Rebound of anti-topoisomerase I antibody titres after plasma exchange

Sir: Serum levels of a specific antibody induce a negative feedback on the synthesis of antibody of the same specificity. If this feedback inhibition of antibody synthesis is reduced by diminishing the concentration of antibody in the circulation by plasma exchange (PE), an enhancement of antibody synthesis, also termed 'antibody rebound', occurs. This rebound phenomenon has been shown to occur, among others, in autoimmune mediated diseases such as systemic lupus erythematosus.

Plasma exchange, alone or combined with immunosuppressive therapy, has been used in the treatment of systemic sclerosis, though its effectiveness in this disorder remains questionable. Changes in autoantibody concentrations during PE treatment of patients with scleroderma have been used to monitor the efficacy of PE.

We would like to present the case of a 50 year old woman who had had Raynaud's phenomenon since the age of 30 and a four year history of sclerodactyly. Over a few months skin thickening progressed to upper arms, face, neck, and chest. A diagnosis of rapidly progressing systemic sclerosis was made. Treatment with azathioprine 100 mg (2 mg/kg) daily was started. Four weeks later, as no improvement had occurred, PE treatment was started. At that time laboratory results included haemoglobin 103 g/l, white blood cell count 7.3×10^9/l, platelets 428×10^9/l, Westergren erythrocyte sedimentation rate 48 mm/h, and creatinine clearance 70 ml/min. Total haemolytic complement, circulating immune complex levels, C3/C4 complement components, and concentrations of immunoglobulins A, M, and G were within normal range. Both IgG and IgA isotypes of anti-topoisomerase I antibodies (ATA) could be detected, but the IgM isotype could not.

Radiological examination disclosed reduced peristalsis of the oesophagus; results of chest x ray examination and pulmonary function tests were within normal limits. During a 29 day period PE was carried out 11 times. At each session 2000 ml of plasma was exchanged using cryoglobulin free plasma for replacement. The interval between PE sessions varied from one to five days. Before the start of azathioprine treatment and immediately before and after each PE, total IgA and IgG concentrations were established, as well as IgG and IgA ATA titres, using an enzyme linked immunosorbent assay (ELISA) with a recombinant topoisomerase I as antigen source. After the 1st sessions PE was stopped at the patient's request. Azathioprine was given during the whole period of PE and was continued when this treatment was stopped.

No change in titres of total IgA and IgG or ATA could be detected. During the four weeks of azathioprine treatment, when PE was started. After each PE, however, IgG and IgA ATA titres were reduced (Figure A and B). IgG ATA titres decreased on average 40 (SD 16%) (range 18–72%) and IgA ATA titres 51 (14%) (range 29–77%). Total IgA and IgG levels decreased in the same amount as IgA and IgG ATA concentrations. Within one to five days after each PE, ATA titres increased to 80–125% of the levels before PE; although an increase in total IgA and IgG was also noted, this increase never exceeded values before PE. Five days after the last PE IgG and IgA ATA levels were respectively 77% and 83% of the initial values. Five weeks after the last PE, with the patient still receiving azathioprine, both IgG and IgA ATA levels equalled pretreatment values. No changes in the physical condition of the patient could be seen during the PE treatment.

To our knowledge this rebound of ATA after PE in a patient with systemic sclerosis has not been reported before. The mechanisms of antibody rebound, sometimes leading to antibody concentrations after treatment exceeding values before treatment, remain unsolved. A conjectural explanation might be clonal expansion of antibody producing B cells, caused by re-exposure of antigenic determinants after a decrease in antibody levels or by removing blocking anti-idiotypic antibody. Therefore, PE applied in the treatment of autoimmune diseases is usually combined with cytotoxic drugs to inhibit B cell proliferation.

In our patient azathioprine 100 mg daily could not accomplish a decline of ATA titres and nor could it prevent the rapid increase of ATA after PE. Five days after the last PE, however, the combination of azathioprine and PE had caused a reduction of about 20% of both IgG and IgA ATA titres. In the study performed by Ferri et al, who treated six patients with scleroderma with PE without concomitant cytotoxic treatment, autoantibody levels were largely unaffected after a prolonged period of PE despite clinical benefit to their patients. It was suggested that the unchanged antibody concentration might be attributed to a rapid resynthesis of autoantibodies rather than to insufficient PE. The rebound of ATA titres seen in our patient confirms this presumption. Therefore, in monitoring autoantibody levels during PE treatment in systemic sclerosis, rebound of ATA should and presumably all other autoantibodies, should be considered.

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Polyarteritis nodosa following angioplasty

Sirs: Polyarteritis nodosa is a rare condition characterised by necrotising arteritis of small and medium sized arteries. Infection may act as a trigger in some instances. In a recent study, 10% to 54% of patients being hepatitis B surface antigen positive, but evidence of infection cannot be found in all patients. We report a case of PAN which occurred after femoral angioplasty.

A 54 year old man with a one year history of bilateral claudication was admitted for angioplasty and angiography. A heavy smoker from the age of 20, he otherwise had no significant past medical history. There was no relevant family history of vascular disease. A preoperative full blood count, urea and electrolytes, fasting lipids, electrocardiogram, and results of a chest x ray examination were normal. Femoral angiography confirmed the presence of a short segment bilateral atheromatous stenoses of the femoral arteries at the level of the adductor hiatus. As symptoms were more marked on the left he underwent angioplasty of that side. The immediate postoperative period was uneventful.

One week after discharge he developed pain and swelling of the small joints of the hands, wrists, elbows, shoulders, and ankles. His condition was managed by his general practitioner. An initial full blood count was unremarkable, erythrocyte sedimentation rate (ESR) was 6 mm/h, and rheumatoid latex was negative.

His condition continued to deteriorate. Six weeks after the onset of his symptoms he was admitted for investigation over a 24 hour history of pain and swelling of the left calf.

On admission he was febrile (38°C, blood pressure 120/70 mm Hg). There was an acute polyarthritis of proximal interphalangeal and metacarpophalangeal joints of wrists, elbows, shoulders and knees, and ankles. Proximal muscle grooves were tender, the left calf was painful and swollen. There was no rash. Investigation showed haemoglobin 139 g/l, neutrophils 8 x 10^9/l, ESR 68 mm/h, urea and electrolytes normal, alkaline phosphatase 281 IU/l, alanine transaminase 46 IU/l, creatine kinase 400 mg/l. Autoantibodies, including rheumatoid arthritis latex, antinuclear antibodies, and antinuclear and antiphospholipid antibodies, were negative. Blood cultures and hepatitis B surface antigen were negative. Midstream urine showed 3+ red blood cells. Doppler studies of the calf showed no evidence of deep venous thrombosis.

An electromyogram was consistent with myositis. Muscle biopsy of the left calf disclosed necrotising arteritis, with no muscle fibres affected. Mesanegic arteriography showed numerous small aneurysms of the hepatic, intraperitoneal, and renal arteries, consistent with the diagnosis of polyarteritis nodosa.

He was treated with prednisolone and cyclophosphamide and is currently well.

This case indicates the importance of differentiating the angioplasty and the development of polyarteritis nodosa in this case strongly suggests a link. Vascular damage certainly occurs during angioplasty and up to 2% of all femoral angioplasties require surgical intervention. Several mechanisms might have stimulated the immune response, leading to the development of vasculitis. The simplest of these involves the exposure of previously hidden antigens to which the patient was not tolerant. Besides simple traumatic damage to the vascular endothelium, however, angioplasty may also render the area temporarily ischaemic. In coronary angiography it is known to result in the generation of superoxides.5 In this case it is interesting to note that the left calf was the worst affected area. Could ischaemically generated superoxides have altered endothelial constituents, rendering them antigenic? This is the first reported case of vasculitis after angioplasty. With the increasing use of such techniques, more cases can presumably be expected. The procedure provides an interesting opportunity for further research.

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Buerger's disease and antiphospholipid antibodies in pregnancy

Sirs: Buerger's disease is a vasculitis of unknown cause, in which several factors have been implicated, one of the most important of which is smoking.1 We present a case in which Buerger's disease was associated with a primary antiphospholipid syndrome in a pregnant woman.

A patient aged 38 was sent to our centre in her 32nd week of gestation with a suspected diagnosis of intrauterine growth retardation. Her obstetric history included two intrauterine fetal deaths at 30 and 32 weeks, and between them a male child born alive at term but who was small for the gestational age. The patient had smoked more than 30 cigarettes daily for the previous three years and had had hypertension Raynaud's disease in the fingers and toes for nine years, with distal necrosis of the middle finger of the right hand. On examination, the absence of left radial and pedal pulse and signs of necrosis of the middle finger of the right hand were noteworthy. A uterine height was 22 cm, which clearly was low for the gestational age. Blood analysis showed persistent thrombocytopenia, with a platelet count between 100 and 140 x 10^9/l. Tests for antinuclear antibody, cardiac valve abnormality, and rheumatoid factor were negative. Anticardiolipin antibodies (by enzyme linked immunosorbent assay (ELISA)) were positive at 40 GPL units in two tests done eight weeks apart. (In our laboratory we consider positive levels of IgM or IgG anticardiolipin antibodies to be values greater than 20 GPL or GPL units respectively.) Obstetric sonography showed a live fetus with biometric deviations corresponding to 26 weeks of gestation. The diagnosis was severe symmetrical intrauterine growth retardation.

As we suspected Buerger's disease a Doppler study of proximal arteries was done, and the results were normal. Non-stress tests showed an absence of fetal reactivity, with decrease of variability and presence of late decelerations, and as a result a caesarean section was performed. A live neonate weighing 1000 g was delivered, with an Apgar score of 6-8. His postnatal evolution was favourable. Anatomopathological examination of the placenta indicated multiple infarcts and calcifications, and no signs of vasculitis were noted. An arteriograph of the hands, carried out after delivery, indicated multiple stenoses and screwdriver lesions in radial, ulnar, and palmar arches, which are all compatible with Buerger's disease. The lesions were bilateral.

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