

[CASE REPORT]

Reversible Cognitive Dysfunction in Elderly-onset Systemic Lupus Erythematosus, Successfully Treated with Aggressive Immunosuppressive Therapy

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Abstract:

A 70-year-old Japanese woman presented to our hospital with gait disturbance and cognitive dysfunction. Since she had arthritis, lymphopenia, hypocomplementemia, and anti-nuclear and anti-double-stranded DNA antibodies, she was diagnosed with systemic lupus erythematosus (SLE). T2-weighted magnetic resonance imaging revealed bilateral hyperintensities in the putamen. Based on her cognitive impairment, muscle rigidity, and high levels of interleukin-6 in the cerebrospinal fluid, we believed she had developed a complication of a neuropsychiatric disease and administered corticosteroids and intravenous cyclophosphamide therapy. Her cognitive function fully recovered, and her gait disturbance improved. Attending to cognitive impairment in elderly SLE patients is necessary.

Key words: cognitive dysfunction, systemic lupus erythematosus, immunosuppressive therapy

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Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder with various presentations characterized by remissions and flares (1). Compared to younger patients, elderly-onset SLE patients often present differently and are more challenging to diagnose (2, 3). Elderly-onset patients present with serositis, interstitial pulmonary disease, Sjögren's syndrome, and positive anti-SS-B antibodies more often than those who develop the disease at a younger age (2), whereas younger patients present with arthritis, malar rash, photosensitivity, and nephropathy more often (3).

Mild or moderate cognitive dysfunction is common in patients with SLE (4). However, since an impaired cognitive function among the elderly can be caused by other cognitive diseases, including Alzheimer's disease, cognitive impairment due to elderly-onset SLE patients is often difficult to diagnose.

We herein report a case of a patient with elderly-onset neuropsychiatric SLE (NPSLE) with cognitive dysfunction and gait disturbance that was improved by corticosteroids and intravenous cyclophosphamide (IVCY).

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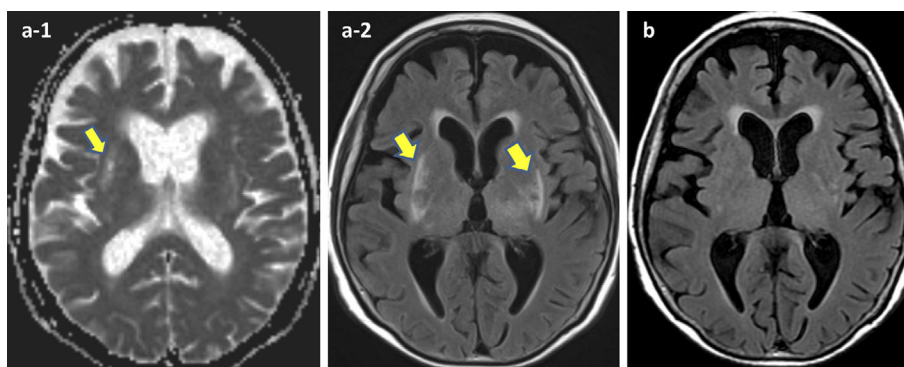


Figure 1. Head MRI findings on admission. a-1: Hyperintensity of diffusion-weighted images in the right corona radiata (arrow). Acute cerebral infarction can be seen. a-2: Hyperintensity of T2-weighted images in the bilateral putamen (arrows). b: The hyperintensity in the bilateral putamen disappeared following treatment by IVCY and corticosteroid. IVCY: intravenous cyclophosphamide, MRI: magnetic resonance imaging

Case Report

A 70-year-old Japanese woman was admitted to our hospital with gait disturbance and cognitive dysfunction. The patient reported bilateral pitting edema of her legs 10 months prior to her admission that impacted her daily routine, making it harder for her to manage her household. Her movement gradually became sluggish, and a lack of expression in her face and voice were noted. In addition, she was unable to walk unassisted one month prior to admission. Her medical history included a previous diagnosis of acute cerebral infarction in the right corona radiata that was diagnosed by another physician based on magnetic resonance imaging (MRI) findings and for which she was receiving aspirin for prophylaxis against future cerebral infarctions. She was referred to our department by her previous physician after testing positive for anti-nuclear antibodies. She had no family history of rheumatic diseases.

On admission, her body temperature was 36.8°C, blood pressure was 109/66 mmHg, and pulse was 89/min. Coarse crackles and no heart murmur were detected on auscultation. Bilateral tenderness and swelling of her ankles and bilateral pitting edema of her legs were noted. She had no skin rashes and was bedridden. A neurological examination demonstrated muscle rigidity, slow voluntary movements, and a mask-like facial expression. There was no evidence of cranial nerve dysfunction. A manual muscle test of the iliopsoas was fair, and that of the quadriceps was good. Her mini mental state examination (MMSE) score was 22/30 with deficits in orientation, attention, and calculation. Her revised Hasegawa's dementia scale (HDS-R) was 19/30.

Laboratory test results revealed a white blood cell count of 4,800/ μ L (neutrophils 93%, lymphocytes 3%, monocytes 2%, eosinophils 0%, and basophils 0%), hemoglobin level of 6.8 g/dL, platelet count of 112,000/ μ L, C-reactive protein level of 8.99 mg/dL (normal values <0.14 mg/dL), erythrocyte sedimentation rate of 44 mm/h (normal range 1-10 mm/

h), serum creatinine level of 0.69 mg/dL (normal values < 1.0 mg/dL), lactate dehydrogenase level of 166 U/L (normal range 124-222 U/L), total bilirubin level of 0.5 mg/dL (normal range 0.4-1.5 mg/dL), ferritin level of 1,037 ng/mL (normal range 16-135 ng/dL), haptoglobin level of 143.9 mg/dL (normal range 119-170 mg/dL), and iron level of 14 μ g/dL (normal range 40-188 μ g/dL). An antinuclear antibody (ANA) test was positive (1:320, homogeneous pattern), anti-double-stranded DNA (anti-dsDNA) antibody levels were elevated at 145 IU/mL, anti SS-B/La antibody levels were elevated at 202.1 U/mL, and anti-phosphatidylserine/prothrombin antibody (aPS/PT antibody) levels were elevated at 30 U/mL (normal values <12 U/mL). In contrast, anti-Smith antibody, anti SS-A/Ro antibody, lupus anticoagulant (LAC), and anti-cardiolipin antibody tests were negative. Complement factors 4 and 3 were decreased to 7.6 mg/dL (normal range 11-34 mg/dL) and 42.2 mg/dL (normal range 73-138 mg/dL), respectively. Direct Coombs test was positive. A urinalysis revealed no hematuria and no casts. Her cerebrospinal fluid (CSF) tests revealed a CSF interleukin (IL)-6 level of 7.3 pg/dL [cut-off for neuropsychiatric systemic lupus erythematosus (NP-SLE): >4.3 pg/dL, (5)] and an IgG index of 0.8. Echocardiography revealed a good contractile function of the left ventricle with no abnormalities, including pulmonary hypertension and valvular disease. Chest computed tomography showed bilateral pleural effusion. MRI of the head showed acute cerebral infarction in the right corona radiata and bilateral hyperintensities in the putamen on T2-weighted imaging (Fig. 1a-1 and a-2). Brain single-photon emission computed tomography showed hypoperfusion of the frontal lobe. 123 I-Metaiodobenzylguanidine myocardial scintigraphy showed no notable findings suggestive of Parkinson's disease or related disorders.

The patient was diagnosed with SLE based on her findings and on the systemic lupus international collaborating clinics classification (SLICC) and updated American College of Rheumatology (ACR) revised criteria (6, 7). In addition,

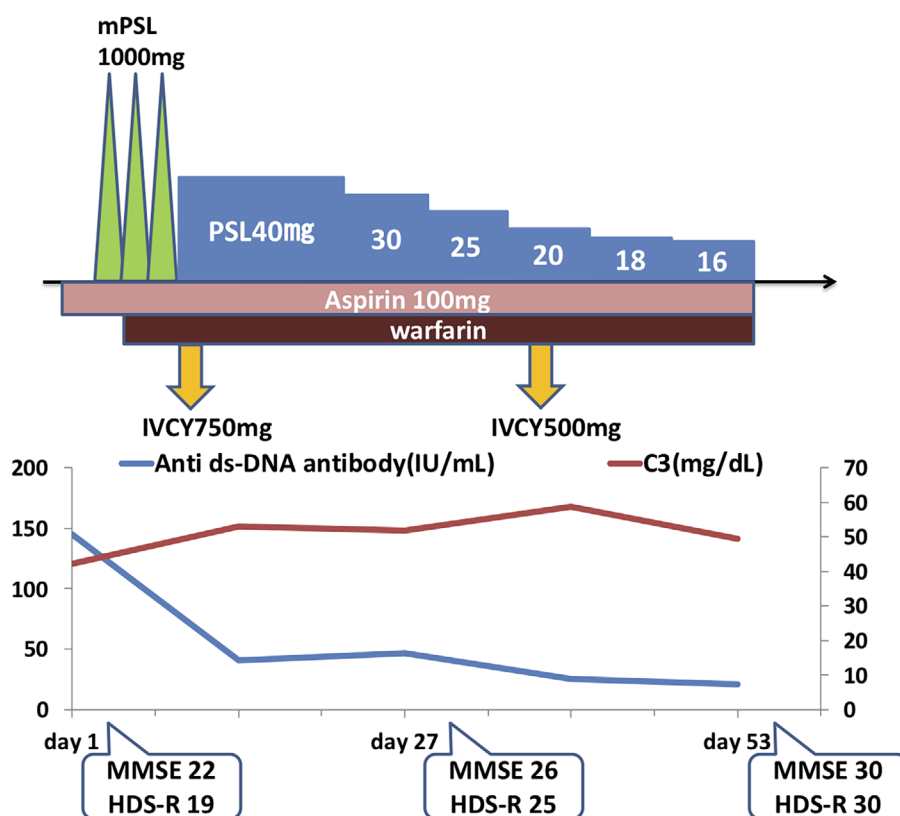


Figure 2. The clinical course of our 70-year-old Japanese woman. IVCY: intravenous cyclophosphamide pulse therapy, mPSL pulse: pulsed methylprednisolone, PSL: prednisolone, anti-ds-DNA antibody: anti-double-stranded DNA antibody, C3: complements 3, MMSE: Mini Mental State Examination, HDS-R: Revised Hasegawa's dementia scale

we diagnosed her with NPSLE based on her neurological symptoms, which were supported by the increased levels of IL-6 in the CSF. Since her MMSE score was suggestive of mild cognitive impairment, we believed that her cognitive dysfunction was a manifestation of NPSLE according to the ACR nomenclature system (8).

We initiated intravenous pulse therapy with methylprednisolone (1,000 mg/day for 3 consecutive days per week) and cyclophosphamide [3 pulses of 750 mg (500 mg/m²) once every 4 weeks] (Fig. 2) with subsequent oral prednisolone at 40 mg/day. Following the second cycle of IVCY, we reduced the dose to 500 mg due to neutropenia. Since the patient had positive aPS/PT antibodies and acute cerebral infarction, we added warfarin to her previously prescribed aspirin while monitoring her for antiphospholipid syndrome (APS). Prior to starting warfarin, we confirmed that she had no gastrointestinal bleeding by esophagogastroduodenoscopy and colonoscopy. Soon after starting treatment, her arthritis symptoms and pitting edema disappeared. In addition, her anti-dsDNA antibody level and hypocomplementemia gradually improved. At 4 weeks posttreatment, her MMSE score improved from 22/30 to 26/30, and the hyperintensities on T2-weighted imaging disappeared (Fig. 1b). At 7 weeks posttreatment, her MMSE and HDS-R scores further improved to 30/30 each. At three months posttreatment, she received the third cycle of IVCY. At her six-month follow-up,

she remained in remission and was able to walk unassisted while continuing her daily 5-mg prednisolone treatment.

Discussion

We herein report a case of a patient with elderly-onset NPSLE complicated with cognitive dysfunction and gait disturbance. Aggressive immunosuppressive therapy with corticosteroids and IVCY improved her cognitive function and gait.

Compared to younger patients, elderly patients with SLE tend to have atypical presentations of SLE. They less often show malar rash, nephropathy, and arthritis (3, 9). In our patient, the typical symptoms of malar rash and nephropathy were absent. We were able to diagnose her with SLE based on the SLICC and ACR revised criteria.

In elderly patients, it is challenging to differentiate between the different causes of cognitive impairment. Acute illness and hospital admission often cause cognitive dysfunction in elderly people. It was reported that recoverable cognitive dysfunction occurred in 39% of elderly patients admitted to the hospital (10). In addition, neurodegenerative diseases, including Alzheimer's disease, which is the main cause of dementia among the elderly, are differential diagnoses. SLE patients often have a mild-to-moderate degree of cognitive dysfunction with an overall benign course (4, 11).

In our patient, since immunosuppressive therapy was effective in resolving her symptoms and abnormal MRI findings, we believed her cognitive dysfunction was a manifestation of NPSLE. Furthermore, since cerebral vasculitis is seen in 3-5% of NPSLE patients (12), we considered the possibility of our patient developing cerebral vasculitis.

It was challenging to determine the cause of cognitive dysfunction in our patient. Cerebral infarcts complicating APS often cause dementia (13). It was reported that over 40% of patients with APS had mild cognitive dysfunction (14). Since our patient tested negative for antiphospholipid antibodies, which is a criterion for the preliminary classification of APS, we did not diagnose her with APS (15). We examined aPS/PT antibody because the aPS/PT antibody is related to the presence of APS and thrombotic events (16). While most patients positive for aPS/PT antibody are also positive for LAC, Atsumi et al. reported that 2.3% of patients with systemic autoimmune diseases were positive for aPS/PT antibody but negative for LAC (17). Her positive test results for aPS/PT antibody made APS a possible cause of her cognitive dysfunction. Following the administration of immunosuppressive therapy, her cognitive impairment rapidly improved, which eliminated the possibility of an APS-induced cerebral infarction, establishing SLE as the cause of cognitive impairment.

To our knowledge, no cases of elderly NPSLE patients with cognitive dysfunction have shown complete improvement. One study reported that immunosuppressive therapy using corticosteroids and IVCY was effective in the treatment of young SLE patients with cognitive dysfunction (18). Given that IVCY following intravenous pulse therapy with methylprednisolone as an induction treatment is more effective than corticosteroids monotherapy for NPSLE patients (19), IVCY is crucial for treating NPSLE. Since elderly patients are generally vulnerable to adverse effects of drugs, including infectious diseases, physicians sometimes refrain from administering aggressive immunosuppressive therapy to elderly patients due to fears of adverse effects. However, if we monitor them closely for adverse effects, we can treat these patients safely.

In conclusion, NPSLE should be considered in the differential diagnosis of cognitive impairment in elderly patients. If treated by the appropriate administration of immunosuppressive therapy, impaired cognitive dysfunction may be reversible.

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

References

- Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* **67**: 195-205, 2008.
- Ward MM, Polisson RP. A meta-analysis of the clinical manifestations of older-onset systemic lupus erythematosus. *Arthritis Rheum* **32**: 1226-1232, 1989.
- Font J, Pallares L, Cervera R, et al. Systemic lupus erythematosus in the elderly: clinical and immunological characteristics. *Ann Rheum Dis* **50**: 702-705, 1991.
- Bertsias GK, Ioannidis JP, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* **69**: 2074-2082, 2010.
- Hirohata S, Kanai Y, Mitsuo A, Tokano Y, Hashimoto H, Subcommittee NR. Accuracy of cerebrospinal fluid IL-6 testing for diagnosis of lupus psychosis. A multicenter retrospective study. *Clin Rheumatol* **28**: 1319-1323, 2009.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* **40**: 1725, 1997.
- Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* **64**: 2677-2686, 2012.
- The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* **42**: 599-608, 1999.
- Sassi RH, Hendler JV, Piccoli GF, et al. Age of onset influences on clinical and laboratory profile of patients with systemic lupus erythematosus. *Clin Rheumatol* **36**: 89-95, 2017.
- Inouye SK, Zhang Y, Han L, Leo-Summers L, Jones R, Marcantonio E. Recoverable cognitive dysfunction at hospital admission in older persons during acute illness. *J Gen Intern Med* **21**: 1276-1281, 2006.
- Panopalis P, Julian L, Yazdany J, et al. Impact of memory impairment on employment status in persons with systemic lupus erythematosus. *Arthritis Rheum* **57**: 1453-1460, 2007.
- Sibbitt WL Jr., Brooks WM, Kornfeld M, Hart BL, Bankhurst AD, Roldan CA. Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. *Semin Arthritis Rheum* **40**: 32-52, 2010.
- Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* **46**: 1019-1027, 2002.
- Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. *Lancet* **376**: 1498-1509, 2010.
- Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* **42**: 1309-1311, 1999.
- Vlagea A, Gil A, Cuesta MV, et al. Antiphosphatidylserine/prothrombin antibodies (aPS/PT) as potential markers of antiphospholipid syndrome. *Clin Appl Thromb Hemost* **19**: 289-296, 2013.
- Atsumi T, Ieko M, Bertolaccini ML, et al. Association of autoantibodies against the phosphatidylserine-prothrombin complex with manifestations of the antiphospholipid syndrome and with the presence of lupus anticoagulant. *Arthritis Rheum* **43**: 1982-1993, 2000.
- Lee SI, Jeon HS, Yoo WH. Reversible dementia in systemic lupus erythematosus without antiphospholipid antibodies or cerebral infarction. *Rheumatol Int* **24**: 305-308, 2004.
- Barile-Fabris L, Ariza-Andraca R, Olguin-Ortega L, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann Rheum Dis* **64**: 620-625, 2005.

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