The Lupus Anticoagulant in Systemic Lupus Erythematosus

N. R. ROWELL and G. M. TATE

Departments of Dermatology and Haematology, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, England

The lupus anticoagulant was found in six of 41 unselected patients with systemic lupus erythematosus (14%). Three of these six patients had episodes of thrombosis. Thrombosis occurred in only one patient in the remainder of the series without the lupus anticoagulant. The lupus anticoagulant should be considered as one of the criteria for the diagnosis of systemic lupus erythematosus, and it may be a useful marker for those patients at risk from thromboembolism. It should be looked for in young adults with thrombotic episodes. *Key word: Thrombosis.* (Accepted July 11, 1988.)

Acta Derm Venereol (Stockh) 1989; 69: 111–115.

N. R. Rowell, Department of Dermatology, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, England.

The lupus anticoagulant is an acquired IgG or IgM antibody directed against specific phospholipids involved in the formation of prothrombin activators (1). It is diagnosed by demonstrating a prolonged coagulation time—activated partial thromboplastin time (APTT), kaolin clotting time (KC) or Russell viper venom time (RVVT)—which cannot be corrected by the addition of normal plasma as in simple clotting factor deficiency. The thrombin time (TT) is normal.

The incidence of the anticoagulant in systemic lupus erythematosus varies between publications from 6–37%. This paper reports the results of a prospective investigation of a series of unselected patients with systemic lupus erythematosus using the APTT (by two methods) and KCT.

MATERIALS AND METHODS

Forty-one unselected consecutive patients with systemic lupus erythematosus fulfilling the criteria of the American Rheumatism Association (2) entered the study.

Venous blood was anticoagulated with one-tenth volume 0.109 M trisodium citrate (dihydrate). Platelet poor plasma was obtained by double centrifuging at 1 500 g for 15 min at room temperature. Prothrombin times (PT) were measured using Manchester Comparative reagent and TT according to the method of Pitney & Brozovic (3). ATPP was measured with Automated APTT reagent (Organon Teknika Corporation) and by the standardised Manchester APTT method (4). A volume of Owren's buffer was substituted for the cephalin reagent in the Manchester APTT to give the KCT. The PT and automated APTT were performed on a Coag-a-Mate ×2 (Organon Teknika Corporation). All tests were done on fresh plasma within two hours of venepuncture. Normal levels for this laboratory are: PT 12–15 sec; TT 12–17 sec; automated APTT 28–35 sec; Manchester APTT 36–45 sec; KCT 60–110 sec.

RESULTS

Six of the 41 patients with systemic lupus erythematosus showed the presence of the lupus anticoagulant (14%). The Manchester APTT was abnormal in all six patients whereas the automated APTT was abnormal in only three. KCT was abnormal in four patients. The PT and TT were normal in all patients.

The features of the six patients with the lupus anticoagulant are summarised in Table I. The duration of lupus erythematosus ranged from two weeks to 38 years. Three of the

patients had thromboses during their illness but in the three others there was no history of thrombosis. Two patients had a Coombs positive haemolytic anaemia. One patient presented with thrombocytopenic purpura but in the other patients the platelet count was normal. Only one patient without the lupus anticoagulant had a history of thrombotic episodes. Serial observations did not suggest a direct relationship between the lupus anticoagulant and clinical activity.

DISCUSSION

We have found the lupus anticoagulant, as defined by prolongation of APTT or KCT not corrected by normal plasma, in 14% of unselected patients with systemic lupus erythematosus. The frequency of the lupus anticoagulant depends on the selection bias of patients and on the type of assay and standardisation of the normal range. In the present series the Manchester APTT method was more sensitive than the automated APTT, all patients having a prolonged Manchester APTT compared with only three by the automated APTT method. The KCT was abnormal in four patients. The lupus anticoagulant can also be determined by prolongation of the Russell viper venom time. Unfortunately there is not always agreement between the APTT and the RVVT (5). The RVVT was said to be more specific in predicting thrombotic events than the anticardiolipin antibody level. Other authors (6), using the prolongation of KCT, found the lupus anticoagulant to be present in 26% of 74 patients with SLE and a statistically significant relationship with thromboembolic events. Thus it seems that these tests may be demonstrating different antiphospholipid antibodies and ideally several tests should be done in parallel.

Thrombosis occurs in between one third (7) and two thirds (8) of patients with systemic lupus erythematosus who have the lupus anticoagulant but the cause of the thrombosis is unknown. It has been suggested that an IgG antibody impairs prostacyclin release from endothelial cells (9), but the presence of the lupus anticoagulant in patients with SLE does not cause inhibition of prostacyclin production (10, 11). IgG factors from patients with the lupus anticoagulant have been shown to inhibit endothelial cell-bound thrombomodulin in the protein C thrombomodulin pathway (12, 13) and this could be a mechanism for thrombosis.

Thrombocytopenia occurs in about one third of patients with systemic lupus erythematosus with the lupus anticoagulant. It has been suggested that anticardiolipin antibodies may play a role in platelet destruction (14). Patients may present with thrombocytopenic purpura. However, bleeding is very rare and in one series bleeding occurred in only one

Table I. *Details of six patients with systemic lupus erythematosus and the lupus anticoagulant*

Case	Sex	Age	Age at onset of LE	Duration of LE	Thrombotic episodes
1	F	24	15	9	Deep venous thrombosis of legs. Repeated pulmonary emboli
2	F	30	30	2	None
3	M	37	20	17	Deep venous thromboses. Myocardial infarction
4	F	65	27	38	?Small cerebral thrombosis
5	F	17	5	12	None
6	F	25	25	2/52	None

patient out of 219 with the lupus anticoagulant (15). This is important, because if surgical operations are necessary they can be safely carried out. Patients with systemic lupus erythematosus and the lupus anticoagulant who are pregnant have an increased risk of abortion and foetal loss, and this risk may be reduced by the oral administration of prednisolone and aspirin (16, 17). Plasma exchange may be worth trying (18).

There is a strong association between the lupus anticoagulant and anticardiolipin antibodies (19). It was not possible to measure anticardiolipin antibodies in the present series, but none of the patients had false positive serology. Complete overlap between the lupus anticoagulant and anticardiolipin antibodies is unlikely (20). They are probably two of a group of antiphospholipid antibodies with different specificities. It has been suggested that a so-called antiphospholipid syndrome is a separate entity from systemic lupus erythematosus (21) but a recent review introduces a note of caution with this view (22).

Systemic lupus erythematosus consists of many subsets. With hindsight, case 3 represents an interesting subset of young men with systemic lupus erythematosus who have recurrent thrombotic episodes, in particular myocardial, in association with the lupus anticoagulant and anticardiolipin antibodies (23). Patients with SLE and the lupus anticoagulant may develop the Budd-Chiari syndrome (24) and pulmonary hypertension (25). Young adults with the lupus anticoagulant may have recurrent episodes of cerebral vascular ischaemia (26).

Cutaneous manifestations include livedo reticularis (27), widespread cutaneous necrosis (28), Degos' disease (29), peripheral gangrene (30), and erythematous and purplish macules of the finger tips and leg ulcers sometimes resembling pyoderma gangrenosum (31). Histology may show microthrombosis of the dermal vessels without vasculitis.

The lupus anticoagulant can occur in drug-induced systemic lupus erythematosus. We have recently seen a 68-year-old woman with hydralazine-induced systemic lupus erythematosus. The rash disappeared within four weeks of stopping hydralazine but the lupus anticoagulant can still be demonstrated after six months. It is not known how frequently the lupus anticoagulant occurs in drug-induced lupus erythematosus but 14 out of 219 patients with the lupus anticoagulant in one series (15) had a drug-related lupus syndrome.

Although thrombosis is a feature of patients with the lupus anticoagulant, repeated thrombotic episodes can occur in patients with lupus erythematosus in the absence of the lupus anticoagulant. One of our patients had repeated thrombotic episodes including thrombosis of axillary, mammary and jugular veins, transitory left homonomous hemianopia and transitory blurring of vision. At no time was the lupus anticoagulant demonstrated.

Management of patients with systemic lupus erythematosus and the lupus anticoagulant is a matter of judgement. If the condition is inactive and there have been no thrombotic episodes treatment may not be indicated, but this means taking a risk that thrombosis could occur. On the other hand, patients may thrombose even when on anticoagulants (5). In cases which are clinically active and who have had a recent thrombosis, prednisolone, anticoagulants and, possibly, aspirin, are required. Occasionally cases have responded to plasma exchange (30).

All patients with systemic lupus erythematosus, especially if pregnant, should be examined for antiphospholipid antibodies. The lupus anticoagulant is only one of several antiphospholipid antibodies and ideally it is best to use multiple tests such as the Manchester APTT, KCT and RVTT, as well as an ELISA for cardiolipin antibodies (32).

REFERENCES

1. Byrom MA. The clotting defect in systemic lupus erythematosus. Clin Rheum Dis 1982; 8: 137–151.
2. Subcommittee for SLE Criteria of the American Rheumatism Association Diagnostic and Thera-

peutic Criteria Committee. The 1982 revised criteria for the classification of SLE. Arthritis Rheum 1982; 25: 1271–1277.
3. Pitney WR, Brozovic M. Investigations of the haemostatic mechanism. In: Dacie JV, Lewis SM, eds. Practical haematology 6th ed. Edinburgh: Churchill Livingstone, 1984: 208–223.
4. Kelsey PR, Stevenson KJ, Poller L. The diagnosis of lupus anticoagulants by the activated partial thromboplastin time—the central role of phosphatidyl serine. Thromb Haemostasis 1984; 52: 172–175.
5. Petri M, Rheinschmidt M, Whiting-O'Keefe Q et al. The frequency of lupus anticoagulant in systemic lupus erythematosus. A study of sixty consecutive patients by activated partial thromboplastin time, Russell viper venom time, and anticardiolipin antibody level. Ann Intern Med 1987; 106: 524–531.
6. Derksen RHWM, Bouma BN, Kater L. The prevalence and clinical associations of the lupus anticoagulant in systemic lupus erythematosus. Scand J Rheumatol 1987; 16: 185–192.
7. Lechner K, Pabinger-Fasching I. Lupus anticoagulants and thrombosis. A study of 25 cases and review of the literature. Haemostasis 1985; 15: 254–262.
8. Jungers P, Kiote F, Dautzenberg MD et al. Lupus anticoagulant and thrombosis in systemic lupus erythematosus. Lancet 1984; i: 574–575.
9. Carreras LO, Defreyn G, Machin SJ et al. Arterial thrombosis, intrauterine death and "lupus" anticoagulant: detection of immunoglobulin interfering with prostacyclin formation. Lancet 1981; i: 244–246.
10. Petrafuelo W, Bovill E, Hoek J. The lupus anticoagulant does not inhibit the release of prostacyclin from human endothelial cells. (Abstract) Thromb Haemostasis 1987; 58: 390.
11. Rustin MHA, Bull HA, Dowd PM et al. Presence of the lupus anticoagulant in patients with systemic lupus erythematosus does not cause inhibition of prostacyclin production. (Abstract) Thromb Haemostasis 1987; 58: 390.
12. Comp PC, Debault LE, Esmon NL, Esmon TC. Human thrombomodulin is inhibited by IgG from two patients with non-specific anticoagulants. (Abstract) Blood 1983; 62: Suppl 1, 299a.
13. Cariou R, Tobelem G, Caen J. L'anticoagulant circulant de type, facteur de risque thrombotique par inhibition de l'activation de la protéine C. CR Acad Sci Ser III-Vie 1986; 303: 113–118.
14. Harris EN, Asherson RA, Gharavi AE et al. Thrombocytopenia in SLE and related disorders: association with anticardiolipin antibody. Br J Haematol 1985; 59: 227–230.
15. Gastineau DA, Kasmier FJ, Nicols WL, Bowie EJW. Lupus anticoagulant: an analysis of the clinical and laboratory features of 219 cases. Am J Haematol 1985; 19: 265–275.
16. Branch DW, Scott JR, Kochenour NK, Hershgold E. Obstetric complications associated with the lupus anticoagulant. N Engl J Med 1985; 313: 1322–1329.
17. Lubbe WF, Butler WS, Palmer SJ, Liggins GC. Fetal survival after prednisone suppression of maternal lupus-anticoagulant. Lancet 1983; ii: 1361–1363.
18. Frampton G, Cameron JS, Thom M et al. Successful removal of antiphospholipid antibody during pregnancy using plasma exchange and low-dose prednisolone. Lancet 1987; ii: 1023–1024.
19. Harris EN, Gharavi AE, Boey ML, Patel BM et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet 1983; ii: 1211–1214.
20. Derksen RHWM, Biesma D, Bouma BN et al. Discordant effects of prednisone on anticardiolipin antibodies and the lupus anticoagulant. Arthritis Rheum 1986; 29: 1295–1296.
21. Grob JJ, Bonerandi JJ. Les anticorps antiphospholipides. Une nouvelle donnée dans la pathogénie des collagénoses. Ann Dermatol Venereol 1986; 113: 811–818.
22. Sontheimer RD. The anticardiolipin syndrome. A new way to slice an old pie, or a new pie to slice? Arch Dermatol 1987; 123: 590–595.
23. Asherson RA, Mackay IR, Harris EN. Myocardial infarction in a young man with systemic lupus erythematosus, deep vein thrombosis, and antibodies to phospholipid. Br Heart J 1986; 56: 190–193.
24. Averbuch M, Levo Y. Budd-Chiari syndrome as the major thrombotic complication of systemic lupus erythematosus with the lupus anticoagulant. Ann Rheum Dis 1986; 45: 435–437.
25. Asherson RA, Mackworth-Young CG, Boey MI et al. Pulmonary hypertension in systemic lupus erythematosus. Br Med J 1983; 287: 1024–1025.
26. Landi G, Calloni MV, Sabbadini MG et al. Recurrent ischemic attacks in two young adults with lupus anticoagulant. Stroke 1983; 14: 377–379.
27. Weinstein C, Miller MH, Axtens R et al. Livedo reticularis associated with increased titers of anticardiolipin antibodies in systemic lupus erythematosus. Arch Dermatol 1987; 123: 596–600.
28. Dodd HJ, Sarkany I, O'Shaughnessy D. Widespread cutaneous necrosis associated with the lupus anticoagulant. Clin Exp Dermatol 1985; 10: 581–586.

29. Englert HJ, Hawkes CH, Boey ML et al. Degos' disease: association with anticardiolipin antibodies and the lupus anticoagulant. Br Med J 1984; 289: 576.
30. Jindal BK, Martin MFR, Gayner A. Gangrene developing after minor surgery in a patient with undiagnosed systemic lupus erythematosus and lupus anticoagulant. Ann Rheum Dis 1983; 42: 347–349.
31. Grob JJ, Bonerandi JJ. Cutaneous manifestations associated with the presence of the lupus anticoagulant. J Am Acad Dermatol 1986; 15: 211–219.
32. Gharavi AE, Harris EN, Asherson RA, Hughes GRV. Anticardiolipin antibodies: isotype distribution and phospholipid specificity. Ann Rheum Dis 1987; 46: 1–6.