LETTERS TO THE EDITOR

Subungual splinter haemorrhages: A new sign of the antiphospholipid coagulopathy?

Sir: We recently reported two patients with valve lesions and transient ischaemic attacks, including amaurosis fugax, both of whom showed other features associated with the 'antiphospholipid syndrome'.¹ One of these patients, in addition to clubbing, showed florid subungual splinter haemorrhages with no definite evidence for infective endocarditis. Treatment of culture negative infective endocarditis in addition to anticoagulation, nevertheless, resulted in clinical improvement.

A recent paper has drawn attention to the presence of subungual splinter haemorrhages in four patients with amaurosis fugax and antiphospholipid antibodies,² and a similar patient with amaurosis fugax, who was also found to have aortic incompetence, was reported by Kleiner *et al.*³

We have recently encountered two further patients with splinter haemorrhages and antiphospholipid antibodies. The first also developed splinter haemorrhages in association with amaurosis fugax in the absence of valve lesions or vasculitis. The patient, a 43 year old white woman, suffered a right sided cerebral thrombosis in August 1988. This had been preceded by seven months of amaurosis fugax accompanied by subungual splinter haemorrhages. These episodes lasted for approximately 20 minutes at a time, and affected the vision of the left eye predominantly. After discharge from hospital she continued to have episodes of amaurosis fugax accompanied by splinter haemorrhages despite the administration of salicylates (aspirin 300 mg daily).

She had had one spontaneous abortion during the first trimester some 10 years previously. There was no family history of other thrombotic events, nor was she thrombocytopenic. She was referred to St Thomas's Hospital in November 1988 because of the discovery of antibodies to cardiolipin. There was no evidence clinically of systemic lupus erythematosus; she showed a positive test for antinuclear antibodies 1/160, but all other antibodies, including those to double stranded DNA and extractable nuclear antigens were absent. She has remained well on a combination of aspirin (300 mg daily) and anticoagulation with warfarin and has had no further episodes. She was regarded as suffering from a 'primary' antiphospholipid syndrome.

The second patient, a 31 year old Israeli woman, has already been reported.⁴ She had developed a hepatic infarction in association with a lupus anticoagulant, the only such case reported to date. She stated that at the age of 22 years after only one tablet of oral contraceptive (Microgynon), subungual splinter haemorrhages developed in the nail area of the fingers and toes. About one month later the same preparation was again tried with a similar result. Nine years later on becoming pregnant, they again reappeared, lasted for one month, and then disappeared spontaneously. She subsequently aborted at 20 weeks. There was no valve lesion detectable.

In our first patient the splinter haemorrhages

coincided with episodes of amaurosis fugax, as reported in the other patients. In the second, however, there was a clear relation with hormonal influences (oral contraceptives, pregnancy). In neither of these two was any valve lesion present.

Splinter haemorrhages in systemic lupus erythematosus were first reported in 1966 by Fraga and Mintz⁵ and were the subject of a recent review by Young *et al.*⁶

Although larger vascular occlusions are more commonly associated with antiphospholipid antibodies,⁷ smaller size vessels, such as the retinal⁸ or digital or pedal vasculature, with the resultant ischaemic complications of infarctions and gangrene, have been reported.⁹ These lesions have been unassociated with vasculitis.

The presence of subungual splinter haemorrhages may similarly represent evidence of platelet thrombi in the smaller vessels to the nail bed in patients with the 'antiphospholipid syndrome'. A similar mechanism may be causing the transient ischaemic attacks. I wish to draw attention to the presence of this sign and to emphasise the importance of careful examination of this group of patients in order to increase its detection.

RONALD A ASHERSON
Lupus/Arthritis Clinic
The Rayne Institute
St Thomas's Hospital
London SE1 7EH

- 1 Asherson R A. A "primary" antiphospholipid syndrome? *J Rheumatol* 1988; 15: 1742-6.
- 2 Digre K B, Durcan F J, Branch D W, *et al.* Amaurosis fugax associated with antiphospholipid antibodies. *Ann Neurol* 1989; 25: 228-32.
- 3 Kleiner R C, Najarian L V, Schatten S, *et al.* Vaso-occlusive retinopathy associated with antiphospholipid antibodies (lupus anticoagulant retinopathy). *Ophthalmology* 1989; 96: 896-904.
- 4 Mor F, Beigel Y, Inbal A, *et al.* Hepatic infarction in a patient with the lupus anticoagulant. *Arthritis Rheum* 1989; 32: 491-5.
- 5 Fraga A, Mintz G. Splinter haemorrhages in SLE. *Arthritis Rheum* 1966; 9: 648-9.
- 6 Young J B, Will E J, Mulley G P. Splinter haemorrhages: facts and fiction. *J R Coll Physicians Lond* 1988; 22: 240-3.
- 7 Asherson R A, Derksen R H W M, Harris E N, *et al.* Large vessel occlusion and gangrene in systemic lupus erythematosus and lupus-like disease. *J Rheumatol* 1986; 13: 740-7.
- 8 Stafford-Brady F J, Urowitz M B, Gladman D F, Easterbrook M. Lupus retinopathy. *Arthritis Rheum* 1988; 31: 1105-10.
- 9 Asherson R A, Harris E N. Anticardiolipin antibodies—clinical association. *Postgrad Med J* 1986; 62: 1081-7.

Iron chelation in rheumatoid arthritis: clinical and laboratory evaluation

Sir: Chronic inflammatory processes cause a significant change in iron metabolism with a drop in serum iron and a redistribution of iron to the activated reticuloendothelial system. In patients with rheumatoid arthritis (RA) iron accumulates in the synovial membrane, an extension of the reticuloendothelial system, and in synovial fluid.¹ It has been suggested that iron may play an important part in acute and chronic phases of the arthritic inflammatory process.² Iron may catalyse free radical production in the joints, leading to lipid peroxidation and membrane disruption.³ An abnormal accumulation of iron may promote an infiltration of lymphocytes and macrophages into the synovium of affected joints.⁴

Serum concentrations of β_2 microglobulin, a low molecular weight protein (11 815 daltons) associated with the light chains of cellular membrane HLA antigens, have been signifi-

cantly correlated with the clinical activity of RA and other rheumatic diseases.^{5,6} It seems to be a global marker of the number of lymphocytes implicated in the autoimmune processes and of the alteration in the various lymphocyte subsets.⁶

We evaluated serum ferritin and β_2 microglobulin concentrations and other laboratory and clinical indices in patients with RA treated with desferrioxamine, a metal chelating agent with a very high affinity for iron,⁷ to assess the usefulness of iron chelation in reducing chronic inflammation.

Eighteen female patients, aged 23 to 64 years, with RA according to the 1987 revised American Rheumatism Association diagnostic criteria, were treated with desferrioxamine (0.5 g twice a day) by subcutaneous injections into the lower anterior abdominal wall for 14 days. No patients had received systemic steroids or immunosuppressive or disease modifying drugs within three months before the enrolment. All were receiving non-steroidal anti-inflammatory drugs (diclofenac 100 mg/day). Active disease was defined by the following criteria: morning stiffness of at least 30 minutes' duration, six or more tender joints, three or more swollen joints, and an erythrocyte sedimentation rate of at least 50 mm/1st h. Eleven patients (group A) had two or three of the four preceding criteria and seven (group B) had all four criteria.

Haematological, biochemical, and immunological measurements and clinical indices were evaluated before the start of treatment, at the 14th day, and at the 28th day.

Serum concentrations of ferritin and β_2 microglobulin were determined by radioimmunoassays.

Statistical analysis was performed using Student's *t* test. The table shows the laboratory and clinical results.

Group A patients had low or normal serum ferritin concentrations (range 10.4-76.3 μ g/l) in contrast with group B patients who had high serum ferritin values (ranging from 119.7 to 1075.1 μ g/l).

We found no significant differences in serum iron, transferrin, and iron binding capacity between the two groups at the beginning of the study, though serum iron was lower in group A and transferrin and iron binding capacity higher than in group B. Erythrocyte sedimentation rate and β_2 microglobulin were significantly higher in group B ($p < 0.05$). There were no significant differences in morning stiffness, grip strength, and Ritchie index between groups A and B, though they were slightly worse in group B.

A notable increase in IgG concentrations was seen in both groups at the 14th day and 28th day.

β_2 Microglobulin concentrations increased at the 14th day in both groups A and B ($p < 0.01$), showed no variation at the 28th day in group A, but had decreased significantly by the 28th day in group B compared with the 14th day and with the initial value.

At the end of the study significant improvements of morning stiffness, grip strength, and Ritchie index were seen in both groups of patients ($p < 0.01$).

No statistical differences were noted in erythrocyte sedimentation rate, haemoglobin, serum iron, transferrin, iron binding capacity, and complement concentrations compared with basal values.

An ophthalmological examination was normal in all patients studied. Electro-ocular tests were not performed because of the short period of desferrioxamine administration.

Laboratory and clinical evaluation of 11 patients with mild active rheumatoid arthritis (group A) and of seven patients with severe active rheumatoid arthritis (group B). Results are given as means (SD)

	Start of treatment	After 14 days	After 28 days
Group A			
Ferritin ($\mu\text{g/l}$)	30.40 (25.80)	22.00 (15.60)	26.10 (21.00)
ESR* (mm/h)	56.16 (28.20)	57.20 (30.10)	59.08 (34.50)
IgG (g/l)	14.30 (5.75)	15.51 (5.81)	16.02 (6.24)
β_2 Microglobulin (mg/l)	2.24 (0.84)	2.97 (0.88)	2.82 (0.78)
Ritchie index	22.66 (14.01)	15.58 (10.63)	13.08 (9.23)
Grip strength	67.91 (23.32)	90.83 (29.49)	91.66 (28.30)
Morning stiffness (min)	49.16 (15.15)	10.83 (6.76)	8.33 (6.05)
Group B			
Ferritin ($\mu\text{g/l}$)	368.30 (147.9)	405.5 (124.7)	379.1 (110.0)
ESR (mm/h)	90.16 (37.80)	95.10 (30.20)	102.3 (24.30)
IgG (g/l)	19.82 (4.13)	24.00 (5.60)	23.35 (5.84)
β_2 Microglobulin (mg/l)	3.70 (1.38)	4.83 (1.40)	3.05 (0.60)
Ritchie index	26.00 (10.64)	15.00 (6.80)	12.00 (5.88)
Grip strength	51.66 (32.99)	82.50 (23.76)	85.83 (20.08)
Morning stiffness (min)	68.33 (29.45)	53.33 (13.84)	49.16 (25.41)

*ESR=erythrocyte sedimentation rate.

Desferrioxamine, a metal chelating agent with high affinity for iron, has been found to suppress tissue injury in animal models of inflammation.⁸ Few studies have been performed in humans, and these have given conflicting results. Giordano *et al* showed an improvement of clinical conditions and a significant increase of serum iron and haemoglobin with a marked progressive decrease of serum ferritin in patients with RA with hypsideraemic anaemia in a short desferrioxamine treatment.⁹ Fudman *et al* by intra-articular administration of desferrioxamine noted predominantly systemic effects with decreased serum ferritin and decreased serum concentrations of lipid peroxidation products.¹⁰ Blake *et al* treated patients with RA with larger doses of desferrioxamine and found serious side effects consisting of loss of consciousness and of pigmentary retinopathy.¹¹ Pall *et al* observed ocular toxicity after a low dose of desferrioxamine.¹² Polson *et al* found no significant changes in rheumatological indices or in immunological markers of disease activity of patients with RA refractory to conventional treatment and receiving desferrioxamine for six months.¹³

Recent studies have shown that desferrioxamine affects lymphocyte function. It can inhibit proliferation of human lymphocytes, probably by inhibition of ribonucleotide reductase and DNA synthesis.¹⁴ It is found that desferrioxamine treatment impairs the expression of interleukin 2 binding receptors on lymphoid cells in response to mitogen¹⁵ and markedly reduces interleukin 2 production by mitogen stimulated cells.¹⁵

In this study we noted a statistically significant improvement of clinical indices in the patients with RA at the 28th day. Patients had no side effects. A notable increase of serum β_2 microglobulin concentrations was noted in all patients at the 14th day followed by a statistically significant decrease at the 28th day in patients with more active disease. This increase in β_2 microglobulin at the end of desferrioxamine administration (14th day) without a worsening in clinical indices has not been explained. It may be due to a polyclonal B lymphocyte activation effect in these patients determined by desferrioxamine displacement of iron or other metals. Polyclonal B lymphocyte activators are mitogens that non-specifically stimulate lymphocytes to secrete immunoglobulins, and both groups of patients had significantly increased concentrations of immunoglobulins after desferrioxamine treatment.

High serum ferritin concentrations seem to

correlate with the severity of arthritic involvement. In this study patients with more active RA had higher serum ferritin concentrations than patients with less active disease. On the other hand, low serum ferritin concentrations may be connected with iron deficiency and in this study patients with RA and low serum ferritin concentrations had lower serum iron and higher transferrin and iron binding capacity than patients with higher serum ferritin.

In patients with severe active RA the association of raised concentrations of ferritin and β_2 microglobulin suggests that conspicuous iron deposits may play a part in the stimulation of lymphoid cells. Desferrioxamine seems to reduce lymphocyte activation and function, probably by inhibiting DNA synthesis and interleukin 2 action in these patients. In patients with less active RA and low or normal serum ferritin concentrations the desferrioxamine effects do not seem to influence lymphocyte activity.

M MAGARO*

A ZOLI

L ALTOMONTE

L MIRONE

G CORVINO

Istituto di Clinica Medica

Divisione di Reumatologia

Università Cattolica del Sacro Cuore

Rome, Italy

S STORTI

R MARRA

B M RICERCA

L PAGANO

L DI CESARE

Istituto di Semeiotica Medica

Università Cattolica del Sacro Cuore

Rome, Italy

Correspondence to: Professor M Magaro*, Istituto di Clinica Medica, Università Cattolica del Sacro Cuore, Largo A Gemelli 8, 00168 Rome, Italy.

- 1 Senator G B, Muirhead K D. Concentration of iron in synovial membrane, synovial fluid, and serum in rheumatoid arthritis and other joint diseases. *Ann Rheum Dis* 1968; 27: 49-54.
- 2 Blake D R, Hall N D, Bacon P A, Dieppe P A, Halliwell B, Gutteridge J M C. The importance of iron in rheumatoid disease. *Lancet* 1981; ii: 1142-4.
- 3 Rowley D, Gutteridge J M C, Blake D R, Farr M, Halliwell B. Lipid peroxidation in rheumatoid arthritis: TBA reactive material and catalytic iron salts in synovial fluid from rheumatoid patients. *Clin Sci* 1984; 66: 691-5.
- 4 De Sousa M, Dynesius-Trentham R, Mota-Garcia F. Activation of the synovium by iron in rats [Abstract]. *Arthritis Rheum* 1987; 30: 510.
- 5 Manicourt D, Brauman H, Orloff S. Plasma and urinary levels of beta 2 microglobulin in rheumatoid arthritis. *Ann Rheum Dis* 1978; 37: 328-32.
- 6 Font J, Coca A, Molina R, *et al*. Serum beta 2

microglobulin as a marker of activity in systemic lupus erythematosus. *Scand J Rheumatol* 1986; 15: 201-5.

- 7 Keberle H. The biochemistry of desferrioxamine and its relation to iron metabolism. *Ann NY Acad Sci* 1964; 119: 758-68.
- 8 Andrews F J, Morris C J, Kondratovich G, Blake D R. Effect of iron chelation on inflammatory joint diseases. *Ann Rheum Dis* 1987; 46: 327-33.
- 9 Giordano N, Sancasciani S, Marcolongo R, Borghi C, Fioravanti A. Antianemic and potential antiinflammatory activity of desferrioxamine: possible usefulness in rheumatoid arthritis. *Clin Exp Rheumatol* 1986; 4: 25-9.
- 10 Fudman E J, Till G O, Fox I M. Desferrioxamine induced decrease of lipid peroxides in rheumatoid arthritis. *J Rheumatol* 1987; 14: 686-91.
- 11 Blake D R, Winyard P, Lunec J, *et al*. Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; 56: 345-55.
- 12 Pall H, Blake D R, Winyard P, *et al*. Ocular toxicity of desferrioxamine—An example of copper promoted auto-oxidative damage? *Br J Ophthalmol* 1989; 73: 42-7.
- 13 Polson R J, Jawad A S M, Bomford A, Williams R. Treatment of rheumatoid arthritis with desferrioxamine. *Q J Med* 1986; 236: 1153-8.
- 14 Sato A, Bacon P E, Cory J G. Studies on the differential mechanism of inhibition of ribonucleotide reductase by specific inhibitors of the non-heme iron subunit. *Adv Enzyme Regul* 1984; 22: 231.
- 15 Sia D Y. Immuno-modulation of human lymphocyte function by desferrioxamine (Desferal). *Immunopharmacology* 1987; 14: 134-5.

Azathioprine and warts

Sir: In 1963 we began treatment of patients with rheumatoid arthritis with azathioprine,¹⁻⁵ and we are still following up six patients who have been treated with this drug for more than 25 years. At the start we used a dose of 2.5 mg/kg daily and now we use 50 mg a day. Aspirin was added for pain relief when necessary.

The course of their disease has been quite satisfactory with a minimum of discomfort and they have led a fairly active life. The treatment has not prevented the appearance of classical bone deformities, however.

During the past two years, four of our six patients, whose ages range from 60 to 83 years, developed skin lesions on hands and feet, which were diagnosed as warts. To confirm that diagnosis one patient was biopsied. The anatomical diagnosis was 'hyperkeratotic seborrheic wart' (Professor La Chapelle, University of Louvain).

Hyperkeratotic warts are fairly common among old people. It is impossible to draw any conclusion from a group of only six patients but we wonder if the high incidence of warts among our azathioprine treated patients is related to their treatment.

Chr MOENS

Ph MOENS

G PHILIPPART

Centre Médico Social de Bruxelles
Brussels

Correspondence to: Dr Chr Moens, Centre Médico Social de Bruxelles, Rue des Chartreux 69, B-1000 Brussels, Belgium.

- 1 Moens Chr. Les antimétabolites dans le traitement de la P.C.E. *Revue Médicale de Louvain* 1964; 8: 272-8.
- 2 Moens Chr, Brocteur J. Treatment of rheumatoid arthritis with immunosuppressive drugs. I. Clinical study. *Acta Rheumatologica Scandinavica* 1965; 3: 212-20.
- 3 Brocteur J, Moens Chr. Treatment of rheumatoid arthritis with immunosuppressive drugs. II. Immunological study. *Acta Rheumatologica Scandinavica* 1965; 3: 221-300.
- 4 Moens Chr. Traitement de la PCE par des substances immunosuppressives. Etude clinique et immunologique. *Journal Belge de Médecine Physique et de Rhumatologie* 1966; 21: 5-10.
- 5 Moens Chr. Traitement de longue durée de la PCE au moyen de substances à visée immunosuppressive. *Rhumatologie* 1967; 7: 231-4.