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, in association with antiphospholipid antibodies.1 In one of these patients, who was suffering from aortic valve disease, the amputated aortic valve leaflet showed specific changes characteristic of the so-called antiphospholipid syndrome.1,2 These findings are in contrast with previous reports on the cervical localization of antiphospholipid antibodies in stroke patients,3-5 and suggest that this syndrome may have aortic as well as cervical localization.6 Apart from the association of antiphospholipid antibodies with the aortic valve disease, there were no other findings suggestive of the antiphospholipid syndrome in these patients, and no evidence of significant aortic valve disease in one patient with this syndrome.6

The diagnosis of antiphospholipid antibodies was based on the demonstration of the presence of antiphospholipid antibodies in the patient's serum.1,2 The presence of these antibodies was confirmed by the use of a solid-phase radioimmunoassay.1,2

We agree with the points raised by Asherson et al.1 with respect to the clinical application of antiphospholipid antibodies in the diagnosis of aortic valve disease. We believe that the use of antiphospholipid antibodies as a diagnostic tool for aortic valve disease is limited at the present time.7

Our findings are in agreement with those of Asherson et al.1,2 and with the results of other studies.3-5

We therefore conclude that the aortic valve disease in our patients was caused by antiphospholipid antibodies.1,2


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 elevation 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, reduce the activity of antioxidants, and 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 β₂-microglobulin, a low molecular weight protein (18 615 daltons) associated with the light chains of cellular membrane HLA antigens, have been significantly correlated with the clinical activity of RA and other rheumatic diseases.5 It seems to be a global marker of the number of lymphocytes implicated in the autoimmune processes and of the alteration in the various lymphocytes subsets.6

We evaluated serum ferritin and β₂-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 each month.7 Desferrioxamine has 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 by mouth daily). 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 50 mm in 1 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 β₂-microglobulin were determined by radioimmunoassay.

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 μg/l) in contrast with group B patients who had high serum ferritin values (ranging from 119 7 to 1075 1 μg/l).

We found no significant differences in serum iron, transferrin, and transferrin 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.

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

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-oculot tests were not performed because of the short period of desferrioxamine administration.

We thank Dr R. A. Asherson for permission to quote his observations.

R. M. A. F. ALMEIDA

Desferrioxamine, a metal chelating agent with high affinity for iron, has been found to suppress tissue injury in animal models of inflammation. 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 desferrioxamine treatment. Blake et al by intracutaneous administration of desferrioxamine noted predominantly systemic effects with decreased serum ferritin and decreased serum concentrations of lipid peroxidation products. Patients treated with RA with larger doses of desferrioxamine and found serious side effects consisting of loss of consciousness and of pigmentary retinopathy. Pall et al observed ocular toxicity after a low dose of desferrioxamine. Poisson 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.

Recent studies have shown that desferrioxamine affects lymphocyte function. It can inhibit proliferation of human lymphocytes, prevent activation of lymphocytes and reductase and DNA synthesis. It is found that desferrioxamine treatment impairs the expression of interleukin 2 binding receptors on lymphoid cells in response to mitogen and markedly reduces interleukin 2 production by mitogen-stimulated cells. 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 iron, 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 iron, 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 expansion 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 β2 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 function.

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Azathioprine and warts
Sir: In 1963 we began treatment of patients with rheumatoid arthritis with azathioprine, 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 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 needed to sample. 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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