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Effects of Comprehensive Rehabilitation on Patients with Progressive Multifocal Leukoencephalopathy Due to Systemic Lupus Erythematosus: A Case Report

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Abstract

Introduction: Little is known about the feasibility and effectiveness of rehabilitative treatment for systemic lupus erythematosus (SLE) in individuals with progressive multifocal leukoencephalopathy (PML). We describe a patient with SLE complicated by PML and ameliorated by comprehensive rehabilitation. We also review the epidemiology, pathology, imaging characteristics, and treatment of PML. **Patient Concerns:** We found a patient with SLE with PML improved by multidisciplinary rehabilitation techniques. **Diagnoses, Interventions, and Outcomes:** We diagnosed a PML with a 13-year history of SLE and lupus nephritis after longtime immunosuppressive therapy. The patient underwent a comprehensive, multifaceted rehabilitation program, including drug therapy, integrated physical therapy, occupational therapy, acupuncture, music therapy, computer-aided cognitive rehabilitation training, and behavioral management training. This rehabilitation program improved her motor function and activities of daily living. **Conclusions:** Her condition improved in the short term through comprehensive rehabilitation, including physical, speech, and cognitive therapy. Therefore, we recommend comprehensive rehabilitation to improve the function and activities of daily living in patients with PML.

Keywords

Progressive Multifocal Leukoencephalopathy, Systemic Lupus Erythematosus, Rehabilitation, Prognosis, Case Report

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of the central nervous system caused by the activation of the John Cunningham virus (JCV). PML can lead to various neurological deficits with high mortality rates. JCV, a type of polyomavirus, exists in approximately 65% of the general population. JCV infection was thought to involve oligodendrocytes and astrocytes in the white matter of individuals with suppressed immune systems, leading to rare cases of PML [1]. The effective promotion of immunosuppressants and other biochemical therapies has recently significantly increased the incidence of PML [2]. PML is often reported in patients with advanced human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), leukemia or Hodgkin's lymphoma, multiple myeloma, multiple sclerosis (MS), autoimmune disease, and organ transplantation requiring long-term use of immunosuppressive drugs [2] [3].

SLE is an autoimmune disease, and patients often complain of fatigue and low levels of physical activity. Physical exercise can improve fatigue, depression, and life satisfaction in individuals with SLE. Further, 40% of patients with SLE taking a minimal dosage of immunosuppressants in the long-term develop PML, with a mortality rate up to 60% - 75% and a relatively poor prognosis in patients with autoimmune diseases [4] [5]. Little is known about the feasibility and effectiveness of rehabilitative treatment for SLE in individuals with PML. Here, we describe a case of SLE and lupus nephritis with PML.

2. Case Presentation

The patient provided written informed consent for the publication of her medical details. The research procedures were approved by the Ethical Committee of the China Rehabilitation Research Centre and conducted in accordance with the Declaration of Helsinki.

2.1. Chief Complaint

A 47-year-old married woman was admitted to our hospital for rehabilitation treatment on January 13, 2021, due to "poor limb mobility with decreased intelligence for over 7 months".

2.2. Main Medical History

From June 2020, she experienced a loss of appetite and became apathetic. Afterward, she gradually became unable to control urination and defecation or recognize her family and friends. She became unable to walk independently, with obvious fatigue. Subsequently, mental and behavioral abnormalities became increasingly severe. The cranial magnetic resonance imaging (MRI) showed "abnormal signals in the bilateral frontal lobe, corpus callosum, right basal ganglia, paraventricular, and right temporal lobe" (**Figure 1a**).

One month later (July 2020), although her limbs were still movable, she stayed

in bed most of the time and denied having abnormal somatosensory experiences or a sense of girdle pain. MRI showed that the "abnormal lesions are larger" (Figure 1b), and her treatment remained unchanged.

Two months later (August 2020), she was bedridden and had sacrococcygeal pressure sores, mental retardation, and weak limbs when she was admitted to the neurology department of a tertiary Grade A comprehensive hospital. Further laboratory tests showed that JCV DNA from her mid-morning urine sample was >50 million copies/mL, and JCV-DNA sequencing of the cerebrospinal fluid (CSF) was positive. MRI reexamination showed that her temporal lobe lesions were significantly enlarged compared to a month prior, and new pontine lesion could be seen (Figure 1c). Therefore, a diagnosis of PML was made. Mycophenolate mofetil and leflunomide were immediately discontinued and replaced with clonidazole while monitoring the activity of TB cell subsets. The dosage of methylprednisone was reduced to 10 mg once daily, with two rounds of high-dose intravenous gammaglobulin (0.4 g/kg body weight per day, five days each round). The interval between the two rounds was approximately one month. Simultaneously, oral mirtazapine (30 mg) was administered twice a day.

Nearly four months later (September 2020), MRI showed that the lesions were stable with no progression. Six months later (November 2020), her condition was stable, and she was admitted to an inpatient rehabilitation unit of a secondary general hospital for occupational and physical therapy. After a month of rehabilitation training, the strength of the patient's left lower limb improved, but other symptoms did not improve significantly. Thus, she was admitted to our hospital for further rehabilitation. The developmental progress of the disease is shown in Figure 2.

Since the onset of PML, she was diagnosed with cholestatic liver disease and impaired liver function simultaneously, with good sleep, urinary incontinence, and significant weight gain (from <50 kg to >60 kg in seven months).

2.3. Other Medical History

She was diagnosed with SLE in May 2008 and regularly took prednisone (7.5 mg/day) for nearly 10 years. From October 2017, she began taking one dose each of methylprednisolone (12 mg) and leflunomide (10 mg) and two doses of mycophenolate mofetil (0.25 g each) daily to control SLE and its associated lupus nephropathy. From April 2018, she had also taken 10 mg of enalapril once daily to control blood pressure due to the long-term use of glucocorticoids. She reported no history of surgery or trauma, allergies to food or drugs, smoking or drinking, or a family history of SLE or PML.

2.4. Physical Examination

General signs: 120/80 mmHg, 80 times/min; clear mind; moon face; thin skin; multiple ecchymoses on the skin of her limbs; varicose veins in both lower limbs; and palmar erythema of both hands.

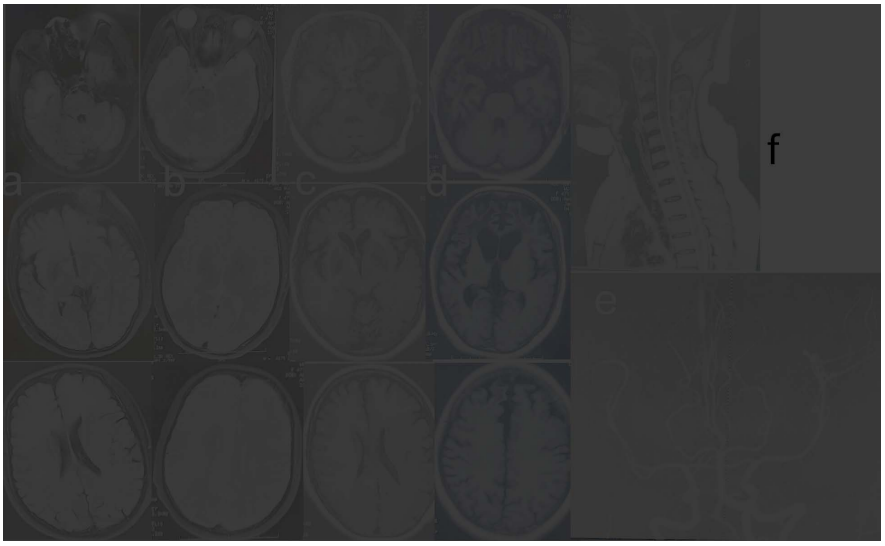

Figure 1. Magnetic resonance imaging (MRI) T2/T2 fluid-attenuated inversion recovery in the course of the disease. Seven months prior, the patient had emotional changes and limb fatigue. MRI shows the bilateral frontal lobes, corpus callosum, basal ganglia, paraventricular nucleus, and right temporal lobe (a). Six months before admission for rehabilitation, a multifocal leukoencephalopathy diagnosis showed that the lesion was larger (b). Five months before rehabilitation, the lesion was stable, but brain atrophy had occurred (c). After admission, brain atrophy was more significant (d). Cranial magnetic resonance angiography showed no significant signs of arteritis (e), and no abnormal signal was found in the cervicothoracic cord (f).

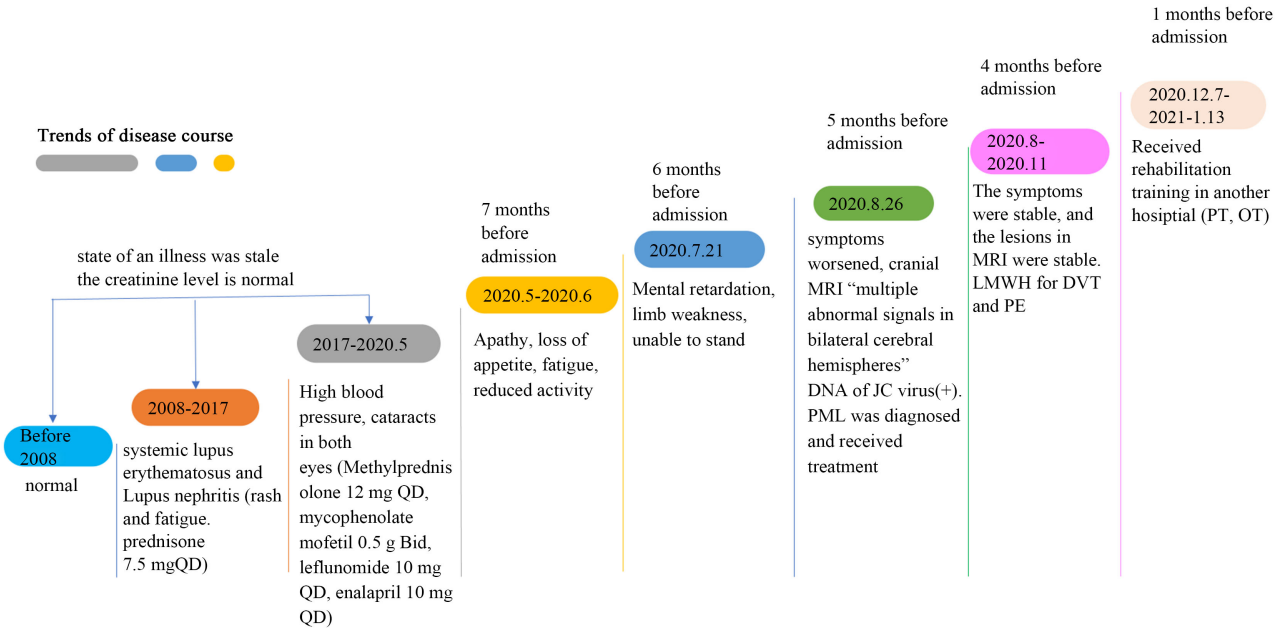

Figure 2. Disease course trend for a patient with systemic lupus erythematosus and progressive multifocal leukoencephalopathy. QD, once a day; MRI, magnetic resonance imaging; LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; PT, physical therapy; OT, occupational therapy.

Cognition and speech: Fluent speech with less active speech; Mini-Mental State Examination score (MMSE) was 13. the Montreal Cognitive Assessment

(MoCA) was 5. Her simple reaction time (SRT) was 756 ms (the normal upper limit is 320 ms), and choice reaction times (CRT) were 944 ms and 1038 ms with many mistakes (the normal value of CRT is no more than 200 ms higher than that of SRT). Her calculation, orientation, logical judgment, spatial structure, and short-term and instantaneous memory capacities were decreased, while her long-term memory remained.

Cranial nerve: Minor horizontal nystagmus (+), left central facial and lingual paralysis. The remaining cranial nerves were normal.

Movement and sensation: Bilateral limb paresis with normal muscle tone, the score of MMT, and the Brunnstrom stages of motor function are shown in Table 1. Right tendon reflex (+++), left tendon reflex (+), bilateral Hoffmann and Babinski signs (+), bilateral palmar chin reflex and sucking reflex (−). Bilateral superficial and deep sensory existed symmetrically.

Table 1. Patient performance on clinical and functional scales before and after comprehensive treatment.

		On admission	At discharge
MMSE (0 - 30 points)		13	15
Chinese edition of MoCA (0 - 30 points)		5	6
FMAS for balance (0 - 14 points)		5	7
Muscle Strength (MMT) 0 - 5 grades	Biceps (left; right)	4+; 5−	5−; 5
	Triceps (left; right)	4+; 5−	5−; 5
	Wrist extensors (left; right)	4−; 5−	5−; 5
	Wrist flexors (left; right)	4; 5−	4+; 5−
	Finger's flexors (left; right)	4−; 4+	4+; 5−
	Iliopsoas (left; right)	2+; 3+	4; 5−
	Quadriceps femoris (left; right)	2; 3+	4; 5−
	Anticus tibialis (left; right)	2; 3+	3+; 5−
	triceps surae (Left; right)	2; 3	3; 5−
FMAS for motor (left limb) 0 - 100 points	Upper (0 - 66 points)	48	51
	Lower (0 - 34 points)	9	13
Brunnstrom stage (I-VI stages)	Left upper limb	V	V
	Right upper limb	V	VI
	Left hand	V	V
	Right hand	V	VI
	Left lower limb	III	IV
	Right lower limb	V	V
FAC (0 - 5 grades)		1	2
BI (0 - 100 points)		20	40

Abbreviations: Mini-Mental State Examination (MMSE); Manual Muscle Strength Test (MMT); Montreal Cognitive Assessment Scale (MoCA); Fugl-Meyer Assessment Scale (FMAS); Barthel Index (BI); Holden Functional Ambulation Classification (FAC).

Ataxia and balance: The right finger nose test was normal, but the bilateral heel knee tibia test could not be completed due to decreased muscle strength. The patient's sitting and standing balance was poor, and she could not stand alone.

Daily living ability: Barthel index score was 20.

2.5. Supplementary Examinations (After Admission)

Brain MRI: The extent of abnormal lesions in the pons was reduced (Figure 1d), and the rest of the lesions were stable. However, brain atrophy was evident.

MRA: No significant signs of vascular stenosis, atherosclerosis, or vasculitis (Figure 1e).

Cervical MRI: No abnormal signals. (Figure 1f).

3. Rehabilitation Evaluation

Based on the patient's medical history and physical examination, the conclusion of the rehabilitation evaluation was as follows:

3.1. Cognitive impairment.

3.2. Dysfunction of limb and limb movement.

3.3. Balance dysfunction.

3.4. Immunodeficiency.

3.5. Emotional and mental disorders.

3.6. Urinary incontinence.

3.7. Poor ADL.

3.8. Decreased ability to participate in society.

4. Therapeutic Interventions

The patient was easily fatigued as she was diagnosed with SLE and PML. Therefore, as part of her individualized rehabilitation training, she needed only a moderate amount of low-resistance training to avoid aggravating fatigue.

4.1. Main Drug Treatment

Oral methylprednisolone 10 mg once daily to control immune diseases. Oral rivaroxaban 10 mg once daily to treat lower limb venous thrombosis. Mirtazapine 15 mg once at night to improve sleep and mood. Oral ursodeoxycholic acid capsules 250 mg three times daily to reduce cholestasis, and enalapril 10 mg once daily to control blood pressure.

4.2. Physical Therapy: 30 Minutes Each Time, Five Times a Week

Muscle strength enhancement exercises; trunk control and balance training; weight-bearing standing; joint range of motion maintenance and expansion to improve movement and mobilization, especially for the left limb; and guided abdominal and lip-retraction breathing.

4.3. Occupational Therapy: 30 Minutes Each Time, Five Times a Week

The therapy goals were to improve the patient's ability to maintain her sitting balance when given certain tasks and to enhance her left-hand grip, lifting ability, and endurance. This included fine motor training, executive ability training, daily life ability training, and expansion of the joint motion range.

4.4. Computer-Assisted Cognitive Impairment Rehabilitation System: 30 Minutes Each Time, Five Times a Week

Inductive classification, digital reading and computing, picture matching memory, and number finding to improve memory, attention, and capacity for calculation.

4.5. Chinese Acupuncture: 30 Minutes Each Time, Five Times a Week

Scalp acupuncture in the foot movement sensory area, motor area, sensory area, language area, and at the *Fengchi* (GB20), *Baihui* (GV20), and *Sishencong* (EX-HN 1) points to improve congestion.

Acupuncture was also applied to the *Pangguangshu* (BL28), *Dachangshu* (BL25), *Xiaochangshu* (BL27), *Chengfu* (BL 36), *Yinmen* (BL37), *Sanyinjiao* (SP6), *Taixi* (KI3), and *Yinlingquan* (SP9) points to improve urine and stool controllability. In addition, electroacupuncture was applied at *Baliao* points for 30 minutes each time.

4.6. Music Therapy: 30 Minutes Each Time, Five Times a Week

Music therapy to improve speech clarity and loudness, control breath and lung function through melodic singing and lip imitation, improve cognitive function through cognitive orientation training, and improve limb movements and cerebral functions by beating instruments according to a melodic rhythm, including music perception training and therapeutic singing. The therapeutic regime included imitating musical beats according to rhythm, cognitive orientation training, and lip-synching.

4.7. Behavioral Management Training

Behavior management training was implemented to control the time and quantity of daily drinking and eating and regularly remind the patient to urinate and defecate. Daily copy, writing, and calculation training were conducted to improve cognition, along with balloon-blowing and whistling training to improve lung function.

5. Follow-Up and Outcomes

After a month of comprehensive rehabilitation, her speaking volume increased, but she still did not take the initiative to communicate. Her intelligence did not

improve significantly. Her right limbs returned to normal, and her left limb muscle strength and movement improved significantly. She could stand alone but easily fell, so she needed assistance to walk (**Table 1**).

6. Discussion and Conclusions

Although previous studies have shown that appropriate rehabilitation, including aerobic exercise, can improve the level of fatigue and quality of life of patients with SLE [6] [7], this is the first report on the benefits of rehabilitation training for patients with SLE with PML. It is suggested that patients with SLE have poor endurance and quality of life, especially when accompanied by PML. However, new treatment and rehabilitation techniques can somewhat improve physical function and life satisfaction.

PML occurs most frequently in immunosuppressed patients; it affects the white matter of the cerebral hemisphere, spinal cord, and brainstem [8] [9]. In 2021, Graf *et al.* [3] retrospectively analyzed the clinical manifestations and disease course of 37 patients diagnosed with PML in a tertiary hospital. Among them, 36 (97%) were immunosuppressed. Among the 36 cases, 46% had HIV, 16% had received monoclonal antibody therapy, 16% had blood or malignant tumors, 14% had sarcoidosis, 3% underwent organ transplantation, and 3% had mixed connective tissue disease. During follow-up, the 24-month survival rate of patients with PML was only 56%.

HIV is considered the leading cause of PML. However, with the use of immunosuppressive drugs to treat SLE, there is an increasing number of cases complicated by PML [3]. To determine the risk of PML in patients with SLE, Columbia University Medical Center and Northwell Health Center retrospectively analyzed PML in patients with SLE, including children. The incidence of PML at the two hospitals was 13 - 27 PML cases/100,000 SLE cases, but there were no cases of PML in the group with rheumatoid arthritis. Among the 5409 patients with SLE at the Columbia University Medical Center, 212 had a history of kidney transplantation, 83 had HIV/AIDS, and none of the pediatric patients with SLE (n = 538) had PML [10]. Henegar [4] reviewed the risk factors of PML in patients with SLE to determine the association between the type of SLE or treatment and PML. The systematic review included studies reported in English from 1984 to 2014, including four observational studies, two case-control studies, and twenty-nine case reports. The incidence of PML in patients with SLE is considered to be 1 - 2.4 cases/1,000,000 persons/year. The increased incidence of PML in patients with SLE compared with the general population may be due to immunosuppressive status, other contributing factors from the underlying disease, treatments prescribed to manage a disease or some combination of these factors.

Gheuens [1] studied the pathology of JCV, focusing on the oligodendrocytes and astrocytes in the white matter of immunosuppressed individuals. In recent years, the recognition of inflammatory syndrome relapse shows that its patho-

physiology has a wide range of influences. Furthermore, JCV variants can also infect neurons, leading to the recognition of two distinct clinical entities, JCV granule cell neuronopathy and JCV encephalopathy [1]. The major genotypes of JCV include type 1 (European), type 2 (Asian), type 3 (African), and type 4 (US). An African-American type 6 strain (#601) was first reported in a patient with SLE and PML in 1998 [11]. It has been suggested that the PML associated with the different races is related to the genotypes of JCV, and there may be different pathophysiological mechanisms in the brain caused by different JCV genotypes. Future studies may investigate whether the different genotypes are related to lesion distribution.

Since JCV lesions mainly involve the gray and white matter junctions, it is often believed that PML lesions mainly involve the cerebral hemisphere. However, more cases have been recently reported on the brain stem, spinal cord, or posterior cranial fossa [8] [9] [12] [13]. Moreover, patients with multiple sclerosis may have asymptomatic PML [14]. Early MRI signs of SLE complicated with PML may only be punctate MRI patterns [15]. In addition, MRI lesions in central SLE may simulate PML [16]. Therefore, routine MRI examinations should be performed for patients at high risk of developing PML. Future studies should analyze the correlation between lesion size and location with PML prognosis. Cheng [17] reported a 27-year-old female patient with SLE and PML and found that the concentration of CSF JCV gradually decreased with the improvement of clinical symptoms and became negative after four months of treatment.

These findings suggest that in addition to MRI screening, the change in JCV concentration according to CSF is also an indicator of diagnosis and treatment. However, the specificity of the CSF for detecting JCV in different diseases associated with PML is different, and the positivity rate may only be approximately 60% in patients with autoimmune diseases [17]. Therefore, the diagnosis of PML requires 1) typical clinical manifestations and symptoms of PML, 2) a positive detection of JCV DNA from CSF, and 3) evidence of typical imaging features associated with PML. A low JCV concentration in the CSF and localized MRI lesions may indicate higher PML survival.

In treating PML, immune reconstitution inflammatory syndrome (IRIS) can easily cause inflammatory nervous system complications. Currently, the best treatment is monitoring for IRIS closely during rapid immune reconstitution. Developing sensitive biomarkers to titrate the best immune response may improve prognosis while encouraging prevention. Early diagnosis can also maximize PML prognosis [18]. Berntsson [19] reported the case of a 34-year-old HIV-negative woman with SLE complicated by PML. Although cidofovir is considered effective in treating HIV with PML, it is not effective in HIV-negative patients with PML. In treating this patient, cidofovir and cytarabine were used. *In vitro* studies showed that the 5-hydroxytryptamine 2A receptor could act as a JCV receptor in glial cells. Because most case studies reported mirtazapine as a potentially effective drug for PML, mirtazapine was added [20] [21]. Berntsson

[19] suggested that severe lymphopenia might have been the cause of JCV reactivation in a case study. Therefore, treating SLE complicated by PML should focus on eliminating the virus and increasing the lymphocyte count. Mefloquine is an antimalarial drug, but data suggest it effectively inhibits JCV infection [20] [22]. A combination of the antiviral agent CMX001, an oral formulation of cidofovir, and recombinant human interleukin 7, an inducer of CD4+ (Cluster of Differentiation 4) and CD8+ (Cluster of Differentiation 8) T cells, has also been reported to treat PML successfully [21].

In 2015, Gialanella reported the functional prognosis of a patient with PML who was bedridden due to a decrease in the activities of daily living. He proposed multidisciplinary rehabilitation and comprehensive home care to improve the function of a patient with PML [23]. In recent years, the rehabilitation of patients with PML has received increasing attention. A case of multiple sclerosis complicated by PML was reported after multidisciplinary rehabilitation. The patient's sensory-motor network was activated, suggesting that short-term rehabilitation can also affect functional brain reorganization [24]. It is believed that the clinical prognosis of PML can be improved with rehabilitation, even if PML is stable for several months before the rehabilitation begins [24] [25]. In the present case of a patient with SLE complicated by PML, she started rehabilitation two months after the condition had stabilized. Thus, the patient's limb motor function, clinical manifestations, and activities of daily living significantly improved. This suggests that comprehensive rehabilitation can effectively improve the quality of life and functional prognosis of patients with PML.

Although fatigue is a common symptom of SLE, a meta-analysis showed that exercise might improve the level of fatigue in patients with SLE, and physical activity can improve the quality of life and cardiopulmonary function and reduce depression [6] [7] [26]. There was no significant improvement in cognitive function in the patient described herein, which may be related to her progressive brain atrophy.

As early as 1998, cognitive impairments in patients with SLE were confirmed [27]. A meta-analysis showed that compared with a control population, patients with SLE are more prone to cognitive impairment. Compared to patients with SLE but without neuropsychiatric symptoms, patients with neuropsychiatric symptoms have more obvious cognitive impairment, manifesting in the decline of attention, memory, and reasoning abilities [28]. Further, it is speculated that the pathophysiological mechanism of cognitive impairment in cases of SLE may be related to corticosteroid use or depression, or there is a "lupus-specific" pattern [27]. In our case, the patient did not complain of obvious fatigue, which may be one of the benefits of the rehabilitation techniques. Concerning the patient's cognitive impairment, we also needed to consider whether it was directly related to the SLE. Currently, there is no large-scale study on whether there is a specific type of cognitive impairment in cases of SLE or PML. The next step is to analyze the cognitive function of patients with different diseases and PML.

In conclusion, although the rehabilitation results in this case report are very encouraging, large-scale and long-term follow-up studies are needed to confirm their general applicability. Additionally, studies are required to compare the white matter fiber tract remodeling (by diffusion tensor imaging) and brain function reorganization (by functional MRI) before and after rehabilitation to more precisely evaluate the rehabilitation effect, whether there are differences in the rehabilitation effect in cases of PML according to cause, and if there are differences in the cognitive impairment and cognitive rehabilitation prognosis associated with different diseases accompanied by PML. Conducting a longitudinal study on cognitive impairment associated with SLE is also necessary.

Patient Perspective

Because of the patient's cognitive problems, it was difficult to obtain her perspective on the treatments she received. However, her family members were very satisfied with the treatment outcomes.

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Ethics Approval and Consent to Participate

This case report was approved by the Ethical Committee of China Rehabilitation Research Centre and was conducted in accordance with the Declaration of Helsinki (CRRC-IEC-RF-SC-005-01).

Consent for Publication

Written informed consent was obtained from the patient's family to publish this case report and any accompanying images.

Availability of Data and Materials

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

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Authors' Contributions

XW contributed to the collection and arrangement of medical records, discussion of analysis and results, and writing and revision of the manuscript. YZ contributed to the collection and arrangement of medical records. XH and LL contributed to the revision of the manuscript. TZ contributed to the study idea, dis-

cussion of analysis and results, and revision of the manuscript. All authors listed approved the manuscript for publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Gheuens, S., Wüthrich, C. and Koralnik, I.J. (2013) Progressive Multifocal Leukoencephalopathy: Why Gray and White Matter. *Annual Review of Pathology*, **8**, 189-215. https://doi.org/10.1146/annurev-pathol-020712-164018

[2] Yukitake, M. (2019) Progressive Multifocal Leukoencephalopathy in Systemic Lupus Erythematosus. *Brain and Nerve*, **71**, 493-505.

[3] Graf, L.M., Rosenkranz, S.C., Hölzemer, A., Hagel, C., Goebell, E., Jordan, S., *et al.* (2021) Clinical Presentation and Disease Course of 37 Consecutive Cases of Progressive Multifocal Leukoencephalopathy (Pml) at a German Tertiary-Care Hospital: A Retrospective Observational Study. *Frontiers in Neurology*, **12**, Article ID: 632535. https://doi.org/10.3389/fneur.2021.632535

[4] Henegar, C.E., Eudy, A.M., Kharat, V., Hill, D.D., Bennett, D. and Haight, B. (2016) Progressive Multifocal Leukoencephalopathy in Patients with Systemic Lupus Erythematosus: A Systematic Literature Review. *Lupus*, **25**, 617-626. https://doi.org/10.1177/0961203315622819

[5] Molloy, E.S. and Calabrese, L.H. (2008) Progressive Multifocal Leukoencephalopathy in Patients with Rheumatic Diseases: Are Patients with Systemic Lupus Erythematosus at Particular Risk? *Autoimmunity Reviews*, **8**, 144-146. https://doi.org/10.1016/j.autrev.2008.07.006

[6] Gavilán-Carrera, B., Vargas-Hitos, J.A., Morillas-de-Laguno, P., Rosales-Castillo, A., Sola-Rodríguez, S., Callejas-Rubio, J.L., *et al.* (2022) Effects of 12-Week Aerobic Exercise on Patient-Reported Outcomes in Women with Systemic Lupus Erythematosus. *Disability and Rehabilitation*, **44**, 1863-1871. https://doi.org/10.1080/09638288.2020.1808904

[7] Bogdanovic, G., Stojanovich, L., Djokovic, A. and Stanisavljevic, N. (2015) Physical Activity Program Is Helpful for Improving Quality of Life in Patients with Systemic Lupus Erythematosus. *The Tohoku Journal of Experimental Medicine*, **237**, 193-199. https://doi.org/10.1620/tjem.237.193

[8] Onwubiko, I.N., Taneja, K., Gupta, N. and Mukherjee, A. (2021) Unusual Case of Progressive Multifocal Leukoencephalopathy in a Patient with Sjögren Syndrome. *The American Journal of Forensic Medicine and Pathology*, **42**, 186-190. https://doi.org/10.1097/PAF.0000000000000656

[9] Breville, G., Koralnik, I.J. and Lalive, P.H. (2021) Brainstem Progressive Multifocal Leukoencephalopathy. *European Journal of Neurology*, **28**, 1016-1021. https://doi.org/10.1111/ene.14617

[10] Kapoor, T., Mahadeshwar, P., Hui-Yuen, J., Quinnies, K., Tatonetti, N., Gartshteyn, Y., *et al.* (2020) Prevalence of Progressive Multifocal Leukoencephalopathy (PML) in Adults and Children with Systemic Lupus Erythematosus. *Lupus Science & Medicine*, **7**, e000388. https://doi.org/10.1136/lupus-2020-000388

[11] Agostini, H.T., Ryschkewitsch, C.F. and Stoner, G.L. (1998) Complete Genome of a JC Virus Genotype Type 6 from the Brain of an African American with Progressive

Multifocal Leukoencephalopathy. *Journal of Human Virology*, **1**, 267-272.

[12] Gonçalves, F.G., Lamb, L. and Del Carpio-O'Donovan, R. (2011) Progressive Multifocal Leukoencephalopathy Restricted to the Posterior Fossa in a Patient with Systemic Lupus Erythematosus. *The Brazilian Journal of Infectious Diseases*, **15**, 609-612. https://doi.org/10.1016/S1413-8670(11)70261-6

[13] Simaniv, T.O., Ivanova, M.V., Bryukhov, V.V. and Zakharova, M.N. (2019) Sluchaĭ Razvitiia Progressiruiushcheĭ Mul'tifokal'noĭ Leĭkoéntsefalopatii Subtentorial'noĭ Lokalizatsii Na Fone Terapii Natalizumabom [A Case of Subtentorial Progressive Multifocal Leucoencephalopathy in a Patient Treated with Natalizumab]. *Zhurnal Nevrologii I Psikhiatrii imeni S S Korsakova*, **119**, 98-106. https://doi.org/10.17116/jnevro20191192298

[14] Zhang, Y., Wright, C. and Flores, A. (2018) Asymptomatic Progressive Multifocal Leukoencephalopathy: A Case Report and Review of the Literature. *Journal of Medical Case Reports*, **12**, Article No. 187. https://doi.org/10.1186/s13256-018-1727-7

[15] Ishii, J., Shishido-Hara, Y., Kawamoto, M., Fujiwara, S., Imai, Y., Nakamichi, K., *et al.* (2018) A Punctate Magnetic Resonance Imaging Pattern in a Patient with Systemic Lupus Erythematosus Is an Early Sign of Progressive Multifocal Leukoencephalopathy: A Clinicopathological Study. *Internal Medicine*, **57**, 2727-27234. https://doi.org/10.2169/internalmedicine.0696-17

[16] Kaye, B.R., Neuwelt, C.M., London, S.S. and DeArmond, S.J. (1992) Central Nervous System Systemic Lupus Erythematosus Mimicking Progressive Multifocal Leucoencephalopathy. *Annals of the Rheumatic Diseases*, **51**, 1152-1156. https://doi.org/10.1136/ard.51.10.1152

[17] Cheng, C.F., Su, J.J., Chen, Y.F., Lin, Y.C., Huang, Y.M. and Li, K.J. (2019) Progressive Multifocal Leukoencephalopathy in a 27-Year-Old Lady with Systemic Lupus Erythematosus—Rheumatoid Arthritis Overlap Syndrome. *Journal of the Formosan Medical Association*, **118**, 1560-1565. https://doi.org/10.1016/j.jfma.2019.05.021

[18] Clifford, D.B. (2015) Progressive Multifocal Leukoencephalopathy Therapy. *Journal of NeuroVirology*, **21**, 632-636. https://doi.org/10.1007/s13365-014-0289-8

[19] Berntsson, S.G., Katsarogiannis, E., Lourenço, F. and Moraes-Fontes, M.F. (2016) Progressive Multifocal Leukoencephalopathy and Systemic Lupus Erythematosus: Focus on Etiology. *Case Reports in Neurology*, **8**, 59-65. https://doi.org/10.1159/000444874

[20] Simopoulou, T., Tsimourtou, V., Katsiari, C., Vlychou, M., Bogdanos, D.P. and Sakkas, L.I. (2020) Progressive Multifocal Leukoencephalopathy in a Patient with Systemic Sclerosis Treated with Methotrexate: A Case Report and Literature Review. *Journal of Scleroderma and Related Disorders*, **5**, NP1-NP6. https://doi.org/10.1177/2397198320926883

[21] De Gascun, C.F. and Carr, M.J. (2013) Human Polyomavirus Reactivation: Disease Pathogenesis and Treatment Approaches. *Clinical and Developmental Immunology*, **2013**, Article ID: 373579. https://doi.org/10.1155/2013/373579

[22] Shin, J.W., Jung, K.H., Lee, S.T., Moon, J., Lim, J.A., Byun, J.I., *et al.* (2014) Mefloquine Improved Progressive Multifocal Leukoencephalopathy in a Patient with Immunoglobulin A Nephropathy. *Journal of Clinical Neuroscience*, **21**, 1661-1664. https://doi.org/10.1016/j.jocn.2013.12.031

[23] Gialanella, B., Prometti, P., Lissi, M. and Tanghetti, L. (2015) Functional Course of Progressive Multifocal Leukoencephalopathy. *Clinical Therapeutics*, **166**, 244-247.

[24] Groppo, E., Baglio, F., Cattaneo, D., Tavazzi, E., Bergsland, N., Di Tella, S., *et al.* (2017) Multidisciplinary Rehabilitation Is Efficacious and Induces Neural Plasticity

in Multiple Sclerosis even when Complicated by Progressive Multifocal Leukoencephalopathy. *Frontiers in Neurology*, **8**, Article No. 491. https://doi.org/10.3389/fneur.2017.00491

[25] Moreh, E., Israel, S., Korem, M. and Meiner, Z. (2017) Rehabilitation Outcome of Progressive Multifocal Leukoencephalopathy in HIV-Positive Patients: A Report of Two Cases. *Disability and Rehabilitation*, **39**, 1893-1896. https://doi.org/10.1080/09638288.2016.1211754

[26] Wu, M.L., Yu, K.H. and Tsai, J.C. (2017) The Effectiveness of Exercise in Adults with Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis to Guide Evidence-Based Practice. *Worldviews on Evidence-Based Nursing*, **14**, 306-315. https://doi.org/10.1111/wvn.12221

[27] Bleiberg, J. and Bunning, R. (1998) Cognitive and Physical Measures in Rehabilitation of Patients with Lupus. *Current Opinion in Rheumatology*, **10**, 442-445. https://doi.org/10.1097/00002281-199809000-00008

[28] Leslie, B. and Crowe, S.F. (2018) Cognitive Functioning in Systemic Lupus Erythematosus: A Meta-Analysis. *Lupus*, **27**, 920-929. https://doi.org/10.1177/0961203317751859