

Methylprednisolone pulse therapy for nonrenal lupus erythematosus

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SUMMARY High-dose intravenous methylprednisolone therapy has previously been shown to be efficacious in the treatment of renal lupus erythematosus. The present report presents 2 patients with life-threatening, nonrenal lupus erythematosus. One patient had coma and seizures, while the other had severe thrombocytopenia and anaemia. Both had failed to respond to oral corticosteroid therapy in high doses but had dramatic clinical responses with intravenous methylprednisolone given in 'pulses.' Possible mechanisms of clinical improvement are discussed.

High-dose intravenous methylprednisolone given in 'pulses' has become an established therapy for the prevention of acute renal graft rejection.^{1,2} Each pulse consists of an intermittent large dose of intravenous methylprednisolone given over several days. This form of therapy has also been tried in severe glomerulonephritis³ and in proliferative lupus nephritis⁴⁻⁶ with improvement in clinical and laboratory parameters of renal disease activity.

While previous reports have shown reversal of deteriorating renal function in lupus erythematosus,⁴⁻⁶ little is known about the effects of pulse therapy in life-threatening, nonrenal manifestations of systemic lupus erythematosus (SLE). We report 2 cases of patients with life-threatening, nonrenal complications of SLE, one with central nervous system (CNS) involvement and one with haemolysis and thrombocytopenia, in which large doses of intravenous methylprednisolone were given after clinical failure with large doses of oral prednisone.

Patients and materials

CASE 1

A 23-year-old white female was admitted to hospital in December 1977 with a 4-month history of fever, myalgias, arthralgias, alopecia, and facial rash. The patient had previously been in good health except

for psoriasis of 11 years' duration recently treated with psoralen and ultraviolet light (PUVA).

In August 1977, within 1 day of a heavy sun exposure, she developed fevers, arthralgias, myalgias, and a macular rash on the face, shoulders, and back. Despite treatment with a brief course of 10 mg prednisone daily and aspirin, her rash and other symptoms persisted. In October 1977 serum fluorescent antinuclear antibodies (FANA) were detected at a titre of 1:100 with normal serum C3 and C4. Proteinuria of 1.3 g per 24 hours was detected.

On admission in December 1977 physical examination revealed an oral temperature of 38.6°C. There was a blotchy erythematous rash on the face, forehead, back, and shoulders, diffuse alopecia, and typical psoriatic plaques at the elbows and knees. The spleen was palpable at the left costal margin.

Laboratory evaluation included a haemoglobin of 11.3 g/dl and white blood cell count of $3.2 \times 10^9/l$ with 30% bands, 49% polymorphonuclear cells, 9% lymphocytes, 10% monocytes, and 2% eosinophils. Urine analysis showed only proteinuria, and a 24-hour urine collection showed 4.5 g of protein and a creatinine of 87 ml/min. Serum fluorescent antinuclear antibodies (FANA) were detected at a titre of 1:512 with homogeneous pattern, and the Westergren sedimentation rate was 88 mm/h. Serum C3 was 150 mg/100 ml (normal 87 to 204) and C4 was 24 mg/100 ml (normal 15 to 24). Serum IgG was 1700 mg/100 ml (normal 655 to 1551), serum IgA was 300 mg/100 ml (normal 63 to 390), and

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IgM was 150 mg/100 ml (normal 60 to 347). (SI: mg/l = mg/100 ml \times 10.)

A renal biopsy showed focal mesangial proliferation. A skin biopsy from the right elbow showed hyperkeratosis, parakeratosis, regular acanthosis, and a mild perivascular inflammation consistent with psoriasis. A second biopsy from the back showed follicular plugging, thinning of the epidermis, and chronic perivascular and periappendaged inflammation 'consistent' with lupus. An immunofluorescent band test was done on uninvolved skin and showed only stippling for C3 at the dermal-epidermal junction.

Initially the patient responded to aspirin, though fever and proteinuria recurred. 40 mg of prednisone daily was added with improvement in clinical condition, though her serum C3 fell to 62 mg/100 ml and serum C4 to 9 mg/100 ml and remained low. A repeat serum FANA titre was 1:1024. Antibodies to extractable nuclear antigens were found at 1:100 000, with both RNAase-sensitive RNP and Sm antibodies being present.

In February 1978, after the dose of oral prednisone had been slowly tapered to 25 mg daily, the patient developed high fevers, grand mal seizures, and obtundation. A single cytoid body was observed. The cerebrospinal fluid showed 40 WBC/mm³, 60% of which were lymphocytes and the rest polymorphonuclear cells. The cerebrospinal fluid (CSF) protein was 147 mg/100 ml (1.47 g/l). Despite 100 mg of daily oral prednisone the patient deteriorated rapidly with coma and seizures. Adequate levels of phenytoin and phenobarbital were ineffective in controlling seizures.

1 g of intravenous methylprednisolone was given daily as a single dose for 3 days with complete resolution of neurological symptoms and fever. Within 1 week of methylprednisolone therapy serum C3 was 155 mg/100 ml and C4 32.8 mg/100 ml and have remained normal. The Westergren sedimentation rate rapidly decreased to 18 mm/h and proteinuria disappeared. Serum IgG decreased to 960 mg/100 ml, serum IgA to less than 60 mg/100 ml, and IgM to 62 mg/100 ml. Repeat lumbar puncture revealed normal CSF findings.

Ten months later the patient is clinically well except for alopecia on 50 mg of prednisone daily.

CASE 2

A 49-year-old black female was admitted to the hospital in March 1978 with complaints of weakness, dizziness, and shortness of breath of 4 months' duration. The patient had noticed weight loss despite a good appetite. She complained of stiffness and arthralgias, primarily in her hands, of 6 months' duration.

Her past history was remarkable in that the bone marrow was examined for anaemia after an operation for ovarian cyst in 1969 and showed a plasmacytosis. No cause was established. Hyperthyroidism was diagnosed in 1972, treated initially with ¹³¹I and subsequently with propylthiouracil and propranolol. These were discontinued in May 1977 for a leucopenia which quickly resolved.

Physical examination on admission revealed frontotemporal alopecia, a dense right cataract, and a left iridectomy scar. Lymph nodes were palpable in the cervical, periauricular, axillary, and epitroclear regions. A grade II/VI systolic ejection murmur was audible at the base and left sternal border. Liver span was 12 cm, with 3 cm palpable below the costal margin. The spleen was not enlarged. The joints were normal except for chronic, post-traumatic changes of the right knee. Neurological testing gave normal results.

Laboratory tests on admission showed a normal chest x-ray and electrocardiogram. Haemoglobin was 7.1 g/dl, leucocytes 7.6 \times 10⁹/l, reticulocyte count 1.6%, and platelets 120 \times 10⁹/l. (A blood count done 2 weeks before admission in evaluation of a self-limited episode of diarrhoea showed a haemoglobin 9.9 g/dl). Urine analysis, liver function tests, and serum electrolytes were normal. The Westergren sedimentation rate was 114 mm/h.

The hospital course was marked by intermittent febrile episodes, though multiple blood, urine, and sputum cultures were negative. She received 2 units of packed red blood cells on admission. Subsequently she developed a positive direct Coombs test, and her haemoglobin again fell to 7.0 g/dl. Serum haptoglobin decreased from 200 mg/100 ml (normal 35 to 200) to 0 mg/100 ml, and urine haemosiderin was found. The platelet count plunged to 13 \times 10⁹/l. The clotting profile revealed normal prothrombin time and partial thromboplastin time, low normal fibrinogen levels of 167 mg/100 ml (normal 150 to 450) and positive fibrin split products of greater than 40 μ g/ml (normal <20 μ g/ml). Bone marrow aspirations on 2 occasions revealed plasmacytosis, increased iron stores, and megakaryocytes. Haematology consultants considered the clotting aberrations were secondary to chronic disseminated intravascular coagulation.

Further examination showed normal upper gastrointestinal x-ray and barium enema, intravenous pyelogram, gallium scan, bone scan, and abdominal ultrasound. A liver-spleen scan revealed hepatomegaly with uniform uptake. A thyroid scan showed slight enlargement and increased uptake of 42% (normal up to 35%), though thyroid function tests were normal. Lymph node biopsy showed a follicular, nodular pattern with no evidence of neoplasia or

vasculitis. Serum FANA was positive on 2 determinations at 1:5120, with homogeneous pattern. Serum rheumatoid factor by latex agglutination was positive at 1:160, and quantitative tests for immunoglobulins revealed IgG 1720 mg/100 ml (normal 800 to 1800), IgA 860 mg/100 ml (normal 70 to 360), and IgM 170 mg/100 ml (normal 70 to 250). Total haemolytic complement (CH50) was markedly reduced at 17% (normal 35 to 65%) and serum C3 was reduced to 35 mg/100 ml (normal 88 to 250). Serum C4 was normal at 16 mg/100 ml (normal 12 to 75). Renal function tests showed creatinine clearance 77 ml/min and 24-hour total protein of 150 mg. Urine analysis remained normal except during one episode of urinary tract bleeding. (SI: mg/l = mg/100 ml \times 10.)

The clinical course was marked by soft-tissue and urinary-tract bleeding. After an infectious cause of the fever was ruled out, prednisone 60 mg/day orally was initiated. This was subsequently increased to 100 mg daily in divided doses. The patient required multiple blood and platelet transfusions over the next 4 weeks while still on 100 mg prednisone daily. Because of no apparent response to prednisone, 1 g of intravenous methylprednisolone was given every morning on 3 successive days. The blood picture stabilised, and subsequently the patient required no further blood product transfusions. Improvements in haemoglobin, the platelet count, and fibrin split products were seen in the next 5–14 days. Repeat FANA was 1:1280. The CH50 returned to normal at 37%, and the sedimentation rate decreased to 70 mm/h (Westergren). The patient was continued on prednisone 50 mg twice daily orally and was successfully tapered to 20 mg of prednisone daily as an outpatient without relapse of her haematological conditions.

Discussion

Our first patient had multiple features of lupus erythematosus,⁷ including fevers, leucopenia, alopecia, proteinuria, arthralgias, and myalgias. In addition serum FANAs were positive and serum complement levels low. While her renal involvement as shown by proteinuria and proved by renal biopsy preceded onset of central nervous system manifestations of SLE, this was not of an immediate, life-threatening nature. Initially she had shown improvement of her creatinine clearance, decrease in proteinuria, and reduction in fever and skin rash on oral prednisone. After the onset of grand mal seizures and high fever accompanied by mental obtundation, she rapidly deteriorated despite large increases in the dosage of prednisone and anti-convulsants. Her response to intravenous pulses of

methylprednisolone was dramatic, with resolution of fever, cessations of seizures, and a return to normal mentation. Return to normal of serum complement components, decrease in erythrocyte sedimentation rate, and a fall in serum IgG levels confirmed her response to therapy (Table 1).

Our second patient had arthralgias, alopecia, fever, and high titre FANA, but her major manifestations of SLE were haematological. These included haemolytic anaemia, thrombocytopenia, and disseminated intravascular coagulopathy. These features continued despite therapy with 100 mg of oral prednisone daily for several weeks and required multiple transfusions of blood and platelets. After pulse therapy with methylprednisolone she required no more transfusion and had a reversal of the clinical parameters of coagulopathy (Table 2). Serum complement levels and erythrocyte sedimentation rate improved promptly.

The use of methylprednisolone pulses for lupus nephritis has been reported to be of value.^{4–6} The regimens described consist of 3–5 days of daily intravenous methylprednisolone and are essentially the same as described in the present patients. Use of this therapy has not been previously reported in patients with nonrenal complications of SLE.

Corticosteroid effects on both the inflammatory and immune responses have been demonstrated in both normal volunteers and ill patients.⁸ Specific anti-inflammatory effects that have been demonstrated include decreased availability of inflammatory cells,⁹ interference in inflammatory cell function,¹⁰ and suppression of noncellular, inflammatory reactions.¹¹

Table 1 *Laboratory and clinical parameters of patient 1 before and after pulse therapy with intravenous methylprednisolone*

	Seizures	Fever	Serum C4	Westergren sed. rate
Before pulse	Many with coma	> 38.5°C	9 mg/100 ml (90 mg/l)	88 mm/hour
After pulse	None	< 37.5°C	32.8 mg/100 ml (328 mg/l)	18 mm/hour

Table 2 *Laboratory parameters of patient 2 before and after pulse therapy with intravenous methylprednisolone*

	Haemoglobin	Platelet count	CH50	Fibrin split products
Before pulse	7.0 g/dl	13 000/mm ³ (13 \times 10 ⁹ /l)	17%	>40 μ g/ml
After pulse	13 g/dl	150 000/mm ³ (150 \times 10 ⁹ /l)	37%	<20 μ g/ml

Many immunological functions also are altered by steroid administration.⁸ Serum IgG levels may be reduced by high doses of intravenous methylprednisolone owing to both increased catabolism and decreased production of IgG.¹² The ratio of IgG to antigen may be altered, and changes in the size of immune complexes may occur. This latter finding may lead to complexes with varying propensity to cause immune deposition in kidneys¹³ and possibly other systems. Medium-sized complexes are most often implicated in renal disease and are reduced in number by intravenous methylprednisone but possibly not by oral prednisone, though this is not clear.^{13,14}

Absolute numbers of circulating T and B cells are dramatically reduced by intravenous methylprednisolone.¹⁵ While adult human lymphocytes are relatively insensitive to lysis by corticosteroids,¹⁶ these high doses routinely decrease circulating lymphocyte numbers within 6 hours of administration. Such alterations in lymphocyte populations, with elimination of lymphokine-producing cells, might alter favourably the clinical picture in patients with SLE.^{4,15}

Recent evaluation by Fan *et al.*¹⁴ of pulse therapy in rheumatoid arthritis casts some doubt on the relative role of the immune mechanism versus anti-inflammatory effects of methylprednisolone. However, overall benefit in clinical parameters was observed acutely, suggesting anti-inflammatory effect was more important in these patients. The prompt clinical response of the 2 patients reported here, as well as an improvement in serum complement levels and other serological tests, suggests that high-dose intravenous methylprednisolone may also lead to favourable immunological changes. Although the possibility of maintaining such a response on smaller, oral doses of corticosteroids is not clear, the course in these 2 patients suggests this may be feasible. The rapid improvement of these patients with intravenous pulse therapy suggests that this therapy may be of use in life-threatening, nonrenal lupus erythematosus. Unlike renal SLE, these nonrenal manifestations are occasionally acute and self-limiting. Such a pulse may therefore be of a long-range benefit by hastening recovery from haematological or central nervous system complications of SLE.

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