CASE REPORT

MYCOPHENOLATE MOFETIL IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

J. JOSE, B. K. PAULOSE, Z. VASUKI, D. DANDA[1]

ABSTRACT

Neuropsychiatric abnormalities frequently occur in patients with systemic lupus erythematosus, affecting as many as 14–75% of people with this disease. High-dose steroid with or without anticoagulation is the mainstay of treatment in neuropsychiatric systemic lupus erythematosus (NPSLE). Use of mycophenolate as a steroid sparing drug may be a potential alternative agent in the therapy of NPLE, but lack of randomized trials and cost prohibit its widespread use. Its safety profile is higher than that of cyclophosphamide and azathioprine. We report a successfully treated case of neuropsychiatric systemic lupus erythematosus, presenting as psychosis, whose long-term remission was maintained on treatment with mycophenolate mofetil.

***KEY WORDS:** CNS vasculitis; cyclophosphamide; mycophenolate mofetil; systemic lupus erythematosus*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with immunoinflammatory injury to tissues and cells mediated by immune complexes and pathogenic autoantibodies. Neuropsychiatric abnormalities frequently occur in patients with SLE, affecting as many as 14–75% of people with this disease. Central nervous system (CNS) involvement in SLE is associated with a worse survival outcome.[1],[2] We report a successfully treated case of neuropsychiatric systemic lupus erythematosus (NPSLE), presenting as psychosis, whose long-term remission was maintained on treatment with mycophenolate mofetil (MMF).

Departments of General Medicine and [1]Clinical Immunology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India
Correspondence to
Dr. D Danda
Professor of Medicine and Rheumatology, Department of Medicine II, Christian Medical College and Hospital, Vellore - 632 004, India. E-mail: debashish.danda@cmcvellore.ac.in

CASE HISTORY

A 24-year-old unmarried graduate lady was diagnosed to have SLE in our department based on the presence of oral ulcer, malar rash, discoid rash, positive antinuclear antibody (ANA), and elevated antidouble-stranded DNA (anti-dsDNA) antibody. At that time she also had depression with somatic symptoms (without psychotic features) and was started on Prednisolone 1 mg/kg body weight/day, Hydroxychloroquine 200 mg/day and Citolapram. Two months later, she presented with 1-week history suggestive of psychotic hallucinations, preoccupation spells, referential ideas and insomnia. On examination, she was afebrile and was in a state of stupor. Choreiform movements were also present. Vitals were stable. General examination was otherwise unremarkable. Examination of CNS revealed no meningeal signs or any other focal deficits. Examination of the optic fundi was normal.

Investigations revealed normal electrolytes and peripheral blood smears were negative for malarial parasites. A cerebrospinal fluid analysis performed ruled out CNS infection. She had hypochromic, microcytic anemia (Hemoglobin 10.7 g/dl), and a platelet count of 142 000/ccmm. Total count was 4100/ccmm. Differential count showed: Neutrophils 71%, Lymphocytes 24%, and Monocytes 5%, all of which were within normal limits. Direct Coombs Test was positive. Urine analysis did not reveal any suggestion of lupus nephritis. ANA was homogenous and speckled. Anti-dsDNA was elevated (55 AU/ml) (normal <30 AU/ml). Serum complements were low (C3: 41.8 mg%, C4: 5.5 mg%) (normal range C3: 90–180 mg%, C4: 10–40 mg%). Lupus anticoagulant by Dilute Russel Viper Venom Time was low positive and IgG anticardiolipin antibody by in house ELISA was positive too (28 IU/ml) (Normal <15 IU/ml). MRI scan showed a hyperintense lesion in the left centrum semiovale in T2-weighted image, which might have been an ischemic change.

Therefore, temporal course of events, clinical findings, psychiatric evaluation and laboratory findings adequately ruled out infection, electrolyte disturbance, metabolic derangements, and drug toxicities including steroid psychosis and favored the diagnosis of NPSLE.

She was given intravenous methylprednisolone pulses in the dose of 1 g daily for 3 days. As her disease continued to be active with only marginal improvement, her parents were equally concerned about her long-term mental and cognitive functions, as well as side effects of steroid, cyclophosphamide, and azathioprine. She was started on MMF in the dose of 1 g twice daily and intravenous immunolglobulin (IVIG) in the dose of 400 mg/kg body weight/day for 5 days every month. Anticoagulant medications (Nadroparine followed by warfarin) were also added in view of the strong possibility of antiphospholipid antibody-mediated microvasculopathy in the CNS. Target INR achieved was between 3 and 4, as recommended in antiphospholipid syndrome. Existing agents were continued and slow tapering of oral steroid was started only after 3 months of its initiation.

By 3 months, her psychiatric symptoms improved and mental state examination was normal. Her anti-dsDNA level and complements levels were also within the normal ranges by then. At this point IVIG was stopped.

Her relapse free clinical, psychiatric, and laboratory status of improvement were maintained on 7.5 mg/day of prednisolone, 200 mg/day of Hydroxychloroquine, warfarin and 1 g twice a day of MMF till the 15th month of

follow up in August 2005. Apart from a cushingoid appearance and minor respiratory infections, she did not have any other side effects from her treatment.

DISCUSSION

First described by Moriz Kaposi in 1872, NPSLE is still a common major morbidity of lupus.[1],[2] The common neuropsychiatric manifestations of active SLE include psychosis, delirium, seizures, and global cognitive dysfunction. Prevalence of psychosis ranges between 14 and 52%, but milder forms are commoner than delusional and severe affective disease.[3]

Autoantibodies to neuronal membranes account for some of the diffuse nonthrombotic neuropsychiatric disease, of which antiribosomal-P seem to correlate best with psychosis. This test was not done in this patient as it would not have altered the management. Antiphospholipid antibodies related microvasculopathy, rather than vasculitis, account for most NPSLE complications, especially in those with focal deficits and involuntary movements.[4]

The patient in this study, had features of both diffuse and silent focal disease manifested by severe psychosis with cognitive decline, as well as choreiform movements with a hyperintense lesion in the left centrum semiovale on MRI scan and positive antiphospholipid antibodies.[5] She was, therefore, put on high-dose steroid and anticoagulation as per standard treatment approach in NPSLE in addition to Hydroxychloroquine, which is only a weak immunomodulator with a mild steroid-sparing effect.

Use of IVIG during the early aggressive disease in this patient was a stop-gap measure, because short, lasting benefits of this highly effective steroid-sparing immunosuppressant is best suited for crisis situations in autoimmune diseases. In the SLE setting, it has been used with good success for refractory thrombocytopenia, pancytopenia, CNS involvement, secondary antiphospholipid syndrome, in lupus nephritis, in severe cases that are nonresponsive to other therapeutic modalities, or when SLE can be controlled only with high-dose steroids.[6],[7]

Therapeutic success of MMF has been reported in severe active lupus, lupus nephritis including cyclophosphamide resistant cases, cytopenias, pulmonary hemorrhage, and several other complications of SLE. MMF also has lesser infective complications, higher tolerability, and better compliance rate, which led to the consideration of this rather than cyclophosphamide or azathioprine in this patient.[5],[8]–[10]

The patient did not have the classical indications of cyclophosphamide, namely WHO class III/IV lupus nephritis and medium vessel vasculitis, nor there was any randomized controlled trial about the efficacy of cyclophophamide or azathioprine in NPSLE. Moreover, reports of benefit with MMF in NPSLE and antiphospholipid syndrome in SLE are also coming up.[11]

Hence, it is felt that MMF may be a viable option as an immunosuppressant in

maintaining remission on a long term basis for patients with NPSLE without any major side effect. However, high cost of therapy with MMF is a limiting factor.

REFERENCES

1. Kaposi MK. Nene beitrage zur kenntnis des lupus erythematosus. Arch Derm Syph 1872;4:36–78.
2. Blanco FJ, Gomez-Reino JJ, de la Mata J, Corrales A, Rodriguez-Valverde V, Rosas JC, et al. Survival analysis of 306 European Spanish patients with systemic lupus erythematosus. Lupus 1998; 7:159-63.
3. McCune WJ, Golbus J: Neuropsychiatric lupus. Rheum Dis Clin North Am 1988; 14:149-167.
4. Isshi K, Hirohata S. Cerebrospinal fluid immunoglobulins and neuronal antibodies in neuropsychiatric systemic lupus erythematosus and related conditions. Arthritis Rheum. 1998; 41:1819-27.
5. G Sanna, ML Bertolaccini and A.Mathieu. Central Nervous system lupus: a clinical approach to therapy. Lupus 2003;12: 935-942.
6. Shoenfeld Y, Katz U. IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients. Autoimmunity. 2005;38:123-37
7. Toubi E, Kessel A, Shoenfeld Y. High-dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. Hum Immunol. 2005;66:395-402.
8. Pisoni CN, Sanchez FJ, Karim Y, Cuadrado MJ, D'Cruz DP, Abbs IC, Khamasta MA, Hughes GR Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. J Rheumatol. 2005;32:1047-52.
9. Kang I, Park SH. Infectious complications in SLE after immunosuppressive therapies. Curr Opin Rheumatol 2003;15:528-34
10. Riskalla MM, Somers EC, Fatica RA, McCune WJ. Tolerability of mycophenolate mofetil in patients with systemic lupus erythematosus. J Rheumatol. 2003;30:1508-12
11. Grisanti M, Nader A, Cacciuttolo R. Central nervous system involvement due to systemic lupus rythematosus/antiphospholipid syndrome: successful treatment with mycophenolate mofetil. Lupus 2001; 10: S31