Thrombokinetis in giant cell arteritis, with special reference to corticosteroid therapy

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SUMMARY Duplicate platelet survival studies were carried out on 8 patients with giant cell arteritis (GCA), once before the institution of any therapy, and the second time when they were in a completely asymptomatic phase after having received corticosteroid treatment. The time interval between the studies ranged between 5 and 14 months. In the first study the mean peripheral platelet count was $486 \pm 25 \times 10^9/l$ and in the second $326 \pm 25 \times 10^9/l$. The difference between the means was highly significant ($P < 0.001$). The mean life-span of the platelets was normal in the duplicate experiments (6.7 ± 0.3 and 7.3 ± 0.4 days, respectively). Platelet production rate was significantly ($P < 0.001$) raised in the first experiment but became normal in response to corticosteroid therapy. It is concluded that the thrombocytosis seen in GCA is reactive to the inflammation present in this disease, and it seems reasonable to assume that the reduction in the peripheral platelet count which occurs in response to corticosteroid therapy accurately reflects the clinical improvement of the patient.

Thrombocytosis is frequently present in patients with untreated giant cell arteritis (GCA) (Olhagen, 1963; Hamrin, 1972; Malmvall and Bengtsson, 1978). No information is available on platelet production and platelet survival in this disease. It is well recognised that corticosteroid treatment is highly effective in GCA. However, its effects on the above mentioned parameters are unknown. In the present report we therefore provide data on platelet kinetics in a group of patients with GCA before and after the institution of corticosteroid therapy.

Material and methods

Eight consecutive patients (2 males and 6 females) with GCA aged 56-80 (mean 69) years were selected for study (Table 1). Six patients had histologically verified arteritis on temporal biopsies, and the remaining 2 were included according to the criteria for the diagnosis of GCA as recently described by Malmvall and Bengtsson (1978). Two of the patients had the clinical picture of temporal arteritis combined with the polymyalgia rheumatica syndrome, 2 had polymyalgia rheumatica, 2 had only general symptoms, and 2 had symptoms of localised temporal arteritis.

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Table 1 Eight patients with GCA in whom duplicate platelet survival studies were carried out

Patients	Age (years)	Sex	Time interval between the 2 platelet survival studies (months)	Maintenance oral dose of prednisolone during the second platelet survival study (mg per day)
1	59	F	5	10
2	71	F	7	10
3	72	F	6	10
4	69	M	6	7.5
5	72	F	6	2.5
6	56	M	7	12.5
7	76	F	14	10
8	80	F	12	10
Mean	69		8	

Platelet survival studies were carried out twice, once before the institution of treatment and the second time when the patients were in a completely asymptomatic phase of the disease after corticosteroid therapy. The time interval between the two studies ranged between 5 and 14 (mean 8) months. During the second platelet survival study the patients received a maintenance dose of 2.5-12.5 mg prednisolone orally per day. The individual data for the patients are given in Table 1. The control group

consisted of 8 healthy volunteers with a mean age of 56 years.

All experiments were carried out with autologous platelets. The labelling technique has been described elsewhere in detail (Kutti and Weinfeld, 1971; Kutti and Safai-Kutti, 1975). Only a brief summary of the procedure is given below.

Whole blood (approximately 250 ml) was collected by gravity in two plastic bags each containing 20 ml of acid ACD (Aster and Jandl, 1964). After centrifugation of the blood (at 260 *g*) the platelet-rich plasma (PRP) was transferred to another bag. PRP was then centrifuged (at 1600 *g*) to provide a platelet button, which was resuspended in 10 ml of platelet-poor plasma (PPP) and incubated with 400 μ Ci of ^{51}Cr in the form of sodium chromate. Thereafter the incubated platelets were washed with PPP and finally injected into the patient. Blood samples were obtained 15, 30, 60, and 120 min after injection of labelled platelets. Subsequent samples were drawn at 24 h intervals during a period of 8 days. All blood sampling was in duplicate, and platelet-bound radioactivity (PBR) was extracted from 9 ml of venous blood as previously reported (Kutti and Weinfeld, 1971).

Platelet recovery, that is the percentage of infused PBR remaining in the peripheral blood shortly after infusion, was calculated from: $\text{PBR per ml of blood} \times \text{BV} \times 100/\text{PBR infused}$. BV denotes the blood volume and was calculated from height and weight measurements (Nadler *et al.*, 1962).

Platelet mean life-span (MLS) was obtained by extrapolating the initial slope of the survival curve to the time axis (Mills, 1946; Dornhorst, 1951). This was achieved by fitting an arbitrary mathematical function:

$$Y(x) = Y(0) \left(1 - \frac{x}{T} - A(1 - e^{-\alpha x}) \right) \dots \begin{cases} 0 < T \\ 0 \leq A \\ 0 < \alpha \end{cases}$$

to the experimental data by the least-squares method using a high-speed digital computer. A weight factor of 1 was applied to every experimental point. The mean of activity and time of day-zero 60 and 120 min samples was taken as the first experimental point, and subsequent data were used until about 20% of the initial activity was reached. $Y(x)$ represents PBR at time x after infusion. From the parameters $Y(0)$, T , A , and α , $Y'(0)$ was calculated, and platelet MLS is given by $-Y(0)/Y'(0)$.

On the assumption of a stationary state **platelet production rate (P)** equals platelet destruction rate (**D**) and is given by N/MLS , where N is the total number of circulating platelets. Consequently, N includes the platelets residing in the splenic pool and can be calculated from: $\text{peripheral platelet count} \times \text{BV} \times 90\%/\text{recovery \%}$, where the term

$90\%/\text{recovery \%}$ is the correction for splenic pooling of platelets (Kutti and Weinfeld, 1971).

The enumeration of platelets was carried out on venous blood by means of phase microscopy (Brecher *et al.*, 1953). The platelet counts reported are the values obtained on day zero.

Standard statistical methods were used. Unless otherwise stated mean values $\pm$ standard error (SE) of the mean are reported. Within the group of GCA the statistical analyses were made with Student's *t* test and calculated on differences between matched pairs. The difference between means was considered statistically significant if $P < 0.05$.

Results

Peripheral platelet count. The mean peripheral platelet count at the first experiment was $486 \pm 25 \times 10^9/\text{l}$. The corresponding mean at the second study was $326 \pm 25 \times 10^9/\text{l}$, and the difference between means was highly significant ($P < 0.001$) (Tables 2 and 3). In every patient the peripheral platelet count decreased after prednisolone therapy.

Table 2 Results of platelet survival studies in 8 untreated patients with GCA

Patients	Peripheral platelet count ($\times 10^9/\text{l}$)	Platelet recovery %	MLS (days)	N ($\times 10^{10}$)	Platelet production rate/day ($\times 10^{10}$)
1	435	72	6.4	207	32
2	502	77	5.2	211	41
3	415	75	6.1	189	31
4	532	73	7.4	308	42
5	568	53	6.3	338	54
6	388	73	7.0	225	32
7	577	82	6.9	215	31
8	471	77	8.2	187	23
Mean	486	73	6.7	235	36
SD	71	9	0.9	18	10
SE	25	3	0.3	6	3

MLS=platelet mean life-span. N=total number of circulating platelets

Table 3 Results of platelet survival studies in 8 patients with GCA after prednisolone therapy

Patients	Peripheral platelet count ($\times 10^9/\text{l}$)	Platelet recovery (%)	MLS (days)	N ($\times 10^{10}$)	Platelet production rate/day ($\times 10^{10}$)
1	298	87	8.2	123	15
2	339	87	6.8	130	19
3	189	89	7.2	78	11
4	334	100	7.2	138	19
5	420	64	7.0	201	29
6	300	81	8.9	167	19
7	397	80	5.4	161	30
8	330	99	7.8	102	13
Mean	326	86	7.3	138	19
SD	70	11	1.0	12	7
SE	25	4	0.4	4	2

MLS=platelet mean life-span. N=total number of circulating platelets.

Platelet recovery. Fig. 1 shows the circulating PBR 2 h after infusion in the duplicate experiments. It is seen that the values for platelet recovery in the second experiment were considerably higher than in the first, and the difference was statistically significant ($P < 0.005$).

The individual values for platelet recovery given in Tables 2 and 3 denote the highest value obtained at 60 or 120 min. The mean platelet recovery in the control group was $73 \pm 4\%$.

Platelet mean life-span (Tables 2 and 3). The average platelet MLS before treatment was 6.7 ± 0.3 days. After corticosteroid therapy the corresponding value was slightly higher (7.3 ± 0.4), but there was no statistical difference between the means. The mean platelet MLS in the control group was 6.6 ± 0.5 (range 4.5–8.7 days).

Platelet production rate (Tables 2 and 3). In the first study the mean for P was $36 \pm 3 \times 10^{10}$ platelets per day. In response to prednisolone therapy in every subject there was a fall in P. The mean for P at the second study ($19 \pm 2 \times 10^{10}$) was significantly lower ($P < 0.001$) and did not differ from the control mean ($21 \pm 2 \times 10^{10}$).

Discussion

In this study the raised values for the peripheral platelet counts in untreated patients with GCA were explained by increased platelet production. Pred-

Fig. 1 Initial platelet recovery in 8 patients with GCA in whom duplicate platelet survival studies were performed. In the first study (○—○) the patients received no therapy. In the second study (●—●) the patients were on prednisolone therapy. The symbols denote mean values $\pm$ SE.

nisolone treatment significantly reduced the peripheral platelet concentration. Platelet MLS was shown to be normal in untreated patients and was unaffected by corticosteroids.

It is generally accepted that disorders associated with thrombocytosis may be designated as either *reactive* or *autonomous* (Harker and Finch, 1969). *Reactive thrombocytosis* may occur with, for example, inflammation, iron deficiency, or neoplasia not arising from haemopoietic tissue (Harker and Finch, 1969). *Autonomous thrombocytosis* on the other hand is the term applied to an increased peripheral platelet count associated with neoplastic proliferation of the megakaryocytes as characteristically seen in the so-called myeloproliferative disorders, for example, primary thrombocythaemia, polycythaemia vera, myelofibrosis with myeloid metaplasia, and chronic granulocytic leukaemia (Harker and Finch, 1969; Kutti and Weinfeld, 1971; Kutti *et al.*, 1973; Weinfeld *et al.*, 1975). Hence, in accordance with the above findings the thrombocytosis seen in GCA should be regarded as reactive to the inflammation present in this disease.

Before the institution of therapy P was about 1.7 times higher than in the controls. After corticosteroid treatment, when the GCA patients were studied in an asymptomatic phase, P was shown to have become normal. This depression of P was reflected by the overall lowering in the peripheral platelet concentration. It therefore seems that the reduction in the platelet count which occurs in response to corticosteroid therapy reflects clinical improvement, as do other laboratory tests such as the ESR and levels of fibrinogen and haptoglobin.

As shown in Fig. 1, the values for platelet recovery, an indirect measure of the size of the exchangeable splenic platelet pool (ESPP), were significantly raised in the second experiment. This is an interesting observation, but it is not easily explained. It is tempting to speculate that corticosteroid therapy affects the magnitude of the ESPP. On the other hand the possibility cannot be excluded that the disorder itself, despite corticosteroid therapy, compromises the splenic microcirculation, so that the ESPP is reduced.

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