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 claudication, showed florid subungual splinter haemorrhages with nail fold haemorrhages.2 Treatment of culture negative infective endocarditis in addition to anticoagulation, nevertheless, resulted in clinical improvement.

A recent paper has drawn attention to the possibility of subungual splinter haemorrhages in patients with amniotic fugax and antiphospholipid antibodies,2 and a similar patient with amniotic 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 amniotic 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 amniotic 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 the patient continued to have episodes of amniotic 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 thorboemic events, nor was she thrombocytopenic. She was referred to St Thomas's Hospital in November 1988 because of the development 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, were negative. She had neither lymphocytosis, nor peripheral blood eosinophils.

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 Mintz2 and were the subject of a recent review by Young et al.4 Although larger vascular occlusions are more commonly associated with antiphospholipid antibodies,1 smaller size vessels, such as the retinal2 or digital or pedal vasculature, and with the resultant complications of infarctions and gangrene, have been reported.6 These lesions have been unassociated with vasculitis.

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

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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 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 β2 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.

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β2 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 values. 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-oculoc tests were not performed because of the short period of desferrioxamine administration.


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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 in clinical conditions and a significant increase of serum iron and haemoglobin with a marked progressive decrease of serum ferritin in patients with RA with hyposideraemic anaemia in a short desferri- oxamine treatment.9 Fedman et al by intracu- taneous administration of desferrioxamine noted predominantly systemic effects with decreased serum ferritin and decreased serum concentrations of lipid peroxidation pro- ducts.10,11 Patients treated with RA with larger doses of desferrioxamine and found serious side effects consisting of loss of consciousness and of pigmentary retino- pathy.11 Pall et al observed ocular toxicity after a low dose of desferrioxamine.12 Polson et al found no significant changes in rheuma- tological indices or in immunological markers of disease activity of patients with RA re- fractory to conventional treatment and receiv- ing desferrioxamine for six months.13 Recent studies have shown that desfer- roxiomine affects lymphocyte function. It can inhibit proliferation of human lymphocytes, probably by reducing lymphocyte re- ductase and DNA synthesis.14 It is found that desferrioxamine treatment impairs the expres- sion 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 signifi- cant improvement of clinical indices in the patients with RA at the 28th day. Patients had no side effects. A notable increase of serum ferritin, 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 ferritin, microglobulin at the end of desfer- rioxamine administration (14th day) without a worsening in clinical indices has not been explained. It may be due to a polyclonal B lymphocyte response to conventional treatment and determined by desferrioxamine displacement of iron or other metals. Polyclonal B lymphocyte activators are mitogens that non-specifically stimulate lymphocytes to secrete immuno- globulins, and both groups of patients had significantly increased concentrations of immu- noglobulins after desferrioxamine treat- ment. High serum ferritin concentrations seem to correlate with the severity of arthritis involve- ment. 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 asso- ciation of raised concentrations of ferritin and microglobulin suggests that conspicuous iron deposits may play a part in the stimu- lation of lymphoid cells. Desferrioxamine seems to reduce lymphocyte activation and function, probably by inhibiting DNA syn- thesis 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 influ- ence lymphocyte activity.

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Azathioprine and warts
Sir: In 1963 we began treatment of patients with rheumatoid arthritis with azathioprine,1–3 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. Aspinin was added for pain relief when neces- sary.

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 seborrhoeic wart’ (Professor La Chapelle, Uni- versity 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 azathoprine treated patients is related to their treatment.

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Iron chelation in rheumatoid arthritis: clinical and laboratory evaluation.

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