Thrombosis in systemic lupus erythematosus: striking association with the presence of circulating lupus anticoagulant

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Abstract

The lupus anticoagulant was found in the plasma of 31 of 60 patients with systemic lupus erythematosus and other connective tissue disorders (mixed connective tissue disease, systemic vasculitis, polyarteritis nodosa, primary sicca syndrome, discoid lupus, Behçet's syndrome, and systemic sclerosis). Strong associations were found with biological false positive seroreaction for syphilis and thrombocytopenia. The most striking association, however, was with the high prevalence of thrombosis. This tendency to thrombosis was independent of disease activity of systemic lupus erythematosus.

The lupus anticoagulant appears to be a useful marker for a subset of patients with systemic lupus erythematosus at risk for the development of thromboembolic complications.

Introduction

A clotting defect due to the so called "lupus anticoagulant" in the plasma of patients with systemic lupus erythematosus was first recognised by Conley and Hartmann in 1952[1] but the first case report was probably that of Aggeler, Lindsay, and Lucia in 1946.[2] Since then it has become apparent that the lupus anticoagulant is an antibody[3] that is a prothrombinase complex inhibitor.[4 5] In vitro the presence of the lupus anticoagulant is characterised by a prolonged kaolin partial thromboplastin time. Paradoxically, in vivo it appears to have a hypercoagulable effect.[6]

We studied 60 patients with systemic lupus erythematosus and other connective tissue disorders. Clinical and serological findings in these patients were related to the presence or absence of lupus anticoagulant.

Materials and methods

Forty nine patients with systemic lupus erythematosus and 11 patients with other connective tissue disorders were studied. All the patients with systemic lupus erythematosus fulfilled the revised criteria of the American Rheumatism Association.[7] Of the 11 patients with other connective tissue disorders, four had mixed connective tissue disease, two systemic vasculitis, and one each of polyarteritis nodosa, primary sicca syndrome, discoid lupus, Behçet's syndrome, and systemic sclerosis. Fifty three patients were female and seven male.

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The clinical manifestations were recorded and complications of thrombosis and/or recurrent abortions sought. Routine haematological tests were performed in addition to the reaginic test for syphilis (Venereal Disease Reference Laboratory) and tests for antinuclear antibody, antibodies to deoxyribonucleic acid (DNA), and antibodies to extractable nuclear antigen.

TESTS FOR LUPUS ANTICOAGULANT ACTIVITY

A modified mixing partial thromboplastin time with kaolin by the method of Proctor and Rapaport was used.[8]

Platelet poor plasma was obtained from nine parts of blood into one part of 3·8% sodium citrate and spun at 3000 g for 15 min; 0·1 ml of this platelet poor plasma was added to 0·1 ml of a diluted (1 in 5) kaolin platelet substitute (Diagen, UK) and incubated for 2 minutes at 37°C, 0·1 ml of 0·025 mol/l calcium chloride was then added. The time from the addition of calcium chloride to the formation of a clot was accurately determined. The test was carried out in duplicate and the mean value obtained.

The test was repeated by mixing 50 μl of patients' plasma or immunoglobulin fraction to an equal volume of a control pooled normal plasma. Prolongation of normal pooled plasma partial thromboplastin time with kaolin by more than 10 seconds—that is, a time of >80 seconds—was considered positive evidence for the presence of the lupus anticoagulant.

SEPARATION OF IMMUNOGLOBULIN FRACTIONS

In an attempt to facilitate the measurement of lupus anticoagulant activity of five patients receiving warfarin, their plasma samples were fractionated.

A 2 ml sample of plasma was used. IgG was isolated by 45% ammonium sulphate precipitation and diethylaminoethanol cellulose (Watman Ltd, UK) ion exchange chromatography with 0·01 mol/l phosphate buffer pH 8·1. Igm was isolated by 45% ammonium sulphate precipitation and Sephacryl S300 (Pharmacia, Uppsala, Sweden) chromatography with phosphate buffered saline as running buffer. Trace amounts of IgG were removed by Sepharose 4B and protein A column. IgG and IgM fractions were concentrated to the original volume of the plasma (2 ml).

STATISTICAL ANALYSIS

The data were analysed by χ^2 test.

Results

AGE AND DURATION OF DISEASE

The mean age at follow up was 32·7 years (range 13-59). Mean age of onset of symptoms was 25·9 years and the duration of symptoms was 5·4 years.

SEROLOGY

A total of 31 of the 60 patients (26 female and five male) were found to have the lupus anticoagulant activity; 25 of these had systemic lupus erythematosus. Biological false positive seroreaction for syphilis was present in seven patients out of 60 and all seven had lupus anticoagulant activity (table I): the association was significant ($p < 0·05$).

Increased titres of antibodies to DNA were present in 11 patients with lupus anticoagulant activity and in 16 without the activity. No association was found with increased DNA binding or the presence of antibodies to extractable nuclear antigen could be shown (table I).

Plasma samples of eight patients were fractionated, and the immunoglobulin fractions were tested for the lupus anticoagulant activity. Five of the eight patients were receiving warfarin. The activity resided in the IgG fraction in all eight patients and in both the IgG and IgM fractions in four.

TABLE I—*Serological and clinical findings in patients with and without lupus anticoagulant*

	Patients with lupus anticoagulant (n = 31)	Patients without lupus anticoagulant (n = 29)	p value
Serological findings:			
Biological false positive reaction for syphilis	7	0	<0·05
DNA binding (>30%)	11	16	NS
Extractable nuclear antigens (ribonucleoprotein, Sm, Ro, La)	13	16	NS
Clinical findings:			
Thrombosis	18	3	<0·01
Previous abortions*	9	5	NS
Thrombocytopenia	9	1	<0·02
Disease of central nervous system	17	10	NS

NS = Not significant.
* 26 women in group with anticoagulant, 27 in group without.

CLINICAL CORRELATIONS

Thrombotic episodes such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, renal vein thrombosis, and axillary vein thrombosis were recorded in 18 of the 31 patients with lupus anticoagulant activity (table II). This increased prevalence of thrombosis in patients with the activity was highly significant ($p<0·01$).

TABLE II—*Thrombotic events in patients with the lupus anticoagulant*

Thrombosis	No of patients
Deep vein thrombosis	11
Pulmonary embolism	3
Cerebrovascular accident	10
Renal vein thrombosis	1
Axillary vein thrombosis	2
Central retinal vein thrombosis	2

Of the 26 female patients with lupus anticoagulant activity, 9 gave a history of one or more abortions. Only five patients without the activity had had abortions.

Nine of the 31 patients with lupus anticoagulant had platelet counts below 100×10^9/l compared with only one of those without the anticoagulant. None of the patients with thrombocytopenia suffered haemorrhages.

Central nervous system disease, as defined by neuropsychiatric manifestations or cerebrovascular accidents, was present in 17 patients with the lupus anticoagulant and in 10 without. No significant correlation was found between the two groups of patients. Catterall reported the association of chronic biologically false positive reaction to the tests for syphilis and "lupoid sclerosis" in six young women who presented with symptoms and signs of a neurological disorder resembling multiple sclerosis.[9] In our present study no patient had evidence of demyelinating disease, although dementia was present in two patients with biological false positive reactions.

Four patients with the lupus anticoagulant had pulmonary hypertension confirmed by right heart catheter studies; this could be more than a chance association.

Discussion

Thrombosis has long been recognised as a complication of systemic lupus erythematosus.[10] In addition to the occurrence of leg vein thrombosis in up to 15% of patients with systemic lupus erythematosus,[1] thrombosis in renal, retinal, cerebral, and pulmonary veins are well recognised.[12] In this study we have extended earlier observations and shown a highly significant association between the presence of thrombotic complications in systemic lupus erythematosus and related connective tissue disorders and the presence of the lupus anticoagulant.

The lupus anticoagulant is an acquired inhibitor of the prothrombin complex (factor Xa, factor V, and phospholipid).[4 5] It has been shown in patients with systemic lupus erythematosus and in a heterogeneous group of patients.[13] It appears to have a specific antiphospholipid activity against the phospholipid portion of the prothrombin activator complex.[14 15] In our study 49 of 60 patients had systemic lupus erythematosus. We confirmed the association between the lupus anticoagulant and the high incidence of another antibody with phospholipid specificity, a biological false positive reaction for syphilis.[16 17] The antibody nature of the lupus anticoagulant has been shown, and is in agreement with the findings of other investigations[3 18]: it is characterised as IgG or IgM or a mixed IgG and IgM.

A very strong association between the lupus anticoagulant and clotting defect was noted in our patients. The presence of the anticoagulant may play a critical but as yet unclear part in the activation of the coagulation system in the complex mechanism of immune disorder. It has been suggested that by its reaction with phospholipid in platelets it could cause cellular damage by interference with release of arachidonic acid, the substrate for production of prostacyclin, which is a physiological inhibitor of platelet aggregation. This vascular endothelial cell injury results in lowered prostacyclin concentrations and this may predispose to thrombosis.[19 20]

The presence of lupus anticoagulant appears to define a subset of patients with recurrent abortions[21] and thrombocytopenia. Although a high fetal wastage has been recognised in women with systemic lupus erythematosus, the exact cause is unclear. The significant association with the lupus anticoagulant, an antibody, adds evidence to the immunological mechanism for spontaneous abortion in systemic lupus erythematosus. The thrombocytopenia could result from antiphospholipid activity of the lupus anticoagulant on platelets. The lack of haemorrhagic tendencies is unexplained and the relation between thrombocytopenia and thrombosis is unknown.

The varied associations of the lupus anticoagulant shown in our study have practical relevance in the management of patients. Administration of steroids may result in reduction or disappearance of the anticoagulant activity.[5 22] The lupus anticoagulant disappeared in one of our patients after plasmapheresis and in another after pulse immunosuppressive treatment for his primary disease. We suggest that the detection and measurement of the lupus anticoagulant could serve both as a marker of disease and in the assessment of disease activity in the follow up of patients.

Finally, the finding of lupus anticoagulant activity in four patients with pulmonary hypertension, one patient with Behçet's disease and thrombosis, and two patients with dementia and recurrent cerebral thrombosis suggests that the presence of the anticoagulant may have implications in thrombotic diseases other than systemic lupus erythematosus.

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SHORT REPORTS

Ascites in breast cancer

Metastatic breast cancer may manifest as serous effusions. Pleural effusions are a common complication of breast cancer, and recent studies have shown that they may be alleviated effectively by early chemical pleurodesis.[1] Patients treated in this way have a mean survival time of 16 months from presentation.[2] To determine whether similar relief might be obtained in patients with the less common complication of ascites, we reviewed patients under the care of this unit who developed ascites during the decade 1972-81; we established the incidence of this complication, the clinical features of the patients, and the duration of survival after presentation with ascites.

Patients, methods, and results

We reviewed the records of 56 patients with histologically confirmed breast cancer who developed clinical evidence of ascites. In 11 (20%) of them ascites had been the first manifestation of metastatic disease. The mean survival time was 5·7 months (range 0-48 months). An arbitary division was made at three months: 38 (68%) of the patients with ascites died within this time (short term survivors), 25 (45%) dying within one month. The short term and longer term survivors were compared to establish clinical features at presentation that might identify potential longer term survivors and establish the most appropriate treatment.

There was no difference in age at diagnosis, clinical stage, disease free interval, and ascites free interval between the two groups. Similar proportions of both groups had undergone oophorectomy or received cytotoxic chemotherapy, or both.

The table shows the pattern of metastatic disease. Eleven (61%) of the longer term survivors compared with only eight (21%) of the short term survivors had previously had skin metastasis ($\chi^2 = 8$, $p < 0{\cdot}005$). The proportions of patients with nodal and bone metastasis and pleural effusion were similar in the two groups. Hepatomegaly or jaundice was present in 60% of the short term survivors and in only 11% of the longer term survivors ($\chi^2 = 12{\cdot}06$, $p < 0{\cdot}001$). This suggests that palpable liver enlargement or jaundice indicates a bad prognosis.

Pattern of metastatic disease among 56 patients with ascites. Figures are numbers (%) of patients

Symptoms and previous metastases and treatment	Longer term survivors (n = 18)	Short term survivors (n = 38)
Ascites first symptom	2 (11)	9 (24)
Hepatomegaly or jaundice	2 (11)	23 (60)
Previous disease:		
Lymph node	2 (11)	4 (11)
Skin	11 (61)	8 (21)
Bone	6 (33)	22 (58)
Pleura	5 (28)	5 (13)
Previous treatment:		
Oophorectomy	5 (28)	7 (18)
Chemotherapy	4 (22)	16 (42)

Of the 25 patients with hepatomegaly or jaundice, 23 (92%) died within three months. Necropsy was performed in four patients who died early; in each the liver was almost completely replaced by tumour deposits. In contrast, laparotomy in three of the longer term survivors showed peritoneal seedlings without evidence of liver metastases. The usefulness of hepatomegaly or jaundice as a prognostic factor is not altered by additional information on previous skin metastasis.

Various treatments were used among both short and longer term survivors. This suggests that it is hepatic metastases rather than any particular treatment that determines survival.

Comment

These findings may have implications for the management of patients with ascites secondary to breast cancer. Of those patients who have associated hepatomegaly or jaundice, 90% will be dead within three months, probably as a result of liver failure, and will gain no benefit from active local treatment of their ascites. In contrast, the longer term survivors will emerge from those patients in whom hepatomegaly and jaundice are absent. These patients with supposed peritoneal metastases may benefit from local treatment provided that they have adequate hepatic function, as assessed by radioisotopic scanning and blood biochemistry tests, and do not have overt disease elsewhere requiring systemic treatment.

Each of the longer term survivors was treated empirically, and ascites was controlled in one third of cases. A similar response rate would be predicted for patients with advanced breast cancer given endocrine treatment or cytotoxic chemotherapy. We do not know whether specific local treatment such as intracavitary adriamycin[3] or peritoneovenous shunts[4] gives any greater benefit than systemic treatment alone. A multicentre controlled trial would be needed to answer this question.

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