Thrombocytosis of active rheumatoid disease

M. FARR,¹ D. L. SCOTT,¹ T. J. CONSTABLE,¹ R. J. HAWKER,²
C. F. HAWKINS,¹ AND J. STUART³

From the ¹Department of Investigative Pathology, Rheumatism Research Wing, ²Department of Surgery, and ³Department of Haematology, the University of Birmingham

SUMMARY Two cross-sectional and one longitudinal study of patients with rheumatoid arthritis showed that platelet number correlated with both clinical and laboratory parameters of disease activity, including erythrocyte sedimentation rate, zeta sedimentation ratio, viscosity of plasma and blood, white cell count, liver enzymes, rheumatoid factor, and several acute-phase proteins. There was also an inverse relationship between platelet number and the haemoglobin and serum albumin levels. ¹¹¹Indium-labelled platelet survival was reduced in 4 patients with active rheumatoid arthritis despite a raised platelet count, with labelled platelets being localised to inflamed joints in the 2 patients studied. Platelet aggregation was normal. We suggest that the raised platelet count of active rheumatoid arthritis may be a useful index of disease activity and may represent a bone marrow stress (syndrome) response to shortened platelet survival, with platelet sequestration occurring in areas of synovial inflammation.

Platelet counts are usually monitored in patients with rheumatoid arthritis (RA) to detect adverse reactions to drugs such as gold and penicillamine, but the platelet may also be directly involved in the disease itself. In 1972 Selroos¹ noted that many patients with RA had a high platelet count, and Hutchinson *et al.*² subsequently showed a relationship between platelet number and some indices of disease activity. Many haematological, immunological, and biochemical parameters are abnormal in RA and are related to disease activity,^{3–11} but none provide a widely accepted method of assessment in RA. It would be of considerable value to know whether the platelet count provides a useful index of disease activity and why thrombocytosis should occur. We have therefore investigated the relationship of platelet count to clinical and laboratory tests of disease activity in RA, and have also investigated platelet survival, aggregation, and localisation in affected joints.

Patients and methods

PATIENTS

All patients with RA had classical or definite disease by the criteria of the American Rheumatism Associa-

tion¹² and were of similar age and sex in each study. Four studies were carried out—2 cross-sectional rheumatoid studies, 1 longitudinal rheumatoid study, and 1 longitudinal Crohn's disease study.

The first cross-sectional study (130 patients; average age 58 years; 94 females) examined the relationship between the platelet count and the following indices of disease activity: total articular index, erythrocyte sedimentation rate (ESR), haemoglobin level, white cell count (WCC), rheumatoid factor level, and serum alkaline phosphatase, 5-nucleotidase, albumin, and immunoglobulins.

The second cross-sectional study (131 patients; average age 56 years; 90 females) examined the platelet count in relation to the ESR, zeta sedimentation ratio, plasma and blood viscosity, acute-phase proteins (C-reactive protein, haptoglobin, orosomucoid, α_1 antitrypsin, fibrinogen), α_1 globulin, α_2 globulin, β and γ globulins and total serum proteins.

In the third rheumatoid study of 15 patients followed up for 3–4 years (25–40 visits), we followed the platelet count in relation to such changes in disease activity as total articular index, rheumatoid factor level, serum alkaline phosphatase and aspartate transferase levels, serum albumin, ESR, haemoglobin, C-reactive protein, and haptoglobin.

In the longitudinal study of Crohn's disease we followed up 20 patients with radiological and histological evidence of disease during a similar 4-year

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Correspondence to Dr M. Farr, Department of Investigative Pathology, Rheumatism Research Wing, University of Birmingham, Birmingham B15 2TJ.

period of comparative purposes to determine the relationship between platelet count and ESR.

In addition platelet survival was estimated in 8 patients with RA, 4 patients with inflammatory bowel disease (3 Crohn's disease, 1 ulcerative colitis), and 31 healthy controls. In 2 of the patients with RA (with some inflamed and some quiescent joints) the localisation of ¹¹¹indium-labelled platelets was determined.

Methods

Characterisation of RA. A full clinical examination was carried out and overall disease activity was assessed clinically by calculating the total articular index. On examination of each joint an arbitrary scale of 3 grades + to +++ was given for each of the following: pain on movement, stiffness, swelling, heat, and tenderness of each joint. The total articular index was calculated by a summation of these grades in all the joints.

Haemoglobin level and white cell counts were determined with the Coulter counter model S (Coulter Electronics Ltd, Luton). Serum albumin, alkaline phosphatase, 5-nucleotidase, rheumatoid factor (SCAT titre), and immunoglobulins were determined as previously reported.⁵ The ESR, zeta sedimentation ratio, plasma and blood viscosity, and the acute-phase proteins were measured as described by Kenny *et al.*¹³

Platelet studies. Platelet counts were measured with the Coulter Thrombofuge-Thrombocounter

System (Coulter Electronics Ltd, Luton). The coefficient of variation for platelet values of more than $100 \times 10^9/l$ was 3.5% ($n=20$) and, for values below this, 8% ($n=20$).

Platelet survival was measured by ¹¹¹indium (Amersham International Ltd) as previously described by Hawker *et al.*¹⁴ Blood was removed aseptically from 8 rheumatoid patients, platelets were separated and labelled with ¹¹¹indium, and platelet survival was calculated from blood samples taken over a 10-day period. Platelet localisation was determined 24 hours after injection by means of a large field-of-view gamma camera (Searle).

Platelet aggregation with adenosine diphosphate (ADP) was determined with a Payton aggregometer, as described by Born.¹⁵

Statistical methods. Correlation coefficients between the platelet counts and parameters of disease activity were carried out by Pearson's correlation coefficient (r value).

Results

CROSS-SECTIONAL STUDIES

The first cross-sectional study showed a statistically significant correlation between the platelet count and 8 of the 9 indices of disease activity (Table 1). Platelet counts were higher in patients with more active disease. This relationship was present in both males and females, in patients receiving gold and penicillamine, and in those on nonsteroidal anti-inflammatory drugs alone. The second cross-sectional study showed a statistically significant correlation between the platelet count and 11 of the 14 laboratory tests studied (Table 2).

LONGITUDINAL STUDIES

Platelet counts were related to the activity of RA in most patients followed up longitudinally. In 9 of the 15 patients they correlated with the ESR ($r=0.36$ or more; $p<0.05$) and they showed a similar correlation with the C-reactive protein level and other indices of activity. An example is shown in Fig. 1. However, this relationship was not specific for RA, since 5 of the 20 patients with Crohn's disease, who were followed up longitudinally over a similar time period, also showed a correlation between platelet count and erythrocyte sedimentation rate ($r=0.36$ or more; $p<0.05$).

PLATELET SURVIVAL, LOCALISATION, AND AGGREGATION

The studies with ¹¹¹indium-labelled platelets showed decreased survival in the 4 most severely affected of

Table 1 Correlation between platelet count and tests of disease activity in the first cross-sectional study of 130 patients with RA

Parameters	n	r	p
Erythrocyte sedimentation rate (mm/h)	130	0.407	<0.01
Haemoglobin (g/dl)	130	-0.405	<0.01
White cell count ($\times 10^9/l$)	130	0.406	<0.01
Total articular index	116	0.385	<0.01
Rheumatoid factor (sheep cell agglutination titre)	126	0.24	<0.02
Serum alkaline phosphatase (KA/l)	130	0.24	<0.02
Serum albumin (g/l)	130	-0.397	<0.01
Serum 5-nucleotidase (IU/l)	113	0.25	<0.02
Total serum immunoglobulins (g/l)	126	0.159	NS

KA = King-Armstrong units.

Table 2 Correlation between platelet count and laboratory tests in the second cross-sectional study of 131 patients with RA.

Parameter	n	r	p
Erythrocyte sedimentation rate (mm/h)	131	0.61	<0.001
Zeta sedimentation ratio	131	0.31	<0.01
Plasma viscosity (25°C)	128	0.53	<0.001
Whole-blood viscosity (27°C)	128	0.46	<0.001
Serum C-reactive protein (mg/l)	121	0.71	<0.001
Serum orosomucoid (g/l)	131	0.56	<0.001
Serum alpha-1-antitrypsin (g/l)	131	0.41	<0.001
Serum haptoglobin (g/l)	130	0.62	<0.001
Serum fibrinogen (g/l)	126	0.51	<0.001
Serum alpha-1-globulins (g/l)	131	0.587	<0.001
Serum alpha-2-globulins (g/l)	131	0.485	<0.001
Serum beta-globulins (g/l)	131	0.167	NS
Serum gamma-globulins (g/l)	131	0.17	NS
Total serum proteins (g/l)	131	0.027	NS

Fig. 1 Relationship between platelet count, C-reactive protein level, and ESR during a 4-year period in a patient with RA.

the 8 with RA (Fig. 2), and the survival curve showed an initial rapid fall of platelets with a subsequent curvilinear pattern, in contrast to the normal linear relationship, suggesting that platelets were being actively removed. There was, however, no correlation between shortened platelet survival and a low platelet count. Indeed the 4 patients with shortened survival showed platelet counts of 800, 760, 690, and $1000 \times 10^9/l$ (reference range $150-450 \times 10^9/l$).

Platelets were localised in regions of actively inflamed joints but not in inactive ones in the 2 patients in whom gamma-camera imaging was performed 24 hours after the injection of labelled platelets (Fig. 3). Splenic uptake of labelled platelets

Fig. 2 Platelet survival in 8 patients with RA, 4 with inflammatory bowel disease, 3 Crohn's disease, 1 ulcerative colitis (UC), and 31 healthy controls. The broken lines represent mean $\pm$ 2 SD for the controls.

Fig. 3 Platelet localisation in active rheumatoid synovitis of the knees by means of ^{111}In indium labelled platelets and demonstrated by gamma-camera imaging. Activity is prominent in both suprapatellar pouches (arrowed) and in the left infrapatellar pouch.

appeared normal in both patients. Platelet aggregation with ADP was normal in RA in all 9 cases studied with the exception of one patient with spontaneous aggregation, the cause of which could not be determined.

Discussion

Platelet counts were higher in association with active disease, and this provides the probable explanation for previous reports of thrombocytosis in RA.^{1,2} Our results with a large number of patients in 2 cross-sectional studies show that a close relationship exists between the platelet count and clinical, biochemical, haematological, and immunological assessments of disease activity in patients with RA. The highest correlations were with the ESR and C-reactive protein level, and this is strengthened by the temporal relationship between these 3 measurements during serial studies in individual patients. Although the erythrocyte sedimentation rate, plasma viscosity, and C-reactive protein level are already accepted as useful indicators of disease activity in RA,⁵ the platelet count, which will already be available in most

patients receiving second-line drugs, may provide additional information about the activity of RA and its response to treatment.

Thrombocytosis occurs in many inflammatory disorders, including inflammatory bowel disease^{16,17} and in a number of arthropathies in addition to RA.¹⁸ Furthermore, as we showed, the platelet count is related to disease activity in some patients with Crohn's disease. Thus the relationship of the platelet count to disease activity is not a specific feature of RA and may be a nonspecific bone marrow response to disease¹⁹ similar to the acute-phase protein response of the liver.²⁰

In active RA we have shown that a high platelet count may occur in parallel with decreased platelet survival, as determined by ^{111}In indium-labelled platelets. A similar result was reported by Hutchinson *et al.*² using a different labelling technique. The curvilinear survival of labelled platelets in our patients with active RA suggests that platelets may be removed from the circulation as part of the disease process; this is supported by our finding of localisation in inflamed joints. Thus the increase in platelet count in our patients probably represents marrow overproduction in response to increased consumption. Decreased platelet survival was not seen in the patients with inflammatory bowel disease, and so platelet removal as part of the disease process may be specific for RA.

There are a number of possible alternative but less likely explanations for these changes in platelet counts in relation to the disease activity of RA. Thrombocytosis is a feature of chronic blood loss and could be secondary to analgesic-induced occult gastrointestinal bleeding, particularly in patients with active disease. In addition in RA thrombocytosis may be due to the chronic anaemia characteristic of active disease. However, Hutchinson *et al.*² found that, although there was an inverse correlation between high platelet counts and low haemoglobin, thrombocytosis was not associated with gastrointestinal blood loss. Iron metabolism is also abnormal in RA,²¹ and iron deprivation may act as a marrow stimulant. Reizenstein¹⁹ introduced the concept of the haematological stress syndrome in patients with chronic systemic disease, and the disease-related increase in platelet count in RA can be considered as an example of this.

The mechanisms leading to platelet deposition in inflamed joints requires further study. Zvaifler²² has suggested that RA is an extravascular immune-complex disease; platelets may be involved in this phenomenon, either as a component of microthrombi within inflamed synovial membrane, or by immune-complex damage and premature phagocytosis in hyperactive reticuloendothelial cells

of the synovial membrane. Whatever the explanation, further studies of platelet turnover, and of the relationship between platelet level and disease activity, in rheumatoid arthritis are indicated.

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