Neuropsychiatric Systemic Lupus Erythematosus with Cerebral Vasculitis and Lupus Nephritis Successfully Treated with High-dose Glucocorticoids and Mycophenolate Mofetil

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Abstract:
Neuropsychiatric systemic lupus erythematosus (NPSLE) with cerebral vasculitis is rare, and its prognosis is unfavorable. High-dose glucocorticoids and cyclophosphamide are widely used for the treatment of NPSLE, but cyclophosphamide has a risk of cervical intraepithelial neoplasia and ovarian insufficiency, which may discourage its use in young women. We experienced a case of NPSLE with cerebral vasculitis and lupus nephritis that responded successfully to glucocorticoids and mycophenolate mofetil (MMF). MMF might be a treatment option for NPSLE without concern for reproductive toxicity. However, there are only a few reports on the efficacy of MMF in NPSLE, and further investigations are needed.

Key words: neuropsychiatric systemic lupus erythematosus, cerebral vasculitis, mycophenolate mofetil

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Introduction

Among cases of systemic lupus erythematosus (SLE), the cumulative incidence of neuropsychiatric systemic lupus erythematosus (NPSLE) is 30-40% (1). Among NPSLE cases associated with cerebrovascular disease, cerebral vasculitis is rare, and its prognosis is not favorable (2). High-dose glucocorticoids and cyclophosphamide are used for the treatment of nonthrombotic NPSLE (3), but cyclophosphamide is associated with a risk of cervical intraepithelial neoplasia (CIN) (4) and ovarian insufficiency (5), which may discourage its use in young women. Although mycophenolate mofetil (MMF) has been established as being as effective as cyclophosphamide for remission induction therapy in lupus nephritis (6), no clinical trials have tested its efficacy in NPSLE.

We herein report a case of SLE complicated by NPSLE with cerebral arterial vasculitis and lupus nephritis that responded to high-dose corticosteroids and MMF.

Case Report

A previously healthy 34-year-old woman with no family history of connective tissue diseases presented with erythema of the face, skin rashes on the extremities, oral ulcers, and polyarthralgia 1 month before presentation. Her fever and malaise worsened, so she was evaluated in the clinic, where leukopenia, positive urinary protein, and a high antinuclear antibody (ANA) titer (1:1,280, speckled) were observed. The physician referred her to our department for a further investigation and treatment.

Upon admission to our hospital, a physical examination of the patient revealed hair loss on the head; malar rash; erythema on the face, both auricles, both arms, and part of the back; numerous oral ulcers; obvious ascites; and edema.

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of the lower extremities. Blood tests indicated elevated hepatobiliary enzymes, hypoalbuminemia, hypocomplementemia, a high ANA titer (1:2,560, speckled), positivity for anti-Sm and anti-ribonucleoprotein (RNP) antibodies, and negative anti-dsDNA antibodies (Table). The 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE was met with a total of 36 points, and we made the diagnosis of SLE. A urinalysis showed a urine protein/creatinine (Cr) ratio of 22.4 g/gCr, suggesting that the patient had lupus nephritis. Upon an evaluation of the nervous system, the patient was conscious and had no focal symptoms, such as motor paralysis or sensory disturbances. However, she was slow in responding to questions, could not speak fluently, and had a low frontal lobe function test score (Frontal Assessment Battery (FAB) 13/18). Serum anti-ribosomal P antibody was elevated to 117 U/mL, and an electroencephalogram (EEG) showed an elevated interictal 60 Hz frequency, suggesting a possible diagnosis of neuropsychiatric lupus.

Magnetic resonance imaging (MRI) postgadolinium T1-weighted arterial wall images revealed concentric wall enhancement of the vessel wall in the M2 region of the left middle cerebral artery, suggesting the presence of cerebral arterial vasculitis. Brain magnetic resonance angiography showed no significant stenosis of the major cerebral arteries (Fig. 1A, B). Incidentally, there was no elevation of autoantibodies associated with antiphospholipid antibody syndrome.

Fig. 2 shows the patient’s clinical course. We administered prednisolone (PSL) 50 mg/day, followed by 3 days of pulse steroid therapy (1 g/day), after which the patient continued on high-dose PSL, with 2,000 mg/day MMF and hydroxychloroquine (HCQ) as remission induction therapy. The patient developed symptoms suggestive of steroid psychosis during the 40-mg dose of PSL, which improved with a reduction in the PSL dose 20 mg/day and the use of antipsychotics. After initiating treatment, frontal lobe function tests improved (FAB 16/18 points), and the IL-6 level in the CSF decreased. In addition, concentric enhancement of the vessel wall of the left middle cerebral artery was improved

Table. Laboratory Data on the Admission of Our Hospital.

| Urinalysis | Chemistry |
|------------|-----------|
| Protein ++++ | AMY 54 U/L |
| Occult blood + | CK 106 U/L |
| Erythrocyte <1/F | BUN 7.1 mg/dL |
| Hyaline cast 100-999 /WF | Cre 0.64 mg/dL |
| Cellular cast 20-29 /WF | Na 136 mEq/L |
| Protein/Creatinine 22.4 g/gCr | K 3.2 mEq/L |
| | Cl 105 mEq/L |
| | Glu 147 mg/dL |

| Complete blood count | Serology |
|----------------------|----------|
| WBC 2,500 /μL | CRP 0.75 mg/dL |
| Neutrophils 1,840 /μL | IgG 2,305 mg/dL |
| Lymphocytes 510 /μL | C3 24 mg/dL |
| Monocytes 100 /μL | C4 9 mg/dL |
| Eosinophils 0 /μL | CH50 14 mg/dL |
| Basophils 0 /μL | C1q 2 μg/mL |
| RBC 452 ×10^4/μL | ANA 1:2,560 (speckled) |
| Hb 12.8 g/dL | Anti-Sm antibody ≥600 U/mL |
| Platelet 17.4 ×10^4/μL | Anti-ds DNA antibody 12 IU/mL |

| Chemistry | Anti-ribosomal P protein antibody 117 U/mL |
|-----------|------------------------------------------|
| TP 5.89 g/dL | Anti-SS-A antibody 720 U/mL |
| Alb 1.73 g/dL | Anti-SS-B antibody 67.3 U/mL |
| AST 183 U/L | Anti-cardiolipin antibody <8 U/mL |
| ALT 113 U/L | Anti-CLβ2GP1 antibody <1.2 U/mL |
| LDH 521 U/L | Anti-Clβ2GP1 antibody 1.2 |
| ALP 478 U/L | Anti-T. pallidum antibody Negative |
| γ-GT 231 U/L | Anti-nuclear antibody DNA: deoxyribonucleic acid, RNP: ribonucleoprotein, CLβ2GP1: cardiolipin beta-2 glycoprotein 1, LAC: lupus anticoagulant

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GT: glutamyltransferase, T-bil: total bilirubin, AMY: amylase, CK: creatine kinase, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Glu: glucose, CRP: C-reactive protein, IgG: immunoglobulin G, C3: complement component 3, C4: complement component 4, CH50: 50% hemolytic complement activity, C1q: complement component 1q, ANA: antinuclear antibody, DNA: deoxyribonucleic acid, RNP: ribonucleoprotein, CLβ2GP1: cardiolipin beta-2 glycoprotein 1, LAC: lupus anticoagulant
Figure 1. Findings of magnetic resonance imaging. (A) Magnetic resonance angiography showed no significant stenosis of the major cerebral arteries. (B) Magnetic resonance imaging after gadolinium T1-weighted arterial wall images of left middle cerebral artery M2 with concentric wall enhancement (shown by arrow). (C) Arterial wall image with improved wall enhancement (shown by arrow).

Figure 2. Clinical course of treatment, the urinalysis, and cerebrospinal fluid findings. PSL: prednisolone, mPSL: methylprednisolone, MMF: mycophenolate mofetil, HCQ: hydroxychloroquine, TAC: tacrolimus

(Fig. 1C).

Because of the nephrotic features observed in the patient, including severe proteinuria and hypoalbuminemia, and lack of hematuria, lupus nephritis was presumed to be Class V according to the International Society of Nephrology/Renal Pathology Society classification. No renal biopsy was performed because the patient had a poor general condition, and treatment with PSL and MMF was started. Severe edema resulting from nephrosis was treated with diuretics and a switch from PSL to methylprednisolone (mPSL), which has a weaker mineralocorticoid effect. After treatment initiation, the amount of urinary protein decreased to about half of the admission level, but the patient’s daily protein level remained about 6-7 g/day. There was an increase in the number of cellular casts, which was considered to indicate the manifestation of proliferative changes.

It was speculated that the patient had class III+V lupus nephritis. Therefore, we added tacrolimus (TAC) 2 mg/day. Thereafter, the daily urinary protein level decreased to 5.2 g/day, and the patient was discharged with a reduction in mPSL to 14 mg/day. MMF and TAC were continued with a gradual decrease in PSL, and no relapse of NPSLE occurred. Proteinuria gradually decreased, and the cellular casts disappeared. Incidentally, hepatobiliary enzymes were elevated on admission, suggesting lupus hepatitis or drug-induced liver injury, but a liver biopsy could not be performed because of ascites. These findings resolved after the administration of PSL. Due to gastrointestinal symptoms such as nausea and anorexia, MMF was reduced to 1,000 mg/day and HCQ was discontinued. Resumption of HCQ resulted in the recurrence of gastrointestinal symptoms, and HCQ was discontinued again.
Discussion

Based on cohort studies, the cumulative incidence of NPSLE in individuals with SLE is 30-40%, with NPSLE with cerebrovascular disease being relatively common (5-10%), although cerebral vasculitis is rare (1). Headache, mood disorder, anxiety, and mild cognitive impairment are common symptoms in NPSLE (1), but NPSLE with cerebral vasculitis presents with a variety of symptoms, including headache, sensory disturbance, dysarthria, and disturbance of consciousness (2). However, cerebral vasculitis has no specific symptoms. In terms of the diagnosis, NPSLE with cerebrovascular disease has a mortality rate as high as 15% (3), but a review of 15 cases of cerebral vasculitis from 1994-2020 by Nishigaichi et al. showed a more severe prognosis, with 40% (6/15) of patients showing worsening or no change in symptoms in response to treatment (2).

The diagnosis of NPSLE is based on a combination of tests, including lumbar puncture, electroencephalography, cognitive function tests, and MRI, which are recommended to be selected based on the patient's symptoms (1). A CSF examination by lumbar puncture is useful for ruling out central nervous system infection in patients suspected of having NPSLE. In addition, elevated IL-6 levels in the CSF have been reported in several retrospective cohort studies to be useful for the differentiation of NPSLE from other psychiatric symptoms (7). In our case, the IL-6 level in the CSF was elevated. Furthermore, serum anti-ribosomal P antibodies, which were elevated in our case, have been reported to have limited efficacy for the diagnosis of NPSLE, with a sensitivity of 25-27% and a specificity of 75-80% (3). Although a brain biopsy remains the gold standard for diagnosing cerebral vasculitis (3), imaging studies, such as vessel wall imaging using MRI have been reported to be useful for the diagnosis and evaluation of the effect of treatment of cerebral vasculitis (8). Karaman et al. reported that concentric wall thickening and vessel wall contrast enhancement (VWE) on MRA are useful for the differential diagnosis of primary angiitis of the central nervous system (PACNS). Using concentric thickening and VWE features, the sensitivity and specificity for distinguishing PACNS and other vasculopathies were reported to be 95.2% and 75% and 95.2% and 68.8%, respectively (9). The specificity of these findings is not very high, and these findings may be observed in reversible cerebral vasocostriction syndrome, Moya Moya disease, and rarely in atherosclerosis. In the present case, MRI post gadolinium T1-weighted arterial wall images showed concentric enhancement of the vessel wall and improvement after treatment; thus, we diagnosed this case as cerebral vasculitis due to SLE.

The treatment of NPSLE should be tailored to its pathogenesis, such as cerebral vasculitis, thrombosis, or their coexistence (1). Although there is no standard treatment for central nervous system vasculitis associated with SLE, Nishigaichi et al. reported that cyclophosphamide was used for induction remission therapy in 60% (9/15) of patients (2), and rituximab can be used for exacerbation and relapse (3). With regard to the use of MMF, one study verifying the efficacy of MMF and intravenous cyclophosphamide (IVCY) in lupus nephritis included three patients with NPSLE in the MMF group, all of whom improved (10). A retrospective cohort study of 75 SLE patients treated with MMF revealed 2 cases of NPSLE that showed improvement (11). Furthermore, only one case of cerebral vasculitis has been reported as being successfully treated with MMF (12). In the present case, we chose MMF for remission induction therapy because of its reported side effects. Common side effects of cyclophosphamide include alopecia, nausea, vomiting, and myelosuppression (13). CIN (4) and ovarian dysfunction (5) associated with an age-dependent cumulative dose have also been reported. The patient was a woman of reproductive age, and she desired to preserve her childbearing ability if possible. In addition, there was severe edema due to nephrosis, so the administration of oral MMF enabled us to avoid the excessive volume load associated with IVCY. However, gastrointestinal symptoms, myelosuppression, and infection are also the main adverse effects of MMF (14). In this case, MMF dose reduction was required because of anemia and gastrointestinal symptoms. Our case of cerebral vasculitis improved after treatment with high-dose corticosteroids and 2,000 mg of MMF, and no flare occurred after steroid reduction. These findings suggest that MMF might be an effective treatment option for NPSLE complicated by cerebral vasculitis.

However, high-dose corticosteroids and MMF did not lead to lupus nephritis remission. In the Japanese SLE guideline 2019, rituximab is positioned as the third-line therapeutic regimen for difficult SLE. However, the efficacy and safety of rituximab for Japanese patients with lupus nephritis remains unclear. In addition, the use of rituximab to treat lupus nephritis is not covered by health insurance in Japan and therefore could not be used at our hospital. Although it might have been better to administer TAC or rituximab earlier, it was necessary to consider both the risks and benefits of rituximab therapy in the present case.

We experienced a case of NPSLE with cerebral vasculitis treated with MMF. There are only a few reports on the efficacy of MMF in NPSLE, so the further accumulation of cases and clinical trials is warranted.

Written informed consent for the publication of this report was obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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