

Cerebral Venous Thrombosis as a Complication of Neuropsychiatric Systemic Lupus Erythematosus

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Abstract

A 51-year-old woman undergoing steroid treatment for systemic lupus erythematosus (SLE) was admitted to our hospital after developing a fever, consciousness disturbance and seizures, leading to a diagnosis of SLE-induced meningoencephalitis. Although steroid therapy improved her symptoms, she complained of post-lumbar puncture thunderclap headaches during follow-up, and cerebral venous thrombosis (CVT) was subsequently diagnosed on magnetic resonance venography and cerebral angiography. This is a rare case of neuropsychiatric SLE complicated by CVT during treatment for aseptic meningoencephalitis. The onset of aseptic meningoencephalitis and administration of the lumbar puncture and steroid therapy may have induced the development of the patient's CVT symptoms.

Key words: neuropsychiatric SLE, cerebral venous thrombosis, thunderclap headache

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Introduction

Systemic lupus erythematosus (SLE) may be complicated by a variety of neuropsychiatric symptoms during its clinical course. The neuropsychiatric symptoms of SLE, including peripheral nerve injury, are classified by the American College of Rheumatology as neuropsychiatric SLE (NPSLE) (1). Although previous studies have reported cognitive disorders and headaches as frequently observed symptoms in such patients (2, 3), a limited number of case reports have reported the rare complication of cerebral venous thrombosis (CVT) (4-10).

We herein describe a case of SLE accompanied by NPSLE symptoms, including convulsions, acute confusion and aseptic meningoencephalitis, with the subsequent development of CVT associated with post-lumbar puncture thunderclap headaches.

Case Report

A 51-year-old woman was admitted to our hospital with a fever and consciousness disturbance after a seizure. She had a past history of encephalitis diagnosed at 36 years of age

(details unknown), secondary epilepsy as an aftereffect of the encephalitis and SLE. She had been treated with anti-convulsants (phenytoin, 240 mg/day; valproic acid, 800 mg/day) and low-dose corticosteroids (prednisolone, 10 mg/day) for SLE at another hospital. She subsequently developed a fever the day before admission to our hospital, followed by tonic convulsions lasting approximately one minute with a consciousness disturbance and fever on the day of admission.

Upon admission, the patient's vital signs were as follows: body temperature, 38°C; blood pressure, 102/56 mmHg; pulse rate, 98 beats/min; and consciousness level according to the Japan Coma Scale, 3. No abnormal findings were observed on cardiovascular, respiratory or abdominal examinations. A neurological examination revealed mild neck rigidity, with no other focal neurological deficits.

A complete blood cell count demonstrated the following normal findings: white blood cells, 8,600/ μ L; red blood cells, 384×10^4 / μ L; and platelets, 24×10^4 / μ L. Blood biochemistry showed an elevated C-reactive protein level and erythrocyte sedimentation rate (19 mg/dL and 58 mm/h, respectively), with a PT of 80.5% (normal, 70-130). Serology was positive for antinuclear antibodies [1:320 (normal, <40-fold)] and negative for anti-ds-DNA IgG [10 IU/mL (nor-

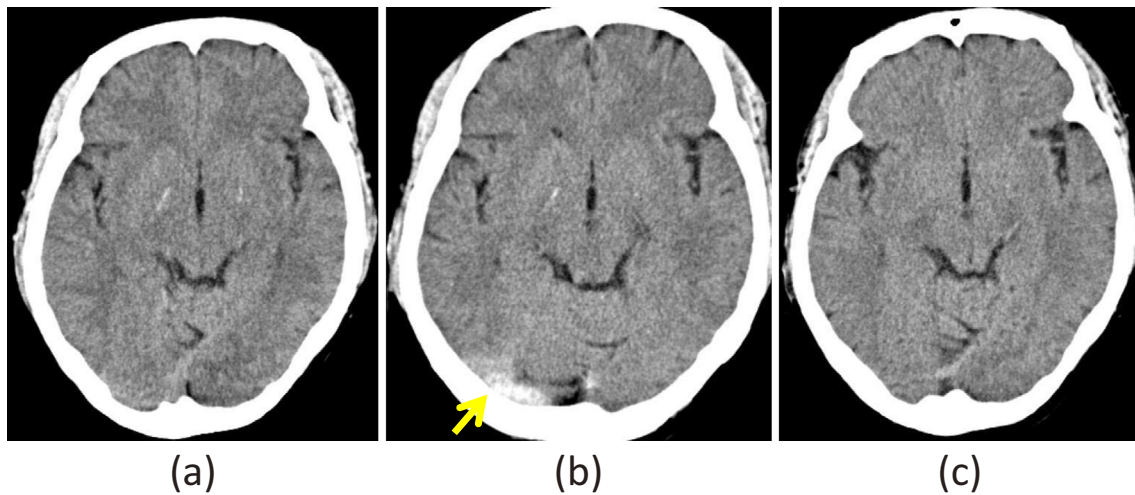


Figure 1. Brain computed tomography (CT) performed upon the appearance of symptoms (b) demonstrated a high-density area in the right transverse sinus (arrow), leading to a suspected diagnosis of cerebral venous thrombosis. Brain CT performed on admission (a) and follow-up (c) showed no abnormalities.

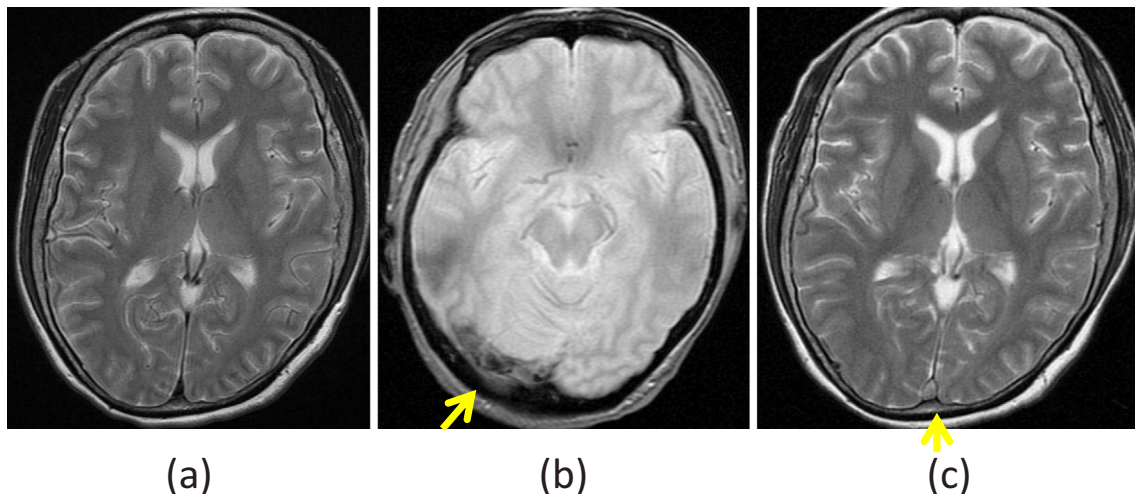


Figure 2. A brain magnetic resonance imaging (MRI) T2*-weighted image (b) showed a low-intensity area in the right transverse sinus (arrow), and a diagnosis of transverse sinus thrombosis was suspected. Thrombosis was subsequently detected in the superior sagittal sinus as an area with an iso-intense signal on a brain MRI T2-weighted image (arrow) (c). A brain MRI T2-weighted image obtained on admission (a) showed no abnormalities.

mal, ≤ 12 IU/mL], anti-ds-DNA IgM [2 U/mL (normal, 6 IU/mL)], anti-Sm antibodies, lupus anticoagulant [1.02 (normal, < 1.3)], anticardiolipin antibody IgG [8 U/mL (normal, < 10 U/mL)] and anticardiolipin antibody IgM [5 U/mL (normal, < 8 U/mL)]. The D-dimer level was not measured.

A lumbar puncture revealed a primary pressure of 100 mm H₂O, cell count of 349/3 μ L (N/L=7/342), protein level of 271 mg/dL, glucose level of 54 mg/dL, myelin basic protein level of 40 pg/mL, elevated interleukin-6 (IL-6) level of 331 pg/mL, the absence of bacteria and tuberculosis microorganisms and negative findings for herpes simplex virus polymerase chain reaction, varicella-zoster virus polymerase chain reaction and oligoclonal bands. Brain computed to-

mography (CT) and magnetic resonance imaging (MRI) showed no abnormalities (Fig. 1, 2).

Although the patient received acyclovir (1,500 mg/day) and antibiotics for aseptic meningoencephalitis, she did not respond to the treatment. A diagnosis of aseptic meningoencephalitis as a complication of SLE was thus made based on the pre-existing SLE and elevated IL-6 level in the spinal fluid. Steroid treatment was administered (prednisolone, 60 mg/day), and her symptoms quickly improved on day 6.

On day 11, a repeated lumbar puncture showed improvements in the data, with a cell count of 44/3 μ L, protein level of 56 mg/dL and IL-6 level of 33 pg/mL. However, the patient suddenly developed a headache two hours after the

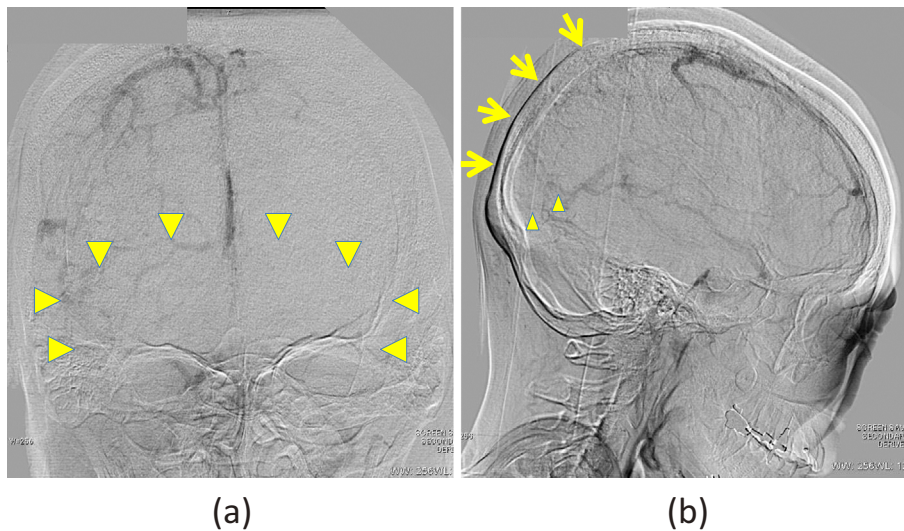


Figure 3. A digital subtraction cerebral angiogram of the right carotid artery (venous phase) (a: frontal view, b: lateral view) did not visualize the superior sagittal sinus (b: arrows), straight sinus (b: arrowheads), bilateral transverse sinus (a: arrowheads) or sigmoid sinus (a: arrowheads); cerebral venous thrombosis was diagnosed.

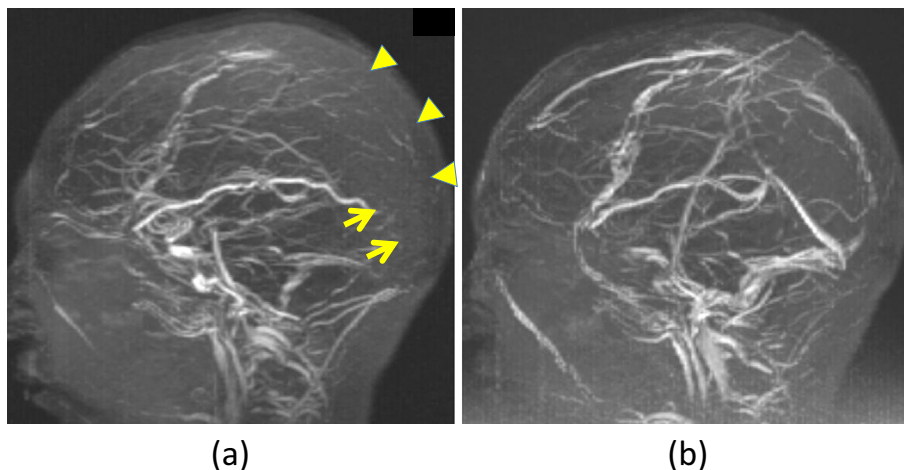


Figure 4. Magnetic resonance venography (MRV) performed upon the appearance of symptoms (a) did not visualize the superior sagittal sinus (arrowheads) or straight sinus (arrows), cerebral venous thrombosis was diagnosed. MRV performed six months later (b) successfully visualized the superior sagittal sinus, transverse sinus and straight sinus; the site of cerebral venous thrombosis had been recanalized.

lumbar puncture that immediately reached a peak in severity (similar to a thunderclap headache). Although an analgesic was administered, the headache was not relieved. In addition, the presence of a high-density area in the right transverse sinus on brain CT (Fig. 1) was suspicious of venous sinus thrombosis. However, no brain lesions were detected, such as cerebral hemorrhage. Nevertheless, an MRI T2-weighted image showed low intensity in the right transverse sinus, and a diagnosis of transverse sinus thrombosis was suspected. Thrombosis was subsequently detected in the superior sagittal sinus based on an iso-intense signal on a brain MRI T2-weighted image (Fig. 2).

Digital subtraction cerebral angiography (DSA) (Fig. 3)

and MR venography (MRV) (Fig. 4) showed occlusion of the superior sagittal sinus, straight sinus, bilateral transverse sinus and sigmoid sinus, confirming the diagnosis of CVT. A blood test showed elevation of the D-dimer level (5.4 $\mu\text{g}/\text{mL}$). Anti-coagulation therapy with heparin-Na was therefore started and subsequently changed to warfarin. No complications involving the brain parenchyma, such as cerebral hemorrhage, were observed after treatment, and the patient's clinical course was uneventful, including the alleviation of her headache. Follow-up MRV (Fig. 4) showed recanalization of the venous sinus.

Table. Reported of the Cases of Cerebral Venous Thrombosis in Systemic Lupus Erythematosus (Negative Antiphospholipid Antibodies Cases)

Reference	Age	Sex	renal disorder	APLA	Treatment	Outcome
5	40	F	-	-	heparin, wafarin	Resolved
7	34	F	+	-	steroid pulse, heparin, warfarin	Resolved
7	55	F	+	-	steroid pulse, heparin, warfarin	Resolved
8	14	F	-	-	heparin, steroid, wafarin	Resolved
8	13	F	-	-	steroid	Resolved
9	39	F	-	-	steroid, cyclophosphamide, anticoagulant	Resolved
10	33	F	-	-	steroid	Resolved
our case	51	F	-	-	steroid, anticoagulant	Resolved

APLA: anti-phospholipid antibody (lupus anticoagulant and anticardiolipin antibody),

+: positive, -: negative

Discussion

The present case report involves a patient who developed a variety of neuropsychiatric symptoms, including convulsions, acute confusion and aseptic meningoencephalitis, during the clinical course of SLE. Moreover, CVT was diagnosed following the onset of a post-lumbar puncture headache.

Previous case reports have reported complication rates of convulsions, acute confusion and meningitis, neuropsychiatric symptoms associated with SLE collectively known as NPSLE, of 9-16%, 7% and 2%, respectively (2, 3). However, no cases of CVT have been described in previous reports, and this symptom is thus considered to be a rare complication.

Although the Virchow triad (a hypercoagulable state, blood flow congestion and structural changes in the vascular wall) is thought to play a role in the onset of CVT, several other causes of this complication are suspected. Acquired causes include infections, such as meningoencephalitis and otitis media, brain tumors, pregnancy and puerperium, oral contraceptive use and surgery, while hereditary causes comprise protein C and S deficiencies. However, SLE accounts for only 1% of underlying causes of CVT (11, 12).

Although the development of CVT during the clinical course of SLE is rare, some cases have been shown to involve anti-phospholipid antibodies (4-6), while others were negative for anti-phospholipid antibodies, with suspected underlying causes of hypercoagulability, vasculitis and hypertrophic pachymeningitis (5, 7-10) (Table).

The present report discusses a case of CVT that occurred after lumbar puncture. Previous reports have suggested that lumbar puncture accounts for 1.9% of all causes of CVT (10), possibly attributable to a reduced amount of cerebrospinal fluid. Other suspected causes of CVT include venous dilatation resulting from cerebrospinal fluid reduction and associated decreases in the venous blood flow, increased venous blood viscosity, stenosis and occlusion of the veins and venous sinuses due to cerebral ptosis (13, 14). In addition, the administration of drugs, such as steroids, may promote the development of CVT after lumbar puncture (15, 16), with lumbar puncture and corticosteroid treat-

ment likely to play a role in the onset of CVT in patients with multiple sclerosis (17-19).

In the current case, the aseptic meningoencephalitis appeared to be a symptom of NPSLE. Moreover, the initially elevated IL-6 level decreased following treatment with corticosteroids.

In patients with NPSLE, the CSF levels of IL-6 and IL-8 are initially elevated and subsequently decrease after successful treatment. Furthermore, analyses of the CSF cytokine levels, particularly IL-6 and IL-8, are useful for making the diagnosis and possibly in providing follow-up in patients with NPSLE (20). Hence, intrathecal immunological inflammation plays an important role in the pathogenesis of NPSLE (21). In this case, anti-phospholipid antibodies were negative and not associated with anti-phospholipid antibodies. Therefore, the direct expansion of inflammation due to meningoencephalitis and the administration of steroid therapy may have induced the development of CVT. Moreover, the lumbar puncture was associated with the onset of the CVT in association with a thunderclap headache.

Taken together, we conclude that the direct expansion of inflammation resulting from aseptic meningoencephalitis and the administration of the lumbar puncture and steroid treatment with prednisolone played a role in the onset of CVT in the present case.

Lastly, the patient's severe post-lumbar puncture headache appeared suddenly, with the severity peaking immediately. Even with the administration of an analgesic, the headache persisted until the following day and resembled the features of a thunderclap headache. The classic symptom of CVT is headache, observed in approximately 90% of cases (11). In addition, Cumurciuc et al. reported that headaches are observed as the only symptom of CVT in 14% of cases, with thunderclap headaches in 17.5% of cases as the only symptom. It has been reported that a diagnosis of CVT should be ruled out on MRI and/or MRV in cases of disease progression with a thunderclap headache, even if CT and spinal tap examinations show normal findings (22). Although headache is a common disease manifestation, CVT must be excluded in patients exhibiting thunderclap headaches and/or progressive deterioration.

We herein reported the case of a patient who developed a variety of neuropsychiatric symptoms, including convul-

sions, acute confusion and meningoencephalitis. Although steroid treatment successfully improved these symptoms, CVT was ultimately diagnosed because the patient developed a thunderclap headache after undergoing lumbar puncture. While a variety of causes may have contributed to the onset of CVT in the present case, the lumbar puncture was likely an aggravating factor. Our findings suggest that the risk of CVT is increased in the context of pre-existing disease and treatment requiring lumbar puncture, a relatively common examination in daily practice in the field of neurological medicine. Therefore, careful follow-up after lumbar puncture is warranted.

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

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