Acta Paediatrica Hungarica, 29 (3—4), pp 293—298 (1988—1989)

Plasma exchange and immunosuppressive therapy in a paediatric patient with systemic lupus erythematosus

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Received 8 June 1987

A case is reported of systemic lupus erythematosus (SLE) associated with steroid-resistant nephrotic syndrome. Serial plasma exchanges (PE) combined with prednisolone treatment induced complete normalization of the immunological findings: the anti-DNA antibody, antinuclear antibody, LE cell phenomenon and circulatory immune complexes became negative. The prostacyclin (PGI_2) production-supporting activity in the plasma increased to the control range; inhibitors of PGI_2 production were eliminated. The creatinine clearance normalized, the urinary protein excretion decreased significantly, and the facial erythema disappeared. Continued treatment with chlorambucil + low-dose prednisolone led to a complete and stable remission of the nephrotic syndrome, and the C_3 complement normalized. The low level of PGI_2 production-supporting activity in the plasma may be explained by the inhibitor of PGI_2 production. PE + immunosuppressive therapy might have beneficial effects on the immunological changes and PGI_2 metabolism, and also on the remission of SLE-nephrotic syndrome.

Systemic lupus erythematosus (SLE) is considered a prototype of the immunologically mediated disease. Nonglomerular circulating immune complexes (CIC) containing DNA antigens and DNA antibodies (and other immunoproteins, autoantibodies) are trapped by small vessels of numerous organs or are formed in situ, leading to disseminated vasculitis [1]. The renal involvement is one of the major causes of mortality [6]. Until recently the most frequently used treatment of SLE involved corticosteroids, azathioprine and cyclophosphamide. The management has changed during the last few years by the availability of dialysis, plasma exchange (PE), large doses of methylprednisolone and antiplatelet agents [2]. We report here on a patient with SLE, associated with steroid-resistant nephrotic syndrome, who was successfully treated by a combination of PE, chlorambucil and prednisolone. The effects of therapy on the immune system and prostacyclin (PGI_2) metabolism were followed.

Case report

A ten-year-old boy was admitted with the symptoms of SLE: facial erythema, persisting microscopic and intermittent macroscopic haematuria associated with proteinuria (6 g/24 hours, urinary protein selectivity in-

dex 0.46) and azotaemia (creatinine clearance: 42 ml/min/1.7 m^2). White blood cell count 2800/μl, platelet count 90 000/μl. The immunological findings corresponded to SLE with respect to the high concentration of anti DNA antibody [8], positive LE cell phenomenon [4], antinuclear antibody (ANA) [3], CIC (7.11) and low level of C_3 complement in the serum. Histological study of the kidney demonstrated a diffuse membranous glomerulonephritis corresponding to class V/D according to the WHO classification [5]. This was combined with diffuse glomerulonephritis and mesangial proliferation with widespread subendothelial deposition. Treatment prior to admission was performed with high-dose prednisolone (2mg/kg bwt/day), which was continued with 1 mg/kg bwt alternate day steroid therapy. As no response was observed, PE-s were performed by Bellco plasmaflow on eight occasions during a period of two months. The removed plasma was replaced by 1.5—2 l fresh frozen plasma. During the first six weeks prednisolone was given on alternate days (1 mg/kg bwt); this was continued with 2 mg/kg bwt steroid treatment daily during the following 2 weeks. Between the 3rd and 5th months the therapy was changed to a 0.2 mg/kg bwt/day chlorambucil and 1 mg/kg bwt alternate day prednisolone regimen. Since the 6th month prednisolone has been continued in the same dose for 14 months.

The kidney function (serum creatinine, urea N, electrolytes, creatinine clearance, protein excretion), serum protein components, immunoglobulins, C_3 complement, anti DNA antibody concentrations in the serum, CIC, LE cell phenomenon and ANA were controlled regularly. The PGI_2-supporting activity (PSA) and inhibitory effect against PGI_2 production were studied in the patient plasma before and after PE-s. The capacity of the plasma to support PGI_2-like activity was assessed by measurement of the platelet antiaggregatory activity by the method of Moncada et al [10]. The principle of this method is that human umbilical arterial rings lose their PGI_2-producing ability following repeated washing with buffer solution. Normal plasma is able to regenerate PGI_2 production from the vascular endothelium in the presence of PGI_2 stimulating factor [13]. In the study of inhibitor of PGI_2 production fresh unexhausted umbilical arterial rings were used the PGI_2-producing ability of which is eliminated by any inhibitors present in the plasma [13].

The inhibitory effect was characterized by the quotient of the aggregations after incubation with patient and control plasma.

Results

Following a transitional increase, the level of proteinuria decreased after the fifth PE, when treatment was continued with high-dose prednisolone. The creatinine clearance normalized (104 ml/min/1.7 m^2). During chlorambucil and low-dose steroid treatment, the urine became negative. In

the 20th month the kidney function remained normal and proteinuria was not detected (Fig. 1). Immunological findings are given in Table I. PE combined with low-dose alternate day prednisolone therapy lowered the anti-DNA antibody concentration. The ANA, LE cell phenomenon and CIC in the serum became negative during PE + high-dose prednisolone treatment. The C_3 complement concentration increased considerably and achieved the normal level during chlorambucil and low-dose prednisolone therapy. The other findings remained negative (Table I.).

The plasma PSA was significantly lower in the patient than in the 10 age-matched controls. This normalized following the first PE, but had decreased again before the second PE. Each PE improved the plasma PSA, but only temporarily. An inhibitory effect against PGI_2 production was demonstrated in the patient plasma prior to the PE-s; this had disappeared following the PE-s. Finally the PSA stabilized (45%) following the eight PE, and increased during remission (60%), no inhibitory activity against PGI_2 production was observed (Table II).

Discussion

A low level of PSA was demonstrated in the plasma from the SLE patient, which might be explained by the inhibition of PGI_2 production. PE enhanced the PSA and inhibitors were eliminated. Steroid therapy alone did not influence the clinical symptoms, PSA level and immunological changes. Our findings support the hypothesis that disturbances in the PGI_2 metabolism might have an im-

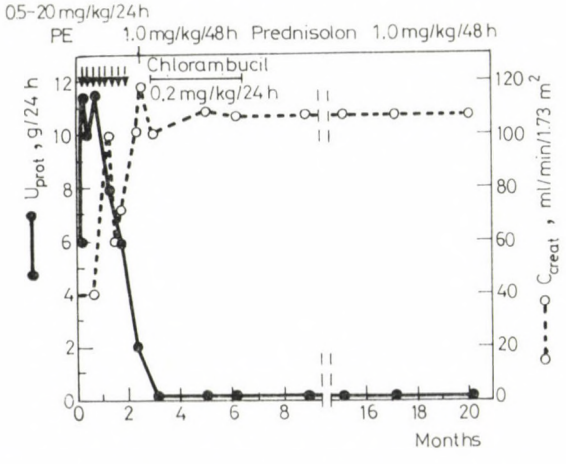

FIG. 1. The changes of creatinine clearance and protein excretion during plasma exchange and immunosuppressive treatment. PE = plasma exchange; U_{prot} = urinary protein excretion; C_{creat} = creatinine clearance

TABLE I

Immunological changes during PE + immunosuppressive treatment

	Prednisolone	Chlorambucil	Anti DNA antibody μg/ml	ANA	LE cell phenomenon	C_3 complement mg/100 ml	CIC
Before 1st PE	2 mg/kg/24 hours		72.5	+	+	60	1 : 64
Following 1st PE	1 mg/kg/48 hours		70.0	+	+	70	1 : 8
Following 2nd PE	1 mg/kg/48 hours		41.0	+	+	68	1 : 8
Following 3rd PE	1 mg/kg/48 hours		32.0	+	+	68	1 : 8
Following 4th PE	1 mg/kg/48 hours		20.0	+	+	63	1 : 4
Following 5th PE	1 mg/kg/48 hours		5.0	+	+	63	1 : 4
Following 6th PE	2 mg/kg/24 hours		2.5	+	+	65	—
Following 7th PE	2 mg/kg/24 hours		5.0	+	—	74	—
Following 8th PE	2 mg/kg/24 hours		1.0	—	—	80	—
3rd—5th month	1 mg/kg/48 hours	0.2 mg/kg/24 hours	1.0	—	—	105	—
6th—20th month	1 mg/kg/48 hours		1.0	—	—	108	—

—: (ANA, LE cell phenomenon, CIC) negative
+: positive

portant role in the pathogenesis of SLE-vasculitis [9]. PGI_2 is a strong vasodilator and inhibits platelet aggregation. In the absence of PGI_2, thromboxane B_2 released from activated neutrophilic granulocytes and aggregating platelets causes vasoconstriction, induces chemotaxis and enhances platelet aggregation. These processes contribute to the development of diffuse renal functional damage [12] with proliferative glomerulonephritis. In addition, endothelial damage decreases PGI_2 production. The chemical structure(s) of the inhibitor(s) of PGI_2 production have not been established. Several kinds of compounds presumably have a similar effect. Serial PE-s resulted in increases of the effects supporting PGI_2 production, and the elimination of inhibitors which blocked PGI_2 release. PE combined with steroid administration contributes to an improvement in kidney function, a decrease in protein excretion and the disappearance of erythema. Immunological findings: anti DNA antibody, ANA, LE cell phenomenon and CIC became negative, and the C_3 complement concentration rose. The clinical importance of the use of PE in SLE appears to be that the dosage and duration of immunosuppressive treatment may be reduced markedly, but a rapid improvement in the clinical symptoms, immunological status and PGI_2 metabolism is still attained. We therefore suggest the use of treatment with combined PE + immunosuppressive therapy in serious SLE associated with nephrotic syndrome.

TABLE II

Plasma PSA and inhibitory effect against PGI_2 production in SLE

	Immunosuppression	PSA (%)	Inhibitor of PGI_2 production
Before 1st PE	Prednisolone	28.5	2.0
After		75.0	1.0
Before 2nd PE	Prednisolone	29.8	1.2
After		55.0	1.0
Before 3rd PE	Prednisolone	10.6	2.6
After		54.3	1.0
Before 4th PE	Prednisolone	33.3	1.3
After		42.2	1.0
Before 5th PE	Prednisolone	23.3	1.8
After		49.5	1.0
Before 6th PE	Prednisolone	32.5	1.3
After		52.3	1.0
Before 7th PE	Prednisolone	27.2	1.5
After		43.2	1.0
Before 8th PE	Prednisolone	33.3	1.3
After		55.0	1.0
3rd—5th month	Chlorambucil + Prednisolone	45.0	1.0
6th—20th month	Prednisolone	60.0	1.0

Plasma PSA control value > 40%
PGI_2 inhibitor control = 1.0

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