Thrombocytosis in rheumatoid arthritis

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Hutchinson, R. M., Davis, P., and Jayson, M. I. V. (1976). *Annals of the Rheumatic Diseases*, 35, 138–142. **Thrombocytosis in rheumatoid arthritis.** Of 75 patients with rheumatoid arthritis, 39 had a thrombocytosis and 36 a normal platelet count. A highly significant relationship existed between the platelet count and disease severity and an inverse correlation with level of haemoglobin. An association appeared to exist between thrombocytosis and extra-articular manifestations of rheumatoid disease. By ⁷⁵Selenomethionine labelling platelet and fibrinogen survival and turnover were determined. In 3 rheumatoid patients with thrombocytosis platelet survival was decreased and turnover increased. In these and a further rheumatoid patient with a normal platelet count there was reduced fibrinogen survival and increased fibrinogen turnover, and in addition excess fibrin degradation products were detected. The results suggest that thrombocytosis accompanies the more severe cases of rheumatoid disease and is due to a compensatory increase in platelet production associated with active intravascular coagulation.

In a wide series of observations platelet counts in healthy individuals lie within the range $150\text{--}450 \times 10^9/\text{l}$ ($150\,000\text{--}450\,000/\text{mm}^3$). Selroos (1972) noted raised platelet counts in one-third of patients with rheumatoid arthritis (RA) and a direct relationship between thrombocytosis and disease activity. He also observed that raised platelet counts correlated with anaemia, sideropenia, leucocytosis, and rheumatoid factor. A possible relationship to amyloid was investigated but discounted later (Selroos and Pettersson, 1973a).

We have similarly noted thrombocytosis in patients with severe RA. Platelet counts in some were $> 1000 \times 10^9/\text{l}$ (1 million/ mm^3), falling to normal in some cases when the disease was controlled by drug therapy. However, in one case thrombocytosis appeared on starting gold therapy, while in another thrombocytosis developed on starting penicillamine treatment.

This study attempts to assess the significance of thrombocytosis in RA, and determine whether platelet counts correlate with parameters of disease activity. Particular attention was paid to any associations with drug therapy. In 4 patients platelet survival and turnover were investigated using ⁷⁵Selenomethionine, an isotope which cohort-labels fibrinogen and platelet precursors.

Methods and materials

Seventy-five patients with classical or definite RA (Ropes, and others, 1959) were studied and comparisons were drawn between those with normal and those with raised platelet counts. The activity and severity of disease were assessed by duration of involvement, presence of extra-articular manifestations, morning stiffness, grip strength, and joint score. Patients were then graded as inactive 0, mildly active 1, active 2, and very active 3. Drug therapy at the time of the platelet count was noted.

Peripheral blood haemoglobin, white cell count and differential were estimated by conventional methods. Platelets were counted by a Coulter thrombocytometer. Standard data and control information from our laboratory suggest the upper limit of normal to be 450×10^9 platelets/ l ($450\,000/\text{mm}^3$). Plasma viscosity was determined instead of the erythrocyte sedimentation rate as it is independent of the haematocrit. Serological investigations included rheumatoid factor by Rose-Waaler and latex techniques, and antinuclear antibodies. Serum immunoglobulins and complement levels were estimated in some cases. As blood loss from the intestine is common among patients treated with anti-inflammatory drugs, the stools were examined for occult blood.

Platelet and fibrinogen kinetics were studied in 4 patients who had given full and informed consent. Three had clinically severe RA with thrombocytosis, and one active RA but a normal platelet count. $200\ \mu\text{Ci}$ ⁷⁵Selenomethionine were injected and the radioactivity of platelet

buttons and fibrin were estimated over the next 14 days (Brodsky and others, 1970, 1972a, b). Surface counting was conducted over the heart, spleen, liver, sacrum, and clinically active and quiescent joints.

HAEMATOLOGY AND SEVERITY OF DISEASE

Table I indicates the platelet counts of the patients according to haemoglobin and disease activity. The platelet counts of 34 patients were normal. 2 patients were notably thrombocytopenic at $85 \times 10^9/l$ ($85000/mm^3$), and 39 had counts above $450 \times 10^9/l$ ($450000/mm^3$). There was a highly significant inverse relationship between the platelet count and haemoglobin concentration ($P < 0.001$) and a direct correlation between platelet levels and severity of disease ($P < 0.001$).

Extra-articular manifestations of rheumatoid disease tended to occur in the rheumatoid patients with thrombocytosis. The numbers of patients with these manifestations and their mean platelet counts are shown in Table II. Cutaneous vasculitis showed a significant relationship with thrombocytosis ($P < 0.05$). In none of the 36 patients with a normal platelet count were lymphadenopathy, pulmonary interstitial fibrosis, Sjögren's syndrome, or peripheral neuropathy found. When present the platelet count was raised but the numbers of cases were too small to draw statistical conclusions. Though nodules were more common in the patients with high platelet counts, the association was not significant ($P > 0.05$).

Serological data are given in Table III. The mean plasma viscosity was significantly increased in the patients with thrombocytosis ($P < 0.01$). Titres of rheumatoid factor of 1:64 or greater occurred more often in those with thrombocytosis, and all 5 patients with a positive antinuclear factor fell in this group. There were insufficient numbers to draw any conclusions as regards complement activation, though depressed levels were found in some of those with raised platelet counts.

Although more patients with thrombocytosis had low serum iron levels, the difference was not statistically significant (Table IV). Six patients had persistently strongly positive occult bloods, but in only one of these was the platelet count raised above normal.

TREATMENT AND PLATELET COUNT

Expressed as a percentage of 75 patients, the following drugs were used: aspirin (23%), phenylbutazone (6.6%), indomethacin (44%), gold (59%), D-penicillamine (22.5%), steroids (41.5%).

There was no meaningful relation between therapy and thrombocytosis. Aspirin ingestion did not correlate with raised platelet counts. This drug specifically inhibits the release of adenosine diphosphate from within the platelet, and thus blocks secondary aggregation (Evans and others, 1968). It would thus prevent platelet thrombus formation rather than enhance it. Penicillamine and steroids were prescribed more frequently in patients with thrombo-

Table I Relationship between platelet count, haemoglobin, and disease activity in 75 patients with RA

Platelet count* ($\times 10^9/l$)	No. of patients	Mean Hb (g/dl)	Disease activity grade			
			0	1	2	3
9-149	2	12.6	0	2(100%)	0	0
150-449	34	12.45 $\pm$ 2.51	2(6%)	15(44%)	15(44%)	2(6%)
450-649	17	11.92 $\pm$ 2.17	0	0	16(94%)	1(6%)
650-999	14	11.49 $\pm$ 2.92	2(14%)	0	3(22%)	9(64%)
1000+	8	10.42 $\pm$ 3.68	1(12.5%)	0	1(12.5%)	6(75%)
Significance against platelet count		P < 0.001	P < 0.001			

* Conversion: SI to Traditional Units—Platelets: $150 \times 10^9/l \approx 150000/mm^3$.

Table II Relationship between platelet count and extra-articular manifestations of rheumatoid arthritis

Extra-articular manifestations	Mean of platelet count ($\times 10^9/l$)	No. of patients with platelet count		Significance
		>450 $\times 10^9/l$	<450 $\times 10^9/l$	
Cutaneous vasculitis	610	8	1	P < 0.05
Lymphadenopathy	600	5	0	NS
Pulmonary				
Pleurisy	320	0	1	
Interstitial fibrosis	1110	2	0	
Sjögren's syndrome	600	2	0	
Amyloid	570	1	1	
Peripheral neuropathy	1000	1	0	
Nodules	702	13	6	P > 0.05
Total no. of rheumatoid patients		39	36	

Table III *Relationship between serological data and platelet count*

Serological parameter	Platelet count		Significance
	$>450 \times 10^9/l$	$<450 \times 10^9/l$	
Mean plasma viscosity	2.00 ± 0.23	1.89 ± 0.16	$P < 0.01$
Rheumatoid factor titre			
$\leq 1:16$	2/27 (7.5%)	4/19 (21.1%)	NS
$1:32$	4/27 (14.8%)	0/19 (0%)	
$\geq 1:64$	21/27 (77.7%)	15/19 (78.9%)	
Antinuclear antibody negative	16/21 (76%)	5/5 (100%)	NS
Antinuclear antibody positive	5/21 (24%)	0/5 (0%)	
C3 complement level			
<0.8 g/l	4/4 (100%)	0/2 (0%)	Insufficient numbers
(normal 0.8–1.4 g/l)			

Table IV *Relationship between haemoglobin, serum iron, and platelet counts in rheumatoid arthritis*

Platelet count	$>450 \times 10^9/l$	$<450 \times 10^9/l$	Significance against platelet count
Mean Hb (g/dl)	11.27 ± 0.77	12.47 ± 0.10	$P < 0.001$
Serum iron < 12 $\mu\text{mol/l}$	23/24 (95%)	6/9 (67%)	$P > 0.05$
Serum iron > 12 $\mu\text{mol/l}$	1/24 (4%)	3/9 (33%)	$P > 0.05$

cytosis than in those without, but these subjects usually had more active disease. In 3 patients with extra-articular manifestations and thrombocytosis, high-dose prednisone therapy produced a fall in platelet counts to normal at the same time as remissions of disease activity.

RADIOISOTOPE STUDIES

The results are shown in Table V and are compared with normal data obtained by ourselves and others elsewhere (Brodsky and others, 1970, 1972a, b). In the 3 patients with thrombocytosis there was a reduced platelet survival and a raised platelet turnover. Serum fibrinogens were raised and there were excess fibrin degradation products, reduced fibrinogen survivals, and increased fibrinogen turnovers, most marked in the patient with the highest platelet count. Even the rheumatoid patient with a normal platelet count showed some evidence of increased fibrinogen turnover.

In 2 of the 3 patients with thrombocytosis there was a persistent increase in uptake of $^{75}\text{Selenomethionine}$ in active joints relative to quiescent joints, but it was impossible to ascertain whether this was due to platelet or fibrin deposition or both.

Discussion

Our results confirm that thrombocytosis is often seen in patients with active RA, and that the height of the platelet count correlates directly with the degree of disease activity and inversely with the haemoglobin level. No significant relationship between thrombocytosis and sideropenia was found. Plasma viscosity was significantly higher in those patients with thrombocytosis. A significant correlation existed be-

tween thrombocytosis and cutaneous vasculitis, and other extra-articular manifestations of rheumatoid disease were more common in those with a raised platelet count. Further evidence that thrombocytosis is related to disease activity was seen in 3 patients by a fall in platelet levels to normal when the disease was suppressed by steroid therapy.

There are several possible explanations for these changes in platelet count. Thrombocytosis is a feature of both acute and chronic blood loss and in RA could be due to the chronic anaemia characteristic of active disease (Mowat and Hothersall, 1968). Although an inverse correlation was found between high platelet counts and low haemoglobin, thrombocytosis was not associated with gastrointestinal blood loss. However, Choie Sun, Simone, and Jackson (1974) have shown that both chronic anaemia and iron deprivation of the normoblast may play some part in the production of thrombocytosis. Platelet homeostasis is controlled by a humoral regulatory factor, thrombopoietin, which influences megakaryocyte size, ploidy, number, and maturation rate (Ebbe, 1974). It is thought that thrombopoietin may be related chemically to erythropoietin as chronically anaemic patients with persistent reticulocytosis and increased erythropoietin levels have higher than normal platelet counts (Pitney, 1972). Similarly, if erythropoietin levels are increased in anaemic rheumatoid patients, then thrombocytosis could result.

Alternatively, increased platelet production may be induced by increased platelet destruction or consumption. Garg, Amorosi, and Karparkin (1971)

Table V Results of platelet and fibrinogen turnover and survival using a ⁷⁵Selenomethionine label

Case no./sex	Mean platelet count (×10 ⁹ /l)	Platelet survival (d)	Platelet turnover (×10 ⁹ /l per d)	Fibrinogen (mg/100 ml)	Fibrinogen (g/l)	Fibrin degradation products (μg/ml)	Fibrinogen survival (d)	Fibrinogen turnover (mg/ml per day)
1 F	340	7·0	50	3·5 (350)		10-40	5·0	0·70
2 F	1080	5·8	186	6·0 (600)		160	2·7	2·22
3 F	1050	5·0	210	5·2 (520)		40	6·8	0·76
4 M	500	5·8	87	5·9 (590)		40	5·8	1·02
Control data	450-515	0·11-0·4	15-22	2-4 (200-400)		>10	5·6-5·9	0·33-0·49

have shown compensated thrombocytolytic states in which shortened platelet survivals were accompanied by increases in megakaryocyte maturation. Although Selroos (1972) found normal active megakaryocytosis in the bone marrow of his RA patients, our results suggest that in RA increased platelet counts may be a compensatory overproduction secondary to increased platelet consumption. Platelet turnover was considerably increased in the patients with thrombocytosis and platelet half-life decreased. The results paralleled the findings seen with fibrinogen, and in 3 cases we have found fibrin degradation products in the serum as previously reported by Bennett, Eddie-

Quarthey, and Holt (1972). The data suggest active intravascular coagulation with compensatory thrombocytosis. Selroos and others (1973b, c) reached similar conclusions with respect to thrombocytosis in rabbits after fibrinogen-induced arthritis and with prolonged antigenic stimulation producing amyloidosis.

Although the aetiology of RA is unknown, studies on its pathogenesis suggest that it is an extravascular immune complex disease (Zvaifler, 1974). Thrombocytosis may be related to the immunological responses in RA, being secondary to microthromboses within the chronically inflamed rheumatoid synovium.

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