

Subarachnoid hemorrhage due to systemic lupus erythematosus associated with multiple intracranial artery aneurysms

Yun Zhang¹, Shu-Fen Liu², Xue-Jun Zeng¹

¹Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China;

²Department of Psychiatry, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China.

To the Editor: Systemic lupus erythematosus (SLE) is an autoimmune-mediated systemic inflammatory disease which involves nearly all organs of the body, and it is associated with premature atherosclerosis, vasculitis, and coagulopathy.^[1] Cases of subarachnoid hemorrhage (SAH) due to cerebral aneurysm associated with SLE are being reported more frequently. However, SAH due to SLE associated with multiple cerebral artery aneurysms that rapidly develop within only 2 months is rare, and the causal relations between cerebral aneurysm and SLE are not clearly understood. Herein, we reported a case of multiple cerebral artery aneurysms due to SLE, with enough evidence to confirm that the cerebral artery aneurysms were solely due to SLE.

A 21-year-old female was presented with a previous diagnosis of SLE, Raynaud's phenomenon, peripheral arthritis, erythema, proteinuria, and fever 1 year ago. Her symptoms disappeared after intravenous methylprednisolone pulse therapy (IMPT; 1000 mg/d for 3 days) followed by oral prednisone (60 mg/d; the dose of prednisone was gradually reduced as advised) and intravenous cyclophosphamide (400 mg/week for 16 weeks). Her lupus was stable, and the dosage of prednisone was tapered to 5 mg/d. One month before admission to the Peking Union Medical College Hospital, she suffered continuous headache after a travel. Three days later, she had a fever, with temperature between 37.5°C and 38.5°C, without chill, cough, and diarrhea. Cranial magnetic resonance imaging (MRI) revealed short T1 and long T2 signal of the left pons; magnetic resonance angiography (MRA) showed normal arteries (Figure 1). Lumbar puncture showed normal intracranial pressure (ICP), elevated white blood cell (WBC) of 94/μL, and elevated protein (PRO) of 3 g/L. Other laboratory results revealed slightly elevated erythrocyte sedimentation rate (ESR), C-reactive protein, and hypocomplementemia. The titers of anti-nuclear antibody

(1:1000) and anti-ds-DNA antibody (36.1 U/mL) were increased remarkably, whereas anti-cardiolipin antibodies (ACL), lupus anti-coagulants (LA), and anti-β2-glycoprotein-1 (anti-β2GPI) antibodies were all negative. The symptoms increased, including vertigo, tinnitus, vomiting, and numbness of the right extremities. The patient was then transferred to the Peking Union Medical College Hospital.

After admission, she was treated with IMPT (1000 mg/d, from day 3–7 and day 14–16, separately) followed by oral prednisone (60 mg/d) combined with intrathecal injection (methotrexate 10 mg + dexamethasone 10 mg/week for 3 weeks) and cyclophosphamide 600 mg/week; as secondary anti-phospholipid syndrome was highly suspected, she was also treated with anti-coagulant therapy (low molecular weight heparin for 10 days, and then warfarin). All the symptoms of the patient were very slowly relieved, except for low-grade fever.

However, on day 52 after admission, she suffered a sudden onset of severe headache, without nausea, vomiting, or weakness. Neurological examination was unremarkable except for slightly neck rigidity. Lumbar puncture was performed. The color of the cerebrospinal fluid (CSF) was pink, and the computed tomography (CT) revealed SAH of the bilateral frontal region without intracerebral hemorrhage (Figure 2a and 2b). She had no risk factors for SAH, such as hypertension, smoking, familial predisposition, or excessive alcohol consumption. Multiple saccular aneurysms were detected by computed tomography angiography (CTA) involving nearly all of the cerebral arteries including bilateral middle cerebral artery (MAC), bilateral anterior cerebral artery (ACA), bilateral posterior cerebral artery (PCA), and bilateral superior cerebellar artery (SCA) (Figure 2c–2f). The anti-coagulation therapy (warfarin 3 mg/d, international normalized ratio of 2.86) was stopped,

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Correspondence to: Dr. Xue-Jun Zeng, Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China
E-Mail: zxpumch@126.com

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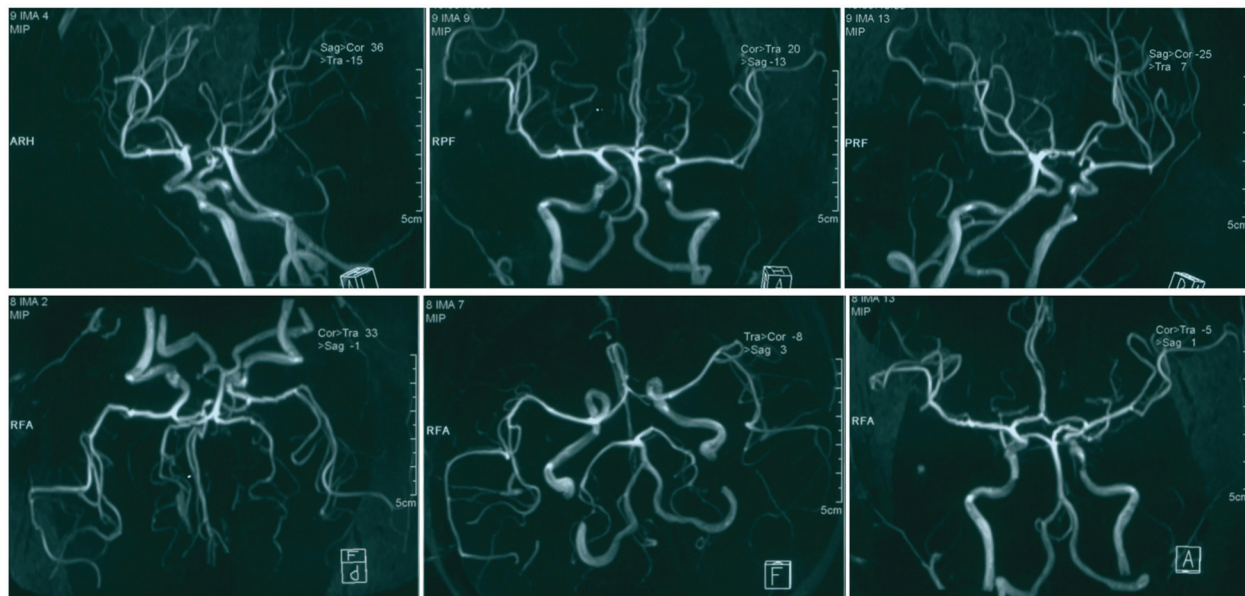


Figure 1: In a 21-year-old female with multiple cerebral artery aneurysms due to systemic lupus erythematosus, images of magnetic resonance angiography before admission were totally normal. No aneurysms, arteriovenous malformations, or dural arteriovenous-fistulas were observed.

and she was asked to stay on the bed for 3 weeks. Prednisone administration at 60 mg/d was continued during the treatment period for SAH. She did not suffer SAH again. The combined regimen led to the improvement of her symptoms and normalization of the laboratory data. The prednisone dosage was tapered, and she was going to be discharged.

Cerebral vascular disease is a common problem in patients with SLE, especially if they are diagnosed with the secondary anti-phospholipid syndrome.^[1] However, SAH due to aneurysm rupture is not common in SLE patients. In large-scale studies on SLE in North America and Europe, the incidence was approximately 0.1% in patients SLE younger than 50 years.^[2] Most of the cases reported previously were from Japan, and the reported incidences of SAH in Japanese patients with SLE were between 1.28% and 3.9%. These patients had different features from the general population, such as earlier onset, higher mortality, and aneurysms' location of posterior circulation.^[3,4] The patient of this case had something in common, including early-onset of disease and aneurysms' location. In recent years, more cases of SAH in patients with SLE were reported. A systemic review of SAH in SLE showed three main patterns of clinical features: distal fusiform aneurysms, multiple saccular aneurysms, and angiographically negative SAH (CTA/MRA/angiography or even surgical pathological specimen did not show any aneurysm).^[5] Some patients underwent aneurysmal clipping or wrapping, but the outcomes of these patients were poor because of the systemic complications of SLE, especially in those with multiple saccular aneurysms.^[5,6]

The mechanism of SAH in these patients remains unclear. Atherosclerosis and hypertension are considered as the

classical risk factors of SAH, which could result in aneurysm formation and rupture, especially in those patients who had used steroids (>10 mg/d) for a long time.^[7] Vasculitis could influence the incidence of SAH when lupus is not well controlled, because inflammation of arteries could narrow the lumen and lead to hemodynamic stress. Some scholars had even found transmural angiitis in fusiform aneurysms.^[8,9] Furthermore, angio-negative SAH was thought to be likely of venous origin, and these patients usually had a benign clinical course and did not rebleed.^[8,10] With respect to this patient, we assumed that the main mechanism of unusual aneurysmal formation in SLE was attributed to vascular inflammation affecting middle-sized arteries, causing local weakness in the walls of arteries. This patient had undergone an MRA scan which showed the cerebral arteries were totally normal before the onset of SAH. So we believed that these multiple saccular aneurysms were due to SLE, which might have combined with the fragility of blood vessels due to large amounts of steroids.

In conclusion, the pathophysiology of aneurysm formation in patients with SLE is unknown, and the origin of primary SAH in patients with lupus is also unknown. We reported a case of rapid growth of multiple aneurysms in a patient with SLE whose disease was highly active. This rare case showed us that patients using steroids for long could suffer from SAH, though with low risk of cerebral vascular disease. Clinicians should bear in mind that SAH due to aneurysm could happen in patients with SLE.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent form. In the form, the patient has given her

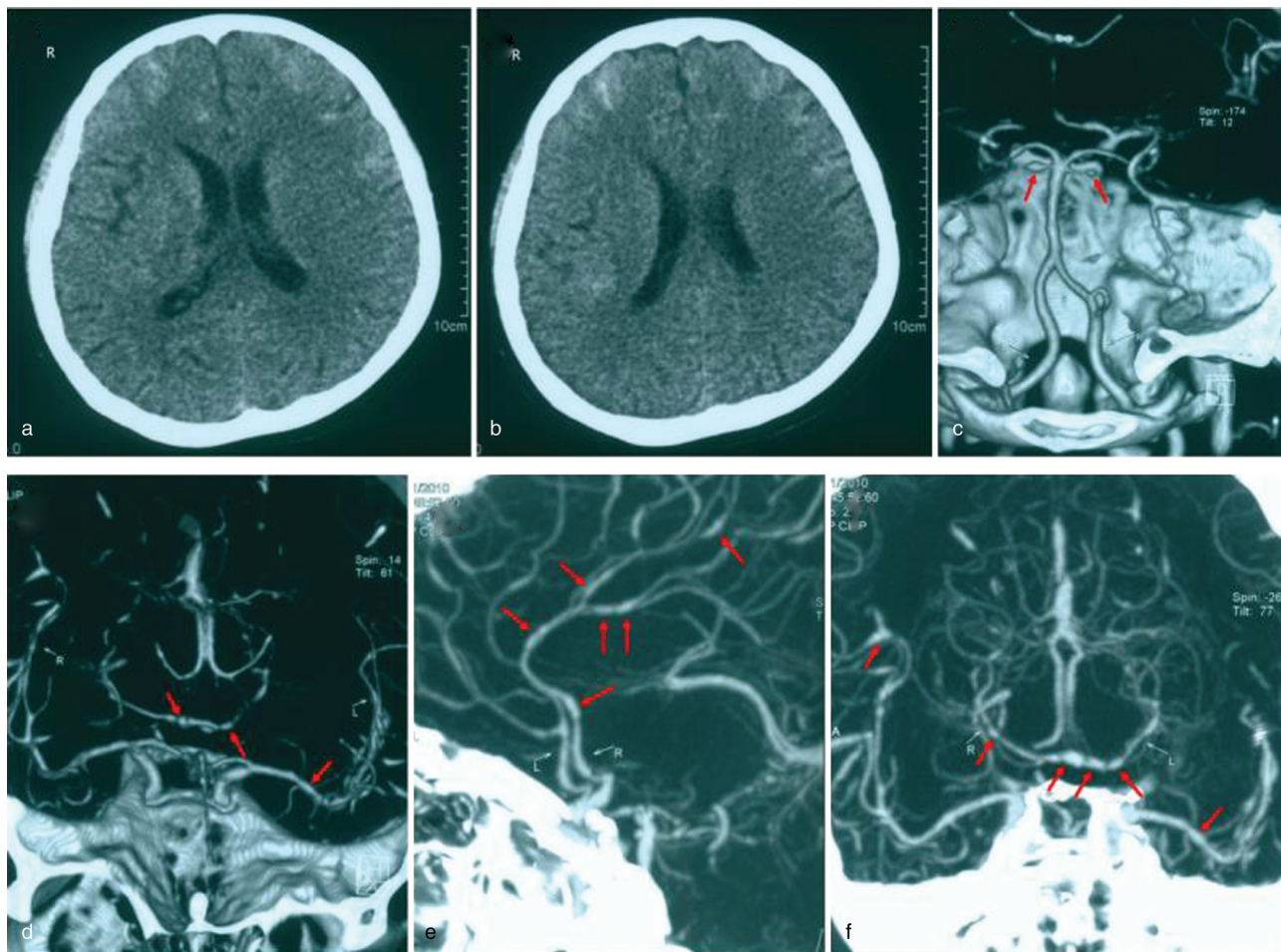


Figure 2: In a 21-year-old female with multiple cerebral artery aneurysms due to systemic lupus erythematosus, brain computed tomography showed a subarachnoid hemorrhage on both sides of the frontal region without intracerebral hemorrhage on day 52 after admission (a and b). Computed tomography angiography and 3-dimensional reconstruction showed multiple saccular aneurysms in nearly all of the cerebral arteries, including bilateral middle cerebral artery, bilateral anterior cerebral artery, bilateral posterior cerebral artery, and bilateral superior cerebellar artery (c–f). Aneurysms are marked with red arrows.

consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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