blood during complete blood count, is known to cause pseudothrombocytopenia. Therefore, the platelets were also counted at the peripheral smear. Platelet level above $400.000/\text{mm}^3$ was accepted as thrombocytosis. Normal mean platelet volume was accepted as 7.8-11 femtoliter. The devices used in measurement and evaluation of these parameters did not change in this 7 years period.

Lungs were evaluated with high resolution computerized tomography in patients who were suspected of pulmonary embolism. Lower extremity vessels were evaluated by color doppler sonography in patients who were suspected of deep vein thrombosis.

The patients who have clinical symptoms of morning stiffness, arthralgia together with elevated ESR and CRP are accepted as at the active stage of the disease.

We excluded other secondary thrombocytosis causes including infection, postsplenectomy or hypo-splenism, malignancy, trauma, hemorrhage, blood loss, or both iron-deficiency anemia, rebound thrombocytosis, asplenia (anatomic or functional).

The demographic and clinic characteristics of the patients were compared using chi-square test and $p < 0.05$ value was accepted as significant.

Table 1. Thrombosis, thrombocytosis incidence

Diagnosis*	Total	Thrombocytosis			Thrombosis		
		Male	Female	Incidence (%)	Pulmonary embolism	Deep Vein Thrombosis	Total
Sjogren's Syndrome	25	3	0	12	0	0	0
RA	197	26	10	18	1	2	3
SLE	62	8	0	13	1	2	3
SNA	119	3	8	9	1	0	1
GA	167	5	0	3	1	1	2
Gout	71	2	3	7	0	0	0
Vasculitis	23	1	0	4	0	0	0
Polymyositis	2	1	0	-	0	0	0
Behçet's Disease	53	1	4	9	2	9	11
APS	29	0	0	-	1	0	1
FM	293	14	0	5	0	0	0
FMF	14	0	1	7	0	0	0
SCL	12	2	0	17	0	0	0
PMR	29	1	0	3	1	0	1
Total	1000	62	27	9	8	14	22

* RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, SNA: Sero-negative Arthritis, GA: Generalized Osteoarthritis, ARF: Acute Rheumatic Fever, FM: Fibromyalgia, FMF: Familial Mediterranean Fever, PAN: Polyarteritis Nodosa, SCL: Scleroderma, APS: Antiphospholipid Syndrome, PMR: Polymyalgia Rheumatica

Table 2. Results of blood tests

	Total	Plt* <150000 mm ³		Plt >400000 mm ³		WBC* <4000 mm ³		WBC >10000 mm ³		MPV* >11	
		F	M	F	M	F	M	M	F	F	M
RA	197	5	2	26	10	0	0	49	29	0	0
SLE	62	6	9	8	0	5	8	8	12	0	0
SNA	119	0	0	3	8	3	2	14	11	0	0
GOA	167	7	4	5	0	2	1	12	7	1	0
Vasculitis	20	2	10	1	0	2	10	2	10	0	0
Sjögren	25	1	4	3	0	1	4	2	10	0	0
GUT	71	1	1	2	3	0	0	17	23	2	4
Polymyositis	2	0	0	1	0	0	0	1	50	0	0
FM	293	7	2	9	0	8	2	18	6	0	0
Behçet	53	2	3	1	4	0	0	17	32	0	0
PMR	29	1	3	1	0	0	0	4	13	0	0
SCL	12	3	25	2	0	1	1	2	8	1	0
ARF	12	1	8	0	0	2	0	1	8	0	0
FMF	12	0	0	0	1	2	0	4	0	0	0
PAN	1	0	0	0	0	0	0	0	0	0	0
Takayasu	2	0	0	0	0	0	0	0	0	0	0
Total	1000	36	71	61	26	26	28	151	219	4	4

* MCV: Mean corpuscular volume, PLT: Platelet, WBC: White blood cell, MPV: Mean platelet volume

RESULTS

Thousand patients, 771 women and 229 men, with a median age of 49 years were included in the study. The most common diagnosis was fibromyalgia, followed by rheumatoid arthritis, generalized osteoarthritis and sero-negative arthritis. Thrombocytosis was identified in 89 (8.9%) patients. The incidence of thrombocytosis in male patients (27%) was found to be significantly different than the incidence in female patients (4%) ($p=.001$). Thrombocytosis was observed in 36 of 197 patients (18%) with rheumatoid arthritis (RA), in 14 of 293 patients (5%) with fibromyalgia, in 8 of 62 patients (13%) with systemic lupus erythematosus (SLE), in 11 of 119 patients (9%) with sero-negative arthritis (SNA), in 5 of 167 patients (3%) with generalized osteoarthritis, in 5 of 53 patients (9%) with Behçet syndrome and in 3 of 25 patients (12%) with Sjögren's syndrome. The involvement of female patients was common in Behçet's disease and in sero-negative arthritis (Table 1). Thrombosis was observed in total of 22 patients (Table 1). Eight patients had pulmonary embolism demonstrated by high-resolution CT, and these patients were treated. Thrombocytosis was identified in 2 of 8 patients with pulmonary embolism (1 of all patients with Antiphospholipid Syndrome (APS), 1 of all patients with SNA).

Pulmonary embolism was observed relatively more common in Behçet's disease (4%). Deep vein thrombosis was observed in total of 14 patients, which is also commonly observed in Behçet's disease (17%).

Thrombocytosis was not identified in patients with deep vein thrombosis.

Eight patients with increased mean platelet volume (MPV) were identified and it was most common in gout. No relation between thrombosis and increased MPV was found. Laboratory evaluations of the patients were summarized in Table 2.

DISCUSSION

Thrombocytosis is one of the factors that can cause thrombosis and thrombosis is among the leading causes of mortality¹. Thrombocytosis can be divided into two categories; essential thrombocytosis and secondary (reactive) thrombocytosis.

Essential thrombocytosis is one of the chronic myeloproliferative disorders such as polycythaemia vera, myelofibrosis and chronic myeloid leukaemia⁷.

Thrombocytosis is observed in all of these abnormalities in association with a particular blood cell type which predominates according to the type of the myeloproliferative disorder. Platelet count is always higher than 1.000.000/mm³ in essential thrombocytosis.

Bleeding and/or thrombosis can be observed related to thrombocytosis in patients with essential thrombocytosis¹.

Reactive thrombocytosis can be observed associated with inflammatory disorders, malignancies (Hodgkin's disease, solid tumors), chronic iron deficiency, infection, acute or chronic blood loss, splenectomy and hyposplenism⁷. Platelet counts are usually below 1.000.000/mm³ but above 400.000/mm³. Reactive thrombocytosis does not indicate any specific treatment except the treatment of underlying disease, because usually unless additional risk factors are present, reactive thrombocytosis is not associated with an increased risk of thromboembolic events^{2,3}. There

is no laboratory criterion to differentiate essential thrombocytosis from secondary thrombocytosis.

The clinical and laboratory evaluation of the patients with thrombocytosis must be done to diagnose any associated systemic disease and to make the differential diagnosis between primary and secondary thrombocytosis. In rheumatologic diseases, secondary thrombocytosis occurs^{8,9,11}.

Reactive thrombocytosis is most commonly seen in rheumatoid arthritis which is associated with iron deficiency anemia⁴. The underlying mechanism of thrombocytosis in RA is not clearly described in the literature. There are some theories.

Interleukins (IL-1, IL-4 and IL-6) can stimulate megakaryocytopoiesis with proinflammatory mediators⁸. Inflammation also can be secondary to the secretion of stem cell factor, leukemia inhibitor factor, granulocyte colony stimulating factor (G-CSF), Trombopoetin (TPO) which stimulate the initiation of the mechanism that cause thrombocytosis^{5,1,12}. Although there is no clear description of the exact mechanism that cause thrombocytosis, it is known that there is positive correlation between the presence of thrombocytosis and clinical activity of the rheumatologic disease^{5,6,9}. Similarly we found that, when the patients are in active stage of the disease, that can be described as increased CRP, RF, ESR levels and presence of morning stiffness, they have the risk of thrombocytosis^{8,9,13}. Cervera et al. reported 39 of 75 RA patients had thrombocytosis¹⁴. In three of these patients they found short platelet half life and high platelet turnover. In another study, thrombocytosis was found in 23 of 26 patients (88%) with juvenile RA¹⁵. In RA patients, predisposition to thrombosis was found to be increased due to high level homosistein or presence of anti-phospholipid (APL) antibody¹⁶. In our study, the frequency of thrombocytosis is 18% (36 of 197 RA patients), the average platelet number in RA patients with thrombocytosis is $464 \pm 48/\text{mm}^3$ and no case of thrombosis was observed in RA patients with thrombosis.

Systemic lupus erythematosus is usually associated with thrombocytopenia rather than thrombocytosis¹⁷. The incidence of thrombocytopenia was reported to be between 15-58% and it was stated to be one of the causes of mortality.

Thrombocytopenia was reported to be a result of autoimmune process in SLE¹⁷. Thrombosis can also be seen in SLE^{17,18}. In a study, the ratio of thromboembolic events in SLE has been found to be 25-28%¹⁹. The most common cause of thrombosis in SLE is antiphospholipid antibodies.

But, the hereditary factors such as Protein C, protein S or antithrombin-III deficiencies, factor V-leiden, prothrombin or methylen tetrahydrofolate reductase (MTHFR) may have a part in thrombosis etiology. Colli S et al. found that protein-C, fibrinogen, D-dimer and homosistein levels were increased in SLE patients which cause thrombosis¹¹. We have 62 patients with SLE and 8 of these patients had thrombocytosis (12.8%). Pulmonary embolism were identified in 1 of all APS patients and 1 of all SNA patients with thrombocytosis among our rheumatologic patients. Thrombosis occurs in the presence of Anti-cardiolipin antibody (ACA)-IgG, ACA-IgM, Lupus antibody in rheumatologic diseases^{20,21}.

Anticardiolipin antibody presence is seen in antiphospholipid syndrome as a primary pathology and can be seen in SLE, RA and scleroderma as well²⁰. However, the mechanism of thrombosis is not clear. ACA can cause APC resistance effecting Protein S - Protein C metabolism. At the same time, it stimulates prostacyclin and tPA secretion from the endothelium. Unikiene et al. reported 38 cases with positive ACA IgG in a heterogenous group of rheumatological patients composed of 242 patients. There is always high levels of positive ACA in rheumatic heart disease, thrombocytopenia and livedo retikularis²². In our study pulmonary embolism was found 1 of all patients with antiphospholipid syndromes. Plasma homosistein level is another important parameter in thrombosis. Aksu et al. found higher homosistein level in patients with Behçet's disease and thrombosis than control group.

Hiperhomosisteinemia in Behçet's disease can be accepted as an independent risk factor for thrombosis²³. Homosistein levels of 29 patients who used methotrexate were found higher than the control group with statistical significance²³. In our study, thrombosis was observed in Behçet's disease, SLE and RA.

High MPV level shows increased platelet turnover and increased number of young platelets in the circulation. Generally in the circulation of patients with high risk of thrombosis, the number of young platelets increases due to consumption. We found MPV > 11 fL in 8 of 1000 rheumatologic cases, 4 cases of gout (4/71), 3 cases of GOA (3/167) and one case with fibromyalgia (1/293), which is opposite to our theory (Table 2).

There was two thrombosis attacks in our patients with reactive thrombocytosis. Presence of reactive thrombocytosis does not increase the risk of thrombosis in rheumatologic patients, if there is no other risk factor, so antiagregan or

anticoagulant prophylaxis for these patients is usually unnecessary².

In conclusion, patients with rheumatologic diseases should be evaluated for secondary thrombocytosis and for possible thrombotic

pathologies in order to prevent further morbidity. Thrombocytosis can be observed in SLE which is not previously mentioned in the literature and patients with Behçet's disease should be closely followed for the occurrence of venous thrombosis.

REFERENCES

1. Barbui T, Finazzi G. When and how to treat essential thrombocythemia. *N Engl J Med* 2005;353: 85-6.
2. Greist A. The role of blood component removal in essential and reactive thrombocytosis. *Ther Apher* 2002;6: 36-44.
3. Schafer AI. Thrombocytosis and thrombocythemia. *Blood Rev* 2001;15: 159-66.
4. Baldwin JG, Sellers GA. Profound thrombocytosis in a patient with iron-lack anemia. *South Med J* 1989;82: 662-3.
5. Farr M, Scott DL, Constable TJ, Hawker RJ, Hawkins CF, Stuart J. Thrombocytosis of active rheumatoid disease. *Ann Rheum Dis* 1983;42: 545-9.
6. Ertenli I, Kiraz S, Ozturk MA, Haznedaroglu I, Celik I, Calguneri M. Pathologic thrombopoiesis of rheumatoid arthritis. *Rheumatol Int* 2003;23: 49-60.
7. Randi ML, Fabris F, Rossi C, Girolami A. Which tests are most useful in distinguishing between reactive thrombocytosis and the thrombocytosis of myeloproliferative disease? *Clin Lab Haematol* 1992;14: 267-8.
8. Ertenli I, Haznedaroglu IC, Kiraz S, Celik I, Calguneri M, Kirazli S. Cytokines affecting megakaryocytopoiesis in rheumatoid arthritis with thrombocytosis. *Rheumatol Int* 1996;16: 5-8.
9. Dahlqvist SR, Nilsson TK, Norberg B. Thrombocytosis in active rheumatoid arthritis. Relation to other parameters of inflammatory activity and confounding effect of automated cell counting. *Clin Rheumatol* 1988;7: 335-41.
10. Ertenli I, Kiraz S, Arici M, Haznedaroglu IC, Calguneri M, Celik I, et al. P-selectin as a circulating molecular marker in rheumatoid arthritis with thrombocytosis. *J Rheumatol* 1998; 25: 1054-8.
11. Colli S, Maderna P, Tremoli E, Colombo F, Canesi B. Platelet function in rheumatoid arthritis. *Scand J Rheumatol* 1982;11: 139-43.
12. Serio B, Accardo S, Garnerio A, Fasciolo D, Cutolo M. Anticardiolipin antibodies, free protein S levels and thrombosis: a survey in a selected population of rheumatoid arthritis patients. *Rheumatology (Oxford)* 1999;38: 675-8.
13. Straneva JE, van Besien KW, Derigs G, Hoffman R. Is interleukin 6 the physiological regulator of thrombopoiesis? *Exp Hematol* 1992;20: 47-50.
14. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;46: 1019-1.
15. Frati Munari AC, Martin Alarcon JS, Martinez-Cairo S. Thrombocytosis in juvenile rheumatoid arthritis. *Bol Med Hosp Infant Mex* 1978;35: 1109-11.
16. Serio B, Fasciolo D, Sulli A, Cutolo M. Homocysteine and antiphospholipid antibodies in rheumatoid arthritis patients: relationships with thrombotic events. *Clin Exp Rheumatol* 2001;19: 561-4.
17. Ward MM, Pyun E, Studenski S. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. *Arch Intern Med* 1996;156: 1337-44.
18. Ziakas PD, Giannouli S, Zintzaras E, Tzioufas AG, Voulgarelis M. Lupus thrombocytopenia: clinical implications and prognostic significance. *Ann Rheum Dis* 2005;64: 1366-9.
19. Afeltra A, Vadacca M, Conti L, Galluzzo S, Mitterhofer AP, Ferri GM. Thrombosis in systemic lupus erythematosus: congenital and acquired risk factors. *Arthritis Rheum* 2005;53: 452-9.
20. Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. *Ann Intern Med* 1990;112: 682-98.
21. Vianna JL, Khamashta MA, Ordi-Ros J, Font J, Cervera R. Comparison of the primary and secondary antiphospholipid syndrome: a European Multicenter Study of 114 patients. *Am J Med* 1994;96: 3-9.
22. Unikiene D, Misiuniene N. Antiphospholipid syndrome in patients with systemic connective tissue diseases. *Medicina (Kaunas)* 2003;39: 454-4.
23. Aksu K, Turgan N, Oksel F, Keser G, Ozmen D, Kitapcioğlu G, et al. Hyperhomocysteinemia in Behçet's disease. *Rheumatology (Oxford)* 2001;40: 687-90.