Failure of aggressive anticoagulant therapy in catastrophic antiphospholipid syndrome

Sirs,

We report the case of a 47-year-old woman who was hospitalized in March 1996 with dyspnoea, tachypnoea and tachycardia. An echocardiopulmonary examination showed right cardiac chamber dilatation due to pulmonary hypertension. Pulmonary perfusion and ventilation scintigraphy suggested a massive pulmonary thromboembolism. Immunological investigations were performed, and a positive antinuclear (homogeneous pattern), antidualenuclear (titer 1:160), anti-SSA, and anti-RNP antibodies were found. A lupus anticoagulant was also evaluated with dR Vvitro and TDXarina/Ecarina tests. Confirmatory assays showed that its inhibitory activity was dependent on phospholipid (1). IgG and IgM isotype cardiolipin antibody (aCL) titers, determined by ELISA, were 100 U/ml and 18.5 U/ml, respectively (cut-off points 14 U/ml).

Intravenous (IV) heparin and then oral anticoagulants were administered, followed by 6-methylprednisolone (60 mg per day). The patient’s condition improved and she was discharged from hospital with the diagnosis of pulmonary thromboembolism in association with systemic lupus erythematosus (SLE) and secondary aPLS. The steroid dosage was reduced to 40 mg/day, while warfarin was continued.

The patient remained well until July 1996, when she was admitted to our division because of a new episode of pulmonary thromboembolism. Immunological tests confirmed the positivity of ANA, high titer anti-DNAAs, and hypocomplementemia, while IgG aCL levels were diminishing due to the risk of haemorrhage. The INR was kept over 3, as recommended (1-3).

Despite aggressive therapy and the obtaining of a high level of anticoagulation, to the point of the risk of major bleeding, arterial and venous thrombosis occurred yet again. Three considerations may be raised to try to explain the course of events in our patient.

The first is that oral anticoagulant agents interfere with the coagulation cascade, reducing the synthesis by the liver of vitamin K-dependent factors, including protein C. Given that APLs seem to compromise protein C function (4, 5), the oral anticoagulant recommended for prevention of recurrent thrombosis could act synergically. Due to our incomplete understanding of the pathogenic effects of these antibodies, the actual recommended therapy is empirical and can fail.

The second consideration is that inflammatory cytokines such as TNFα and interleukin 1 (IL1) seem to have a synergistic effect with APL in inducing an activated endothelial phenotype, stimulating endothelial cells to synthesize Tissue Factor, an inducer of the coagulation cascade, adhesion molecules, and plasminogen activator inhibitor (6, 7). Therefore, the increase in inflammatory cytokines due to a flare in lupus activity could precipitate an already unsafe homeostatic condition, as probably happened in our patient.

The last consideration is that we probably observed a "false" prolongation of the phospholipid-dependent prothrombin time; the elevated INR values could be due both to the warfarin effect and to the inhibiting activity of LA in vitro.

Plasmapheresis is recommended in catastrophic APS and seems to be useful (8, 9).

Given that the IgG aCL levels were diminishing and due to the risk of haemorrhage, we did not resort to this additional therapy.

References