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M A. Rabbani
Aga Khan University

S M. Shah

A Ahmad
Aga Khan University

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Case Report

Sustained Remission in a Case of Lupus Nephritis with Cyclosporin Therapy

Malik Anas Rabbani, Syed Mansoor Ahmad Shah, Aasim Ahmad

Department of Medicine, Aga Khan University Hospital,
Stadium Road, Karachi, Pakistan

ABSTRACT. Systemic lupus erythematosus (SLE) in severe form still presents a major therapeutic challenge. Aggressive treatment of severe renal lesions has improved the prognosis of renal disease over the last decade. However, this benefit is quite frequently offset by the side effects and toxicity of the treatment. Moreover, the disease may appear to be poorly responsive to treatment with steroids and cytotoxic drugs. We report a case of lupus nephritis that relapsed despite having adequate steroid and cytotoxic therapy, but later was successfully treated with cyclosporin. Fifteen months after discontinuing the treatment with cyclosporin, the patient continued to remain in remission.

Key words: Systemic lupus erythematosus, Lupus nephritis, Cyclosporin A.

Introduction

Systemic lupus erythematosus (SLE) in severe form still presents a major therapeutic challenge. Renal involvement in SLE is variable; some patients have minimal clinical and histological involvement, while others have fulminant renal failure and severe proliferative renal lesions on biopsy.[1]

Reprint requests and correspondence to:

Dr. Malik Anas Rabbani
Department of Medicine
Aga Khan University Hospital
Stadium Road, P.O. Box 3500,
Karachi-74800, Pakistan

The World Health Organization (WHO) classification,[2] which defines six major patterns of renal involvement, has greatly helped to study lupus nephritis. Transformation from one pattern of lupus nephritis to another may occur.[3] The optimal treatment of lupus nephritis varies with the type of disease. Aggressive immunosuppression is required for the more severe renal lesions such as diffuse or more severe focal proliferative glomerulonephritis (GN) and severe and progressive membranous GN (WHO Classes III, IV and V) as these lesions are at high risk for progressing to renal failure.[4] Aggressive treatment of the severe renal lesions has

improved the prognosis of renal disease over the last decade. However, this benefit is quite frequently offset by the side effects and toxicity related to drugs.[5] Moreover, disease may itself be poorly responsive to treatment with steroids and cytotoxic drugs.

Cyclosporin A (CSA) is used as a corner stone in the prevention of graft rejection in-patients who receive organ transplants. It has also been used in various autoimmune disorders including systemic lupus erythematosus (SLE) because of its selective immunosuppressive effect.

We report here a case of lupus nephritis, which had frequently relapsed despite high dose steroids and cyclophosphamide and later was successfully managed with CSA based therapy.

Case Report

A sixteen year old boy was admitted at the Aga Khan University Hospital with a one week history of high grade fever associated with chills and rigors, arthralgias involving hands, feet, knee and ankle joints and generalized purpuric rash. On examination, the pulse was 110/min, blood pressure 140/90 mm Hg, respiratory rate 27/min and temperature 39°C. Chest examination revealed bilateral pleural effusions. Abdominal examination revealed hepatosplenomegaly without ascites. Mild pedal edema was noted.

Laboratory investigations revealed hemoglobin of 102 gm/L, WBC 1.6×10^9/L, platelets 2.8×10^9/L, ESR 61 mm/hour.

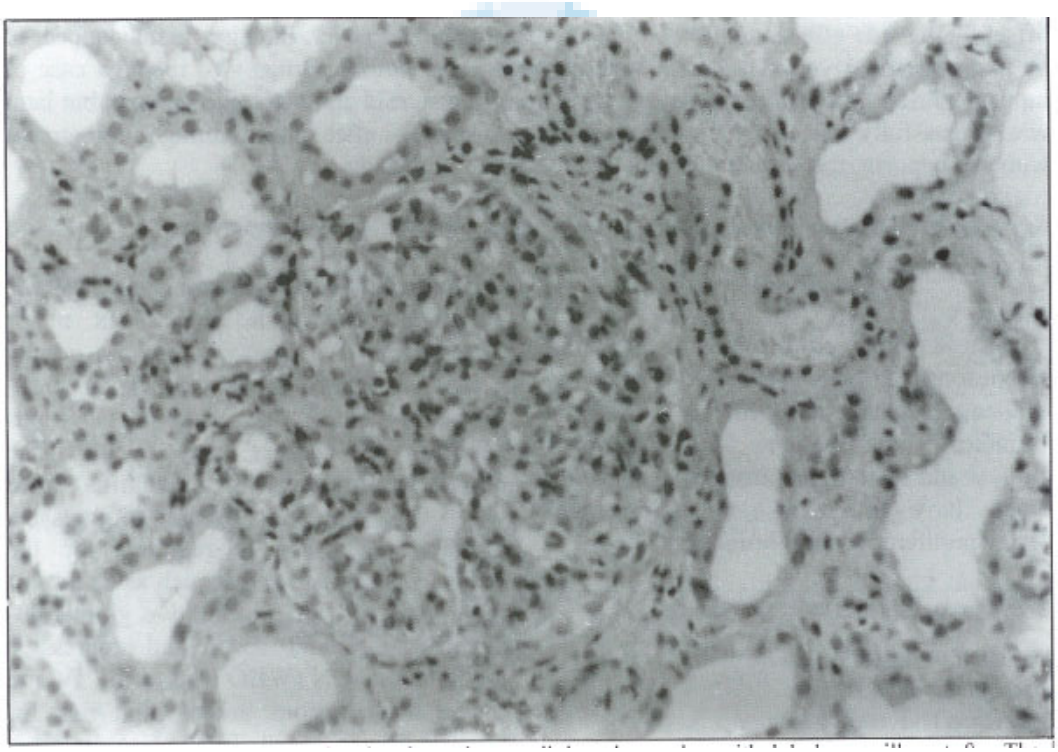

Figure 1. The renal biopsy showing large hypercellular glomerulus with lobular capillary tufts. The capillary lumina are obliterated by endocapillary cell proliferation and leukocytic infiltration. The tubules show vacuolar changes and the interstitium is slightly edematous (H & E Stain, Magnification x 200).

Serum creatinine and electrolytes were within normal range. Serum C3 was 0.123u (N-0.5-0.9), serum C4 < 0.05u, anti (ds) DNA 2451 IU (Range 0-6 IU) and ANA strongly +ve. Liver function tests, prothrombin time and activated thrompoplastin time were normal. Chest x-ray confirmed the presence of bilateral pleural effusions. Urinalysis revealed +3 protein and microscopic hematuria. 24-hour urine specimen revealed creatinine clearance of 98 ml/min and proteinuria of 3.6 gm/day. Renal biopsy was consistent with WHO class IV histological pattern, Figure 1. Immunoflourescence of the renal biopsy revealed immunoglobulin deposits of IgG, IgM, IgA, C3 and C4.

The patient was treated with pulse methylprednisolone one gram/day for three days followed by oral steroids (1 mg/kg of body weight) and Azathioprine (1.5 mg/kg of body weight). The blood counts returned to normal values within a week and the proteinuria decreased from 3.6 gm/day to 158 mg/day over the following three months. In the next six months the proteinuria relapsed twice despite the oral steroids and azathioprine. Each episode was treated with pulse methylprednisolone to which the patient responded well with protein excretion decreasing to less than 500 mg/day. Subsequently, the patient had a third relapse with proteinuria of 5 grams/day. At this point, oral cyclophosphamide (1.5 mg/kg of body weight) was substituted for azathioprine. This resulted in marked improvement as the protinuria disappeared. In order to avoid the risk of gonadal toxicity, cyclophosphamide was withdrawn after 12 weeks and the patient was maintained on oral steroids and azathioprine. Unfortunately, proteinuria relapsed within three months after discontinuing the cyclophosphamide. Cyclosporin was then added along with steroids, which resulted in gradual improvement over the following three months and the proteinuria decreased to less than 100 mg/day. During the first three month of CSA therapy, the drug was given in a dose of 3 mg/kg of body weight and the whole blood CSA level was maintained between 120-180 ng (radioimmune assay (RIA) with monoclonal antibodies). Cyclosporin was continued for further six months in a dose of 1.5-2 mg/kg of body weight and during this period the whole blood CSA level was maintained between 120-150 ng (RIA with monoclonal antibodies). CSA was withdrawn gradually over the following few weeks. Fifteen months after withdrawal of all the treatment the patient continued to be proteinuria free with creatinine clearance of 124 ml/min.

Discussion

Lupus nephritis is a very complex autoimmune renal disease. Successful treatment remains challenging due to lack of understanding of the underlying mechanisms and multiple symptoms ranging from skin rashes to glomerulonephritis. B cell hyperproliferation is characteristic of active SLE, which results in raised levels of circulating immunoglobulins and wide spread deposition of immune complexes in various tissues.[6] Several inflammatory and cell growth modifying processes also contribute to tissue destruction.

Lupus nephritis may run an extremely variable course and though specific therapy is not required in mild cases, a careful surveillance is required to detect possible transformation to a more severe disease state and flare ups.[3] Vigorous treatment should be started early in patients with more severe forms of lupus nephritis that show active lesion in the renal biopsy such

as glomerular cell proliferation, necrosis, crescent formation, significant subendothelial immune complex deposition and inflammation.[7] Therapeutic modalities currently employed in lupus nephritis include oral corticosteroids, high dose pulse steroid therapy, cytotoxic drugs like cyclophosphamide and azathioprine, used either singly or in combination with steroids. Other therapeutic approaches such as mycophenolate mofetil and Tacrolimus have been used in the treatment of severe and difficult cases of SLE and have been shown to prolong life span, reduce proteinuria and prevent progression to nephropathy.[8,9] Intravenous immunoglobulins and monoclonal antibodies have also been used in experiments, but their efficacy was modest.[10,11] Plasma exchange therapy has been used for bulk depletion of immunoreactants. However, multicentre studies have confirmed no additional role of plasma exchange therapy in combination with cytotoxics when compared with sole short-term use of cytotoxics in terms of patient survival, frequency of renal failure and other complications.[12] Total lymphoid radiation has been claimed to be effective in some cases of refractory lupus nephritis, a practical perspective on this form of immunosuppressive therapy has yet to be developed.[13]

Cyclosporin A (CSA) is a highly lipophilic cyclic peptide with 11 amino-acids. It blocks IL-2 synthesis by preventing transcription of IL-2 gene. Key steps are binding of CSA to a specific immunophillin, blocking calcineurin and preventing the transcription of the gene of IL-2.[14] Studies have shown that CSA is effective in reducing the activity of SLE and in controlling changes in clinical and laboratory parameters associated with disease especially in patients with poor response to conventional regimens.[15] The overall clinical benefit is usually observed within 2-4 months of CSA therapy. Therefore, prolonged treatment should be aimed at consolidating rather than achieving further improvement.[16] A large single center, prospective randomized study published from Italy evaluated disease activity according to systemic lupus activity measure (SLAM Score) in 27 patients who completed at least 24 months of treatment with CSA. It confirmed that the mean disease activity score could significantly be reduced in terms of stabilizing renal function, reducing proteinuria, and normalizing leukopenia and thrombocytopenia after six months of CSA therapy. This result was maintained through out the study.[16]

However, the use of CSA is limited mainly by its tendency to induce hypertension and nephrotoxicity as well as the tendency to relapse after discontinuing the treatment.[16] Despite this, we believe that the use of CSA still needs to be further evaluated as an alternative to cyclophosphamide in the management of lupus in young patients, especially in pregnant females in view of its established safety concerning teratogenicity,[17] or as a second line agent for patient whose condition is poorly responsive or less tolerant to more conventional therapy. Prognosis and overall success certainly varies widely among geographically and racially diverse populations.[18]

We reported a case of lupus nephritis that relapsed despite having adequate steroid and cytotoxic therapy, but later was successfully treated with cyclosporin. Fifteen months after discontinuing the treatment with cyclosporin, the patient continued to remain in remission.

References

1. Appel-GB, Valeria A. The course and treatment of lupus nephritis. Annu Rev Med 1994;45:525-37.
2. Diouf B, Toure AO, Ka MM, Pouye A, Diop TM. Management of lupus nephritis in Senegal. Dakar Med 1997;42(2):145-8.
3. Ponticelli C. current treatment recommendations for Lupus nephritis. Drugs 1990;40(1):19-30.
4. Dooley MA, Falk RJ. Immunosuppressive therapy of Lupus nephritis. Lupus 1998; 7(9):630-4.
5. Gourley MF, Austin HA 3rd, Scott D, et al. Methylprednisolone and cyclophosphamide alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;125:549-57.
6. Cross JT, Benton HP. The roles of interleukin-6 and interleukin-10 in B cell hyperactivity in systemic lupus erythematosus. Inflamm Res 1999;48(5):255-61.
7. Schwartz MM, Lan SP, Bernstein J, Hill GS, Holley K, Lewis EJ. Role of pathology indices in the management of severe lupus glomerulonephritis. Kidney Int 1992;42:743-8.
8. Duddridge M, Powell RJ. Treatment of severe and difficult cases of systemic lupus erythematosus with tacrolimus. A report of three cases. Ann Rheum Dis 1997;56(11): 690-2.
9. Godfrey T, Khamashta MA, Hughes GR. Therapeutic advances in systemic lupus erythematosus. Curr Opin Rheumatol 1998; 10(5):435-41.
10. Jordan SC. Intravenous gamma-globulin therapy in systemic lupus erythematosus and immune complex disease. Clin Immunol Immunopathol 1989;53:S164-9.
11. Wacholtz MC, Lipsky PE. Treatment of lupus nephritis with CD5 PLUS, an immunoconjugate of an anti-CD5 monoclonal antibody and ricin A chain. Arthritis Rheum 1992;35:837-9.
12. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. N Engl J Med 1992;326:1373- 9.
13. Strober S, Farinas MC, Field EH, et al. Lupus nephritis after total lymphoid irradiation: persistent improvement and reduction of steroid therapy. Ann Intern Med 1987;107:689-90.
14. Norman DJ. Renal transplantation. Immunosuppression and post operative management. Primary on kidney disease. 2nd ed (75) 482-88.
15. Manger K, Kalden JR, Manger B. Cyclosporin A in the treatment of systemic lupus erythematosus: results of an open clinical study. Br J Rheumatol 1996;35(7): 669-75.
16. Caccavo D, Lagana B, Mitterhofer AP, et al. Long-term treatment of systemic lupus erythematosus with cyclosporin A. Arthritis Rheum 1997;40(1):27-35.
17. Hussein MM, Mooij JM, Roujouleh H. Cyclosporin in the treatment of lupus nephritis including two patients treated during pregnancy. Clin Nephrol 1993; 40(3):160-3.
18. Austin HA, Balow JE. Natural history and treatment of lupus nephritis. Semin Nephrol 1999;19(1):2-11.