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 echodoppler of the lower extremities showed a right popliteal and deep femoral vein thrombosis. Pulmonary perfusion and ventilation scintigraphy suggested a massive pulmonary thromboembolism. Immunological findings included hypocomplementemia, and positive antinuclear (homogeneous pattern), anti-DNAds (titre 1:160), anti-SSA, and anti-RNP antibodies.

The prolongation of the activated partial thromboplastin time (APTT) was not corrected by the addition of normal plasma. Lupus anticoagulant (LA) was also evaluated with the dilute Russel Viper Venom Time (dRVVT) and Texarina/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 die). 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 titre anti-DNAds, and hypocomplementemia, while IgG aCL levels had decreased to 27 U/ml and IgM aCL to 3.2 U/ml.

The patient was treated with cyclophosphamide (75 mg/day), calcium channel blockers, diuretics, digitalis glycosides, methylprednisolone (40 mg/day), and IV heparin for 10 days, and then oral anticoagulants. The INR rose from 3 to 6. On August 19th we had to stop warfarin, due to a continued increase in the INR which reached a value of 10, with the appearance of hematomas over the entire body.

Two days later the patient complained of worsening dyspnoea. To check for heart hemorrhagic tamponade, an echocardiography was carried out and showed enlargement of the right cardiac chambers caused by a further increase in the MPA systolic pressure, indicating the occurrence of a new thromboembolism.

On August 22th the patient presented with signs of circulatory collapse and was admitted to the intensive care unit, where she died a few hours later. The autopsy showed features of pulmonary middle vessel thromboembolism. In the lower extremities no vein thrombosis was found, while the uterine venous plexus was widely thrombosed. A histologic examination ruled out vasculitis, but showed the presence of several focal infarctions in the lungs (Fig. 1), the splenic marginal zone, the adrenal glands, and the kidneys.

In addition to immunosuppressive drugs and steroids, high dose anticoagulant was used for the management of our patient, in order to prevent recurrent thrombosis. First heparin and then warfarin was employed and the INR was kept over 3, as recommended (1-3) .

Despite this 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 as yet 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 synergetic 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.

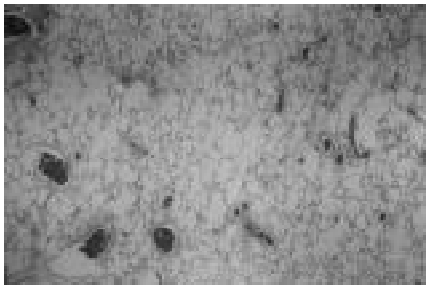

Fig. 1. Histologic examination showing several focal infarctions in the lungs.

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 diminished and due to the risk of haemorrhage, we did not resort to this additional therapy.

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