The lupus anticoagulant, pulmonary thromboembolism, and fatal pulmonary hypertension

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SUMMARY A patient with a circulating lupus anticoagulant in the absence of systemic lupus erythematosus developed recurrent deep venous thromboses and pulmonary emboli. Pulmonary emboli recurred despite prolonged oral anticoagulant therapy and resulted in fatal pulmonary arterial hypertension. Extended anticoagulant therapy alone may not prevent recurrent thromboembolism in patients with a lupus anticoagulant. Pulmonary thromboembolism may be an important factor in the pathogenesis of pulmonary hypertension in patients with a lupus anticoagulant.

Key words: venous thrombosis, antibodies, immunoglobulins, systemic lupus erythematosus.

The lupus anticoagulants are immunoglobulins that interfere with the activation of prothrombin by the prothrombin activator complex.¹ Although the first description of the lupus anticoagulant was in a patient with a bleeding tendency,² it is now recognised that the presence of a lupus anticoagulant is sometimes paradoxically associated with a tendency to thrombosis.^{3–5} An association between the lupus anticoagulant and pulmonary hypertension has been identified amongst patients with systemic lupus erythematosus (SLE).⁶ We describe a patient with a lupus anticoagulant who developed pulmonary hypertension following recurrent episodes of deep venous thrombosis (DVT) and pulmonary thromboembolism despite prolonged anticoagulant therapy.

Case report

A 26-year-old male presented in April 1972 with a two-week history of fever, cough, and pleuritic chest pain, and signs of DVT in the left leg. Serial chest x-rays showed migratory pulmonary opacities and bilateral pleural effusions. A technetium-99m (^{99m}Tc) perfusion lung scintigram showed perfusion defects in the lateral basal segment of the left lung

and the entire right lower lobe. He was treated with intravenous heparin for 10 days and then with warfarin, which was continued until October 1973. A detailed pre-heparin coagulation profile was not done.

He remained well until he presented again in January 1974 with pleuritic pain, dyspnoea, and cough of five days' duration. Examination findings included fever, tachypnoea, central cyanosis, and crepitations at both lung bases. There was atelectasis at the right lung base on the chest x-ray. On a ^{99m}Tc lung scintigram perfusion of the left lung was absent, and there were several segmental perfusion defects in the right lung. Left leg venography showed thrombosis of the deep calf veins and the femoral vein. A venogram of the right leg was normal. He was treated with intravenous heparin and then long-term warfarin.

He was readmitted in October 1978 with a one-month history of epigastric pain. He had been treated continuously with warfarin since 1974. Abnormalities included mild jaundice, elevation of the jugular venous pressure, prominent right ventricular (RV) lift, an accentuated pulmonary component of the second heart sound, a right-sided third heart sound, and oedema of the left leg. The chest x-ray showed cardiomegaly, a prominent main pulmonary artery (MPA), and sparse vasculature throughout the left lung. The electrocardiograph showed right axis deviation, P pulmonale, and RV

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hypertrophy with strain. The RV was dilated on M-mode echocardiography. The ^{99m}Tc lung scintigram was unchanged from the previous study in 1974. At pulmonary arteriography the MPA pressure was 104/40 mmHg (mean 64 mmHg); most pulmonary artery branches were either occluded or stenosed (Figs 1A, B). The findings were consistent with multiple pulmonary thromboemboli. The anti-nuclear factor was present in a titre of 1:32 and anti-smooth muscle antibody 1:16; anti-DNA antibody was not detectable, and serum complement levels were normal. There was a mild polyclonal gammopathy. The direct Coombs test was positive. Syphilitic serology was non-reactive.

Initial coagulation tests (Table 1) showed pro-

longation of the activated partial thromboplastin time (APTT), which was incompletely corrected by the addition of normal plasma, an increased Russell viper venom time (RVVT), and marginal increase in the prothrombin ratio (PR). Further investigations^{7,8} confirmed that these abnormalities were due to the presence of a lupus anticoagulant with inhibitor activity directed against the prothrombin activator complex and against factor XI. The inhibitor was shown to be an IgG immunoglobulin.

Warfarin therapy was continued, and despite the PR being maintained in the therapeutic range he developed signs of a further DVT in the left leg in March 1979. Aspirin, dipyridamole (Persantin), and low-dose subcutaneous heparin were added to

Fig. 1A

Table 1 Initial coagulation investigations

Test	Patient	Normal range
Template bleeding time (min)	2	3-6
Lee and White whole blood clotting time (min)	12	4-10
Prothrombin ratio	1.4	0.8-1.2
Thrombin clotting time (s)	13.3	<18
Activated partial thromboplastin time (APTT) (s)	62.0	25-40
APTT (1+1) (s)	50.0	25-40
Platelets ($\times 10^9/l$)	155	150-400
Russell viper venom time (s)	47	26 (control)

his therapy. He remained restricted by exertional dyspnoea and persistent bilateral ankle oedema. He was readmitted to hospital in September 1980 with a recent increase in dyspnoea and haemoptysis. Examination findings were those of circulatory collapse, severe pulmonary hypertension with pulmonary valve regurgitation, and right heart failure. He died suddenly 48 hours later.

At necropsy there were widespread organising thrombi with focal intimal proliferation and medial hypertrophy within the pulmonary vasculature. The right atrium and ventricle were grossly dilated.

Fig. 1 Pulmonary arteriogram.
A: Right pulmonary artery. B: Left pulmonary artery.

Fig. 1B

Discussion

The lupus anticoagulants are considered to be immunoglobulins, usually IgG or IgM, and occasionally a mixed IgG-IgM type.¹ They interfere with the activation of prothrombin by the prothrombin activator complex of factors Xa, V, and platelet phospholipid.¹ The inhibitor seems to be specifically directed against platelet phospholipid.^{9, 10} The coagulation investigations in our patient were consistent with lupus inhibitor activity against both the prothrombin activator complex and factor XI. Lupus anticoagulant activity against factor XI has been previously described.¹¹⁻¹³ The lupus anticoagulant is encountered in 5-10% of patients with SLE^{1, 12} but has been described in other autoimmune diseases,^{3, 7} with neoplasia,⁷ with certain drugs,^{3, 4} and may appear in people without underlying disease.¹⁴ Our patient had a low titre antinuclear antibody assay and a positive direct Coombs test, but there was no other evidence of SLE. The isolated presence of a lupus anticoagulant may represent an oligosymptomatic form of SLE.⁷

The lupus anticoagulant and anticardiolipin levels, assayed by a new sensitive solid-phase radioimmunoassay,¹⁵ are strongly associated with venous and arterial thrombosis^{3-5, 15} and pulmonary hypertension.^{6, 15} The lupus anticoagulant also is associated with abortions.^{16, 17} The paradoxical association between the lupus anticoagulant and thrombosis is incompletely explained but may be related to reduced prostacyclin formation¹⁸ or activity.¹⁹ In previously reported cases recurrent thrombosis could be prevented by anticoagulant therapy,^{3, 8} but our patient had recurrent pulmonary emboli resulting in fatal pulmonary hypertension despite continuous warfarin therapy for all but three months after his initial presentation. Reduced fibrinolytic activity in the vessel walls¹¹ may contribute to the tendency for pulmonary thromboemboli to produce irreversible pulmonary hypertension in patients with a lupus anticoagulant. Therapy with low doses of streptokinase may be beneficial.

The lupus anticoagulant is rarely associated with bleeding symptoms, even during major surgical procedures^{1, 3, 7} or in the presence of thrombocytopenia.⁵ When bleeding occurs it is usually attributable to another cause.^{1, 7} Our patient had no haemorrhagic complication despite prolonged oral anticoagulant therapy.

An association between the lupus anticoagulant and pulmonary hypertension has been described in patients with SLE.⁶ Suggested possible factors in the pathogenesis of pulmonary hypertension in these patients are vasospasm, arteritis, platelet dysfunction,

and thromboembolism.⁶ Our patient had clinical, radiological, and post-mortem evidence of deep venous thrombosis and extensive pulmonary thromboembolism complicated by the development of fatal pulmonary hypertension. Recurrent pulmonary thromboembolism is an important factor in the development of pulmonary hypertension among patients with the lupus anticoagulant.

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