Reduced prostacyclin activity in systemic lupus erythematosus

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SUMMARY When fresh rabbit aorta is incubated with plasma, prostacyclin, a potent inhibitor of platelet aggregation, is normally released. Plasma obtained from 2 patients with systemic lupus erythematosus (SLE) inhibited prostacyclin activity, while plasma from 22 other patients with SLE and 40 normal control subjects showed normal activity. Absence of prostacyclin activity did not appear to correlate with the clinical severity of the underlying disease. The possible association of this finding and the presence of thrombotic lesions in both patients is discussed.

The incidence of thrombotic lesions in patients with systemic lupus erythematosus (SLE) is well documented and is considerably higher than that found in the general population.^{1,2} The aetiology of these episodes is unknown.

It has recently been demonstrated that blood vessels produce prostacyclin (PGI_2), an unstable product of prostaglandin endoperoxides.³ PGI_2 is a potent inhibitor of platelet aggregation and may be responsible for the lack of adhesion and aggregation of platelets to intact vascular endothelial surfaces.⁴ It is possible that absent PGI_2 activity may predispose to thrombotic attacks. Since plasma from SLE patients may contain antibodies directed against a large number of different antigen systems, it is of interest to determine if it may alter PGI_2 activity. We present 2 patients whose plasma inhibited PGI_2 activity. Both patients had a past history of vascular thrombotic episodes.

Methods

Citrated plasma was obtained from 24 patients with SLE and 40 normal control volunteers by standard techniques. The diagnosis of SLE was made in accordance with the American Rheumatism Association criteria. The age range in both groups was 20 to 50 years. Fifteen patients were taking prednisone 5-20 mg daily, 5 were taking azathioprine 100-150 mg daily, and 5 were on no medication.

At the time of study no patient had received aspirin within 7 days, and platelet counts on all patients studied were within the normal range.

PGI_2 activity was determined by a previously described method.⁵ A healthy New Zealand white rabbit was killed by intravenous pentobarbitone and the aorta removed. Rings of aorta (30-60 mg wet weight) were kept in Tris buffer 0.05 M, pH 7.3, at 4°C for up to 2 hours. 250 ml of the patient's plasma was incubated with a ring of aorta for 5 minutes at 22°C. The supernatant was then added to an equal volume of platelet-rich plasma (PRP) obtained from a healthy volunteer (final platelet concentration of $200 \times 10^9/\text{l}$) for 1 minute at 22°C. To 250 μl of this mixture, adenosine-5-diphosphate (ADP) was added to give a final ADP concentration of 2.5 μM , and platelet aggregation was assessed in a Payton dual channel aggregometer. Normally, inhibition of platelet aggregation by PGI_2 is found. Controls consisted of the patient's plasma added to normal PRP prior to ADP aggregation but without incubation with rabbit aorta. No inhibition of platelet aggregation is normally found.

Case reports

Case 1. A 25-year-old woman was diagnosed as having SLE in 1976. Initial treatment consisted of prednisone and azathioprine. In March 1977 she developed a deep venous thrombosis in her left leg followed by a similar incident in her right leg in February 1978. An acute exacerbation of SLE in August 1978 with joint, renal, and central nervous system involvement was treated with high-dose

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prednisone and plasma exchange. At the time of the present study she was in clinical remission, though high levels of plasma DNA binding activity and circulating immune complexes were present. She was taking prednisone 15 mg daily and azathioprine 100 mg daily. Inhibition of PGI₂ activity following incubation of the patient's plasma with rabbit aorta was demonstrated (Fig. 1). Similar inhibition was found on 2 subsequent occasions during the next 3 months.

Case 2. A 39-year-old woman with a 15-year history of SLE recently developed renal involvement with proteinuria and a reduced creatinine clearance rate. Two months before this she had an anterolateral myocardial infarction. At the time of study she was in complete remission, with normal plasma DNA binding activity and immune complex levels and was taking prednisone 10 mg daily and azathioprine 125 mg daily. Inhibition of PGI₂ activity (similar to that of patient 1) was demonstrated. This was confirmed on a subsequent examination, but at present PGI₂ activity is normal.

Fig. 1 ADP-induced aggregation of platelets after dilution with normal plasma (A) or patient's plasma (B). A₁ represents normal platelet aggregation and A₂ inhibition of aggregation by added prostacyclin. Prostacyclin did not inhibit aggregation in the presence of the patient's plasma (B₂).

Discussion

Prostacyclin is produced by vascular tissue and is a potent vasodilator and inhibitor of platelet aggregation. It has been demonstrated that PGI₂ prevents platelets adhering to normal vascular endothelial surfaces⁴ in an in-vitro system. The role of PGI₂ in the prevention of arterial and venous thrombotic disease is at present unknown. It had been suggested that diseases such as thrombotic thrombocytopenic purpura lack PGI₂ owing to a deficiency of a necessary plasma factor.⁶ PGI₂ has been shown to significantly improve the symptoms of patients with severe, advanced peripheral vascular disease possibly owing to its ability to disperse platelet aggregates.⁷

It is therefore likely that any disease which inhibits the formation of PGI₂ or alters the activity of released PGI₂ renders a patient more susceptible to thrombotic episodes. The plasma from 2 of our 24 patients with SLE clearly impaired the activity of PGI₂ obtained from rabbit aorta. Furthermore, these were the only patients in this study group to have a previous history of thrombotic episodes. While a cause-and-effect relationship cannot be determined on such a small number of patients, the finding is nevertheless interesting and worthy of further study.

While inhibitory activity is no longer detectable in both patients' plasma, it must be recognised that our test system is crude and lacks sensitivity. More sensitive test systems may demonstrate a higher incidence of absent plasma PGI₂ activity in this group of patients.

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