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Systemic Lupus Erythematosus Complicated with Cerebral Venous Sinus Thrombosis
: A Report of Two Cases

A rare manifestation of systemic lupus erythematosus (SLE) is cerebral venous sinus thrombosis (CVST), in which early diagnosis and aggressive therapy are of prime importance for favorable outcome. The pathogenesis of CVST is largely unknown, but it is thought to be caused by cerebral vasculitis, antiphospholipid antibodies or other conditions associated with enhanced coagulability. We describe two cases of SLE with CVST which were not associated with antiphospholipid antibodies. Both cases were treated with immunosuppressants (intravenous methylprednisolone and cyclophosphamide pulse therapy) and anticoagulant drugs (heparin and subsequent maintenance therapy with warfarin). There was a marked improvement of neurologic symptoms with the disappearance of thrombus in a follow-up MRI. The possibility of CVST should be considered in any patients with SLE who show neuropsychiatric manifestations.

Key Words : *Systemic Lupus Erythematosus; Sinus Thrombosis, Intracranial*

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease. Although thrombotic events including thrombosis of deep venous system of extremities, vena cava, renal and mesenteric vein occur in 10-20% of patients with SLE (1), cerebral venous sinus thrombosis (CVST) has been rarely reported in the literature (1-5). Vascular injuries presumably mediated by immune complex deposition and immune mediated venulitis are known to lead to CVST in SLE (2, 6). Other factors such as antiphospholipid antibodies or conditions associated with enhanced coagulability may also be responsible for CVST (2, 7).

We experienced two cases of SLE with CVST who were treated with a combination of immunosuppressants and anticoagulant drugs and showed a favorable outcome.

CASE REPORT

Case 1

A 34-year-old female was admitted with chief complaints of aggravated, dull headache for a one-week period. She had been diagnosed as SLE with nephritis (type IIa) on the basis of renal biopsy, laboratory findings and clinical features such as malar rash, arthralgia, mild headache, oral ulcer and proteinuria (974 mg/day) one month before admission. She had been treated with hydroxychloroquine and low doses of corticosteroids, which improved the musculocutaneous symptoms. However, her headache was not well controlled by the drugs, and it even aggravated. She denied a history of spontaneous abortions, thrombotic events or the use of oral pills.

Vital signs showed the following: body temperature 38.5℃, pulse rate 110/min, and blood pressure 120/80 mmHg. Physical examination revealed no abnormalities. Particularly, focal neurologic deficit or meningeal irritation sign and papilledema were not found. Laboratory findings were as follows: hemoglobin 15.7 g/dL, white blood cell 4,470/μL, platelet 202,000/μL, erythrocyte sedimentation rate (ESR) 4 mm/hr, C-reactive protein (CRP) 0.4 mg/dL. Coagulation time and liver and renal function tests were normal. Antinuclear antibody was 1:160 with a rim pattern and anti-ds DNA antibody was 50 IU/mL (normal; <7 IU/mL). VDRL, anticardiolipin anbibody, and lupus anticoagulant were non-reactive.

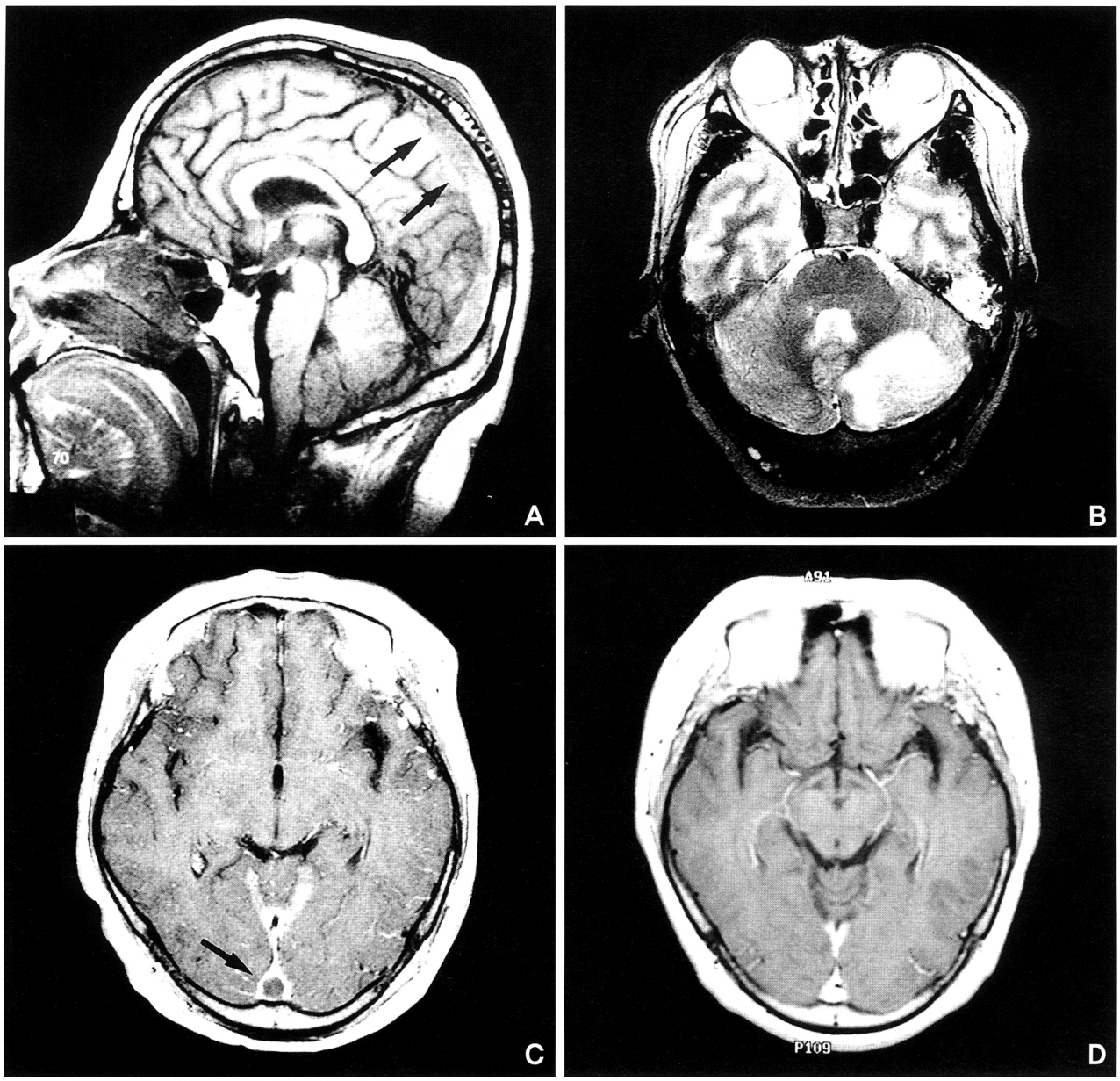

Fig. 1. Case 1. **A:** Sagittal T1-weighted MR image shows isointense lesion (arrows) in the superior sagittal sinus. **B:** Axial T2-weighted MR image shows diffuse high signal intensity in the left cerebellar hemisphere. **C:** Axial T1-weighted MR image shows 'empty delta sign' (arrow). **D:** Follow-up (3 month later) MR image shows the disappearance of the thrombus in the sagittal sinus.

The C3 level was 40.8 mg/dL (normal; 85-194 mg/dL) and the C4 level was 10.0 mg/dL (normal; 12-36 mg/dL). The lumbar puncture showed an opening pressure of 290 mmH_2O. Biochemical and cytological analyses of the cerebral spinal fluid were unremarkable. Brain magnetic resonance imaging (MRI) showed isointense lesions in the superior sagittal, left transverse, sigmoid sinus and internal jugular vein on T1-weighted images and diffuse high signal intensity in the left cerebellar hemisphere on T2-weighted images, suggestive of CVST complicated with cerebellar venous infarction (Fig. 1A, B, C).

She was treated with intravenous methylprednisolone pulse therapy (1 g/day for 3 consecutive days) and cyclophosphamide (750 mg/m^2/month), combined with anticoagulant therapy (heparin and subsequent warfarin). There was a marked improvement of headache, with a disappearance of thrombus in the follow-up (3 month later) MRI (Fig. 1D).

Case 2

A 55-year-old woman was admitted due to generalized edema for a two- months period. She had been diagnosed

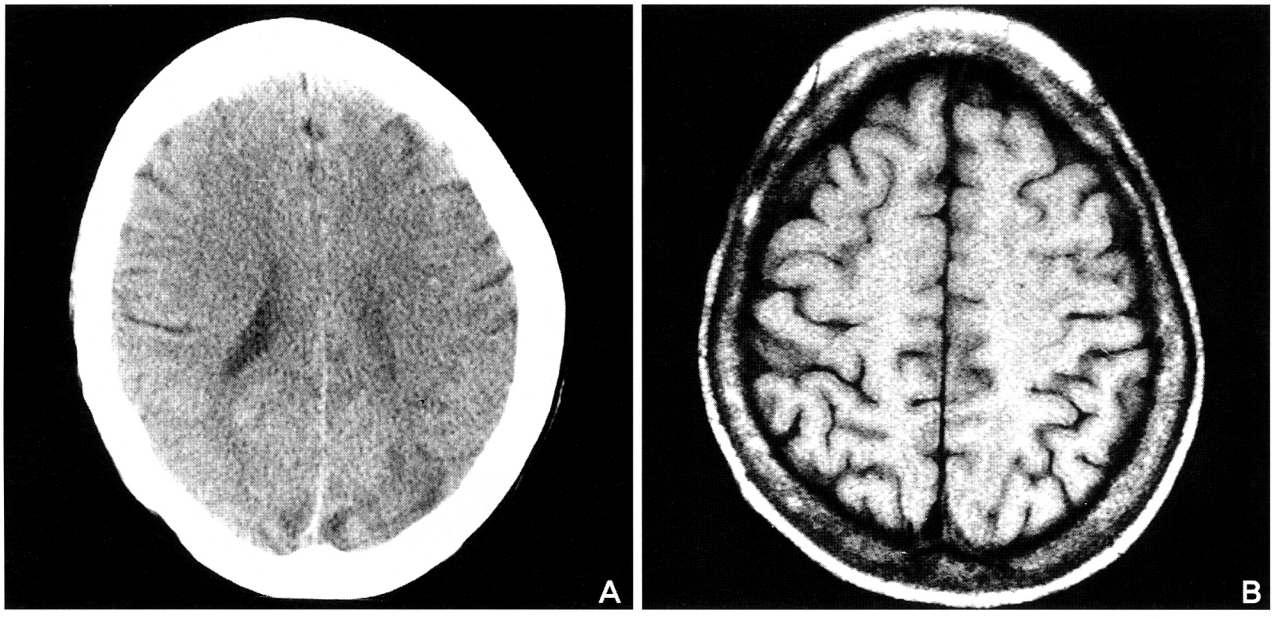

Fig. 2. Case 2. A: CT scan shows low density along the gyrus of both precuneus and cerebral edema of both parietal lobes. B: Follow-up (1 month later) T1-weighted MR image shows no thrombus in the sagittal sinus.

as lupus nephritis (type IV, 24 hr urine protein: 1,720 mg/day) 1 year before admission. A complete resolution of proteinuria was induced after introducing high doses of corticosteroids. At the time of admission, she was taking low doses of prednisolone (7.5 mg/day) and hydroxychloroquine.

Vital signs were as follows: blood pressure 140/90 mmHg, pulse rate 110/min, and body temperature 38.0℃. Physical examination revealed pitting edema on both lower extremities. Laboratory findings included hemoglobin 10.0 g/dL, white blood cell 4,000/μL, platelet 187,000/μL, ESR 83 mm/hr, CRP 0.57 mg/dL. Coagulation time and liver function tests were normal. Antinuclear antibody was 1:160 with a rim pattern and anti-ds DNA antibody was 75.6 IU/mL. Anticardiolipin anbibody and lupus anticoagulant were not detected. The C3 level was 22.9 mg/dL and the C4 level was 7.54 mg/dL. Because of the development of azotemia (BUN/creatinine: up to 81.8/4.1 mg/dL) and increased proteinuria (24 hr urine protein: 5,526 mg/day), the second renal biopsy was performed, which revealed crescentic glomerulonephritis. A few days after the renal biopsy, grand mal seizures developed and was followed by confusion and right hemiplegia. Cerebral computed tomographic (CT) scan revealed a low density along the gyrus of both precuneus with cerebral edema of both parietal lobes, suggestive of CVST complicated with venous infarction (Fig. 2A).

She was treated with the same regimen as in the case 1, leading to a gradual improvement of neurologic symptoms and renal function. A follow-up brain MRI after one month showed no thrombus in the sagittal sinus (Fig. 2B).

DISCUSSION

CVST can occur in the course of SLE, or occasionally as the presenting symptoms of SLE (9). The symptoms and signs of CVST may be nonspecific and vary from headache, intracranial hypertension without focal signs, altered mental status, seizures, focal neurologic deficits, and even death (10, 11). Not surprisingly, there was a great difference in symptomatology of the two subjects. In contrast to the headache being the only manifestation in case 1, rapidly deteriorating neurologic signs were prominent in case 2. Therefore, CVST should be considered in any patient with persistent headache that is unresponsive to analgesics, with or without neurologic signs.

Several mechanisms may explain the formation of thrombus in patients with SLE. Cerebral vasculitis is known to be an important cause of neuropsychiatric SLE (2, 6, 11). The response to immunosuppressive drugs supports this mechanism (3). Lupus anticoagulant and anticardiolipin antibodies are present in about 40% of SLE patients with CNS involvement, and correlates strongly with the formation of thrombus (3, 7). Complex interactions between endothelial cells and antiphospholipid antibodies could inhibit the functions of protein C and protein S (4, 8), which lead to the formation of thrombus. Hypercoagulability caused by defective fibrinolysis, al-

tered antithrombin III function, hyperfibrinemia, and changes in coagulation, frequently observed in nephrotic syndrome, could be another etiologic factor (2, 4). Our cases were not associated with antiphospholipid antibodies, which suggested cerebral vasculitis and/or hypercoagulability related to nephrotic syndrome (in case 2) to be an underlying mechanisms.

The diagnosis of CVST is based on radiologic studies. Usually CT scanning is initially done because acute cerebral hemorrhage may be missed by MRI. The characteristic, but not specific, features on CT images are cerebral swelling and small ventricles with or without infarction which may be hemorrhagic. The 'cord sign' is more specific and consists of a hyperdense line over one of the hemispheres, representing fresh thrombus in the superficial cerebral vein (3, 12). MRI is a sensitive procedure for the diagnosis of CVST, and may become the investigation of choice. The MRI findings are the absence of flow void on T1-weighted images and the appearance of the thrombosed vein as a hypointense cord on T2-weighted images. Secondary findings include cerebral edema, venous infarction, and enhancement of the dural sinus wall around the clot ('empty delta sign') (3, 12). Cerebral angiography was formerly considered to be the standard in the diagnosis of cerebral venous thrombosis, and may still be required in some cases (3, 10). However, MR imaging and MR venogram are now considered to be the preferred diagnostic evaluations because of their ability to directly visualize the thrombus and because of their noninvasive nature (4, 13).

Treatment of CVST in patients with SLE has included corticosteroid, immunosuppressant such as cyclophosphamide, and anticoagulant therapy (3, 5, 14). A prospective study comparing heparin and placebo suggested that patients treated with heparin had better neurologic outcomes than the control patients (14, 15). Long term treatment for CVST has not been standardized. However, many authorities favor long term anticoagulation therapy with warfarin to prevent thrombotic events (3). Rarely, local fibrinolytic therapy has been used in cases of deterioration despite the treatment (10, 15). Plasmapheresis appeared to be beneficial in refractory cases if given early in the course (11). The prognosis of treated SLE patients with CVST is usually favorable (1, 15). Early diagnosis and more intensive therapy may prevent assocated complication with CVST. We chose a combination of intensive immunosuppressants and heparin as an initial therapeutic regimen in both cases, which led to favorable outcomes.

In conclusion, CVST is rare when compared to other thrombotic events in SLE, and may have diverse manifestations from headache to severe neurologic deficits with or without antiphospholipid antibodies. Early suspicion and diagnosis are essential because delayed treatment may lead to a poor clinical outcome.

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