

CASE REPORT

Systemic lupus erythematosus associated with moyamoya syndrome: a case report and literature review

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Moyamoya syndrome (MMS) is a rare, chronic progressive cerebrovascular occlusive disease that is characterized by a stenosis or occlusion of the bilateral internal carotid arteries and the circle of Willis arteries leading to the development of collateral vessels as visualized by cerebral angiography. We report a case of a 24-year-old woman with nephrotic syndrome whose biopsy showed membranous nephropathy. Ten months after the diagnosis she suffered sudden right hemiplegia and seizure. She was diagnosed with MMS by angiogram seven months ago and received decompressive craniotomy. The patient was admitted to our hospital and a diagnosis of systemic lupus erythematosus (SLE) was made. Glucocorticoids and tacrolimus were used to control the symptoms of SLE. Following one month of immunosuppressant treatment, the patient died of brain hemorrhage. This case alongside another six reviewed cases shows that an underlying cerebrovascular lesion of moyamoya in the vessels of patients with SLE is susceptible to cerebrovascular accidents. *Lupus* (2013) **22**, 629–633.

Key words: Systemic lupus erythematosus; moyamoya syndrome; nephrotic syndrome; cerebral vascular hemorrhage; internal carotid artery occlusion

Introduction

Moyamoya disease is a rare, progressive cerebrovascular disorder that is characterized by bilateral supraclinoidal stenosis or occlusion of the internal carotid artery and the development of collateral vessels (moyamoya vessels) around the basal ganglion region. Moyamoya syndrome (MMS) is a term applied to moyamoya vessels associated with underlying disease conditions. This disease was first detected in Japanese patients, when Takeuchi and Shimizu reported the first angiographic finding of this disease in 1957.¹ It occurs mainly in Asian children or young adults.² Transient ischemic attacks or seizures are the usual presentation of moyamoya disease in children, whereas cerebral hemorrhage is the most common symptom in adults. Several reports have described an association between moyamoya disease and autoimmune diseases.^{3,4}

We report a patient with nephrotic syndrome with biopsy showing membranous nephropathy receiving non-regular treatment, who subsequently developed cerebral hemorrhage and was diagnosed with MMS syndrome seven months ago. The patient was admitted to our hospital and an underlying diagnosis of systemic lupus erythematosus (SLE) was made. We have also reviewed the existing literature and identified six additional cases and compared them to our case.

Method

We report a 24-year-old woman who suffered from MMS ten months after being diagnosed with nephrotic syndrome, confirmed by biopsy that revealed membranous nephropathy. She was admitted to the hospital with the diagnosis of SLE. We reviewed the English-language literature using the PubMed database from 1957 to July 2012 with the keywords “moyamoya disease,” “moyamoya syndrome,” “systemic lupus erythematosus” and “lupus.” We also enrolled pertinent articles obtained by searching references in the articles found in the primary search.

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Results

Case report

A 24-year-old woman was admitted to our hospital with a three-week history of vomiting and diarrhea. Seventeen months ago she was admitted to a local hospital because of pedal edema. The laboratory test results are shown in Table 1. Membranous nephropathy-associated nephrotic syndrome was the diagnosis (Figure 1). The patient received three months of prednisone and cyclosporine treatment. There was no obvious improvement with the

treatment; the patient lost confidence and resorted to Chinese herbal medicine and withdrew from immunosuppressive therapy. Seven months ago, she developed right hemiplegia and seizure. A neurological examination showed right hemiparesis with a power of 2/5 in the upper and lower extremities. Brain computed tomography (CT) showed acute hemorrhage in the left basal ganglia. Cerebral angiogram (Figure 2) showed an occlusion of the supraclinoid portion of both internal carotid arteries with rich basal collateral vessels (moyamoya vessels), which is a diagnostic criteria of moyamoya disease. The patient received decompressive craniotomy to relieve the pressure.

The physical examination at admission showed body temperature, pulse and blood pressure of 37.2°C, 104 beats/min and 118/77 mmHg, respectively. The laboratory test results are shown in Table 1. Based on the presence of positive antinuclear antibody (ANA) and a high-titer anti-double-stranded DNA (anti-dsDNA), pancytopenia, nephrotic range of proteinuria and decreased level of complement were suggestive of lupus nephritis.

The above findings proved that membranous nephropathy-associated nephrotic syndrome was caused by SLE 17 months earlier and that MMS was secondary to SLE. Following admission 40 mg methylprednisolone was administered intravenously daily for two weeks, which was followed by oral prednisolone 30 mg once a day combined with tacrolimus 1.0 mg twice a day. One month later, the patient's condition and the symptoms of SLE were well controlled (Table 1). One and a half months later, when the patient had a bowel movement, she suffered a seizure and CT confirmed hemorrhage in

Table 1 Clinical parameters at different time points

	<i>At first diagnosis</i>	<i>At admission</i>	<i>One month later</i>
WBC (cells/mm ³)	4000	2900	4300
Hemoglobin (g/dl)	11.8	5.5	10.2
Platelet count (cells/mm ³)	198,000	46,000	133,000
ESR (mm/h)	40	142	18
Serum albumin(g/dl)	2.1	11.5	21.1
Serum CR (umol/l)	65.2	135	117
Proteinuria	+++++	+++++	++
24-h urine protein (g)	6.54	5.67	1.89
Hematuria (cells/HP)	48	49	25
ANA	ND	1:320	1:80
Anti-dsDNA	ND	+	±
Anti-Sm	ND	Negative	Negative
C3 level (mg/dl)	ND	18.8	43.2
C4 level (mg/dl)	ND	5.1	14.1
LA	ND	Negative	ND
aCL	ND	Negative	ND

WBC: white blood cell; ESR: erythrocyte sedimentation rate; CR: creatinine; HP: high-power field; ANA: antinuclear antibody; Anti-dsDNA: anti-double-stranded DNA; LA: lupus anticoagulant; aCL: anticardiolipin antibodies; ND: no data.

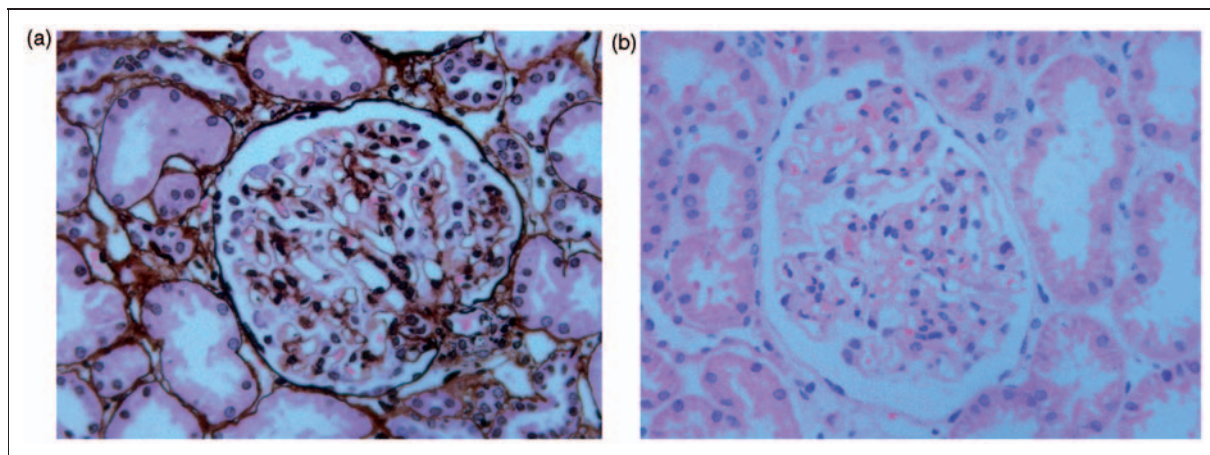


Figure 1 Renal pathological findings in light microscope. In this glomerulus, there are double contours of the glomerular basement membrane (a: PAS × 400; b: HE × 400). PAS: periodic acid-Schiff; HE: hematoxylin and eosin.

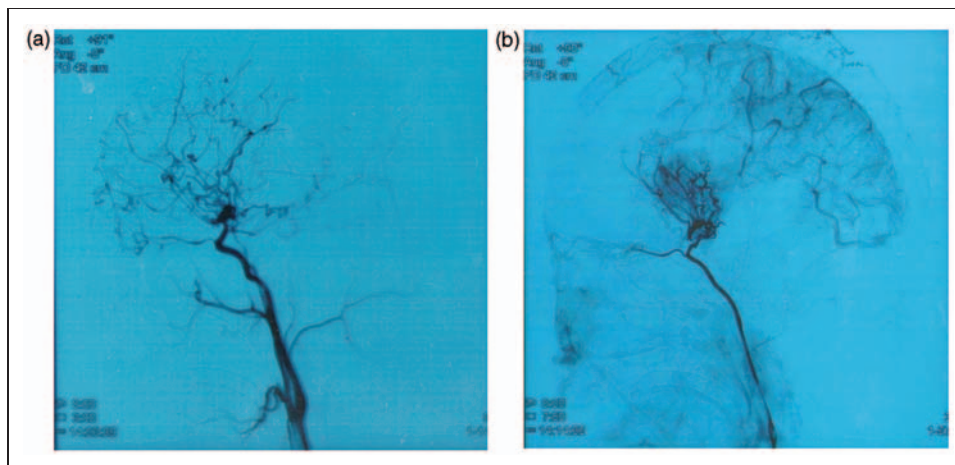


Figure 2 Conventional angiograms of both carotid arteries. (a) Left internal carotid arteriogram showing stenosis involving the supraclinoid portion of the right internal carotid artery with rich basal collateral vessels. (b) Right internal carotid arteriogram showing an occlusion of the supraclinoid portion of the left internal carotid artery with rich basal collateral vessels.

the genu corporis callosi into ventricles of the brain and died.

Literature review

We found six well-described cases in the English-language literature of MMS occurring in SLE patients and we describe one more in this review. Seven cases are detailed in Table 2.

All but one of the seven cases were female adults with the exception being a child. Although the patient in our case was diagnosed with SLE after the occurrence of MMS, from the clinical history we speculate that SLE was the underlying condition when the patient presented with nephrotic syndrome 17 months previously. In the other six cases with SLE the diagnosis was made before the appearance of MMS. The risk factors of MMS were not obvious but one case may have resulted from the cessation of immunosuppressive therapy for one month. Four cases developed MMS with signs of SLE, and all of them received immunosuppressive therapy. Of the other three cases without signs of SLE, two received only aspirin therapy, another received prednisone 60 mg/day and a 1 g pulse of cyclophosphamide therapy and because of recurrent neurological signs received encephaloduroarteriosynangiosis. Of the three patients, one had a previous history of recurrent right homonymous hemianopia without major organ involvement, as reported by Matsuki *et al.*³ A diagnosis of moyamoya disease was made 14 years ago and SLE was diagnosed one year ago. One case had a family history of moyamoya disease in a child, while the

other six cases had no family history. The clinical outcome of six cases were partially improved or well controlled. In our case SLE was partially improved when the patient was under immunosuppressive therapy. However, MMS re-occurred when the patient abandoned treatment.

Discussion

Moyamoya disease was first described in Japan by Takeuchi and Shimizu in 1957.¹ Moyamoya disease occurs predominantly but not exclusively in Japan; many subsequent cases have been reported elsewhere, including North America, Europe and China. The incidence is higher in East Asian countries such as Japan and Korea. The female-to-male ratio was 1.8, and 12.1% of patients had a family history of the disease. The crude prevalence was calculated as 6.03 per 100,000 people, and in 2003, the annual rate of newly diagnosed cases was 0.54 per 100,000 people. In China, the female-to-male ratio was 1.0 to 1.2, and 4.6%–5.2% of patients had a family history of the disease.^{10,11}

The precise mechanism for MMS secondary to autoimmune diseases is unclear. However, in MMS that is positive for ANA, anti-dsDNA has been reported, which suggests that immunological factors might play a role in the pathogenesis of MMS.^{2,5} Fries *et al.* showed that 15% of patients with moyamoya disease had ANA, compared with 0% in controls.¹² Moyamoya patients also often exhibited elevated (23%) anti-dsDNA compared with normal controls (0.3%).¹³ Deposition of

Table 2 Summary of characteristics of seven SLE patients with moyamoya syndrome (MS)

First author and year	Age/sex	SLE diagnosed time	MS history	Past medical history	Risk for MS	SLE activity	Kidney involvement	Neurological signs and symptoms at presentation	Therapy	Prognosis
Matsuki (1997) ³	30/F	12 Months ago	14 Years ago	ND	No	No	ND	Hemianopsia	Aspirin	MS well controlled
Preliepan (1998) ⁵	24/F	Six years ago	Five years ago	Aspirin	No	Yes	Yes	Disoriented, incontinent	Steroid + aspirin	SLE remission
ElRamahi (2000) ⁶	18/M	12 Months ago	No	Steroid + plaquenil	No	No	No	Right side weakness and dysarthria mild right hemiparesis	Steroid + CYC + encephalo arteriosynangiosis	Did not occur during nine-month follow-up
Lee (2003) ⁷	13/F	11 Months ago	Mother had MS	ND	No	No	No	Severe headaches	Aspirin	Mild headaches during two-year follow-up
Jeong (2008) ⁸	18/F	14 Months ago	No	Steroid + MMF	Medication cessation	Yes	Yes	Motor weakness in left arm and leg	Steroid + aspirin	SLE well controlled; MS did not occur
Mok (2011) ⁹	20/F	Ten years ago	No	Steroid + CYC	No	Yes	Yes	Sudden right hemiplegia	Steroid + CYC induce steroid + AZA maintenance	SLE controlled; MS partially improved
Present case	24/F	No	No	CSA + steroid for three months, Chinese herb	No	Yes	Yes	Seizure	Steroid + tacrolimus	SLE partially improved; MS re-occurred and abandoned treatment

SLE: systemic lupus erythematosus; F: female; M: male; ND: no data; MMF: mycophenolate mofetil; CYC: cyclophosphamide; CSA: cyclosporine A; AZA: azathioprine.

immunoglobulins in the intima of the internal carotid arteries has been found in some cases.³ Sub-endothelial infiltration of T cells has also been found by immunohistochemical means in the circle of Willis arteries from five of six autopsied patients. Lin *et al.* found that immune-related factors may be involved in the functional and morphological changes of smooth muscle cells that led to the formation of a thickened intima.¹⁰ The endothelial cell interaction with these antibodies has been proposed as a probable mechanism that predisposes to thrombosis.⁴ From the review of Table 1, we found that MMS occurred later than SLE, and controlling the symptoms of SLE was important. Cessation of immunosuppressive therapy may lead to the appearance of MMS. In our case, the underlying cerebrovascular lesion such as moyamoya vessels, together with the contributing signs of lupus, led to the hemorrhage.

Symptoms of MMS include psychosis, mood disorders, seizures, acute confusion, stroke, as well as subtle cognitive impairment, which are more common and often the presenting symptoms of SLE, rather than severe complications of the central nervous system (CNS). This often leads to a delayed diagnosis. Different CNS conditions occurring in SLE may have the same clinical manifestation, but have different treatments and different prognoses. MMS should be differentiated from other conditions such as posterior reversible encephalopathy syndrome, neuropsychiatric systemic lupus erythematosus and central infection disease, such as progressive multifocal leukoencephalopathy, which accompany SLE.

The presentation of moyamoya disease differs substantially between children and adults. In Japan, children typically present with symptoms attributed to slowly progressive cerebral hypoperfusion and repetitive ischemic symptoms, whereas adults have hemorrhagic events. However, in children with MMS and a hypercoagulable state, whether or not surgery has been performed, prophylaxis and treatment with antithrombotic agents have been recommended.¹⁴ Another study revealed that anticoagulant and antiplatelet agents have shown no remarkable benefit.¹⁵ Only a controlled clinical trial of these pediatric patients could establish whether these therapies can reduce the frequency of thrombotic events and ameliorate the cognitive dysfunction. However, for adults, cerebral hemorrhage is the most common symptom, and from the review of literature, we found in adult patients, especially with immune activity, prophylaxis and treatment with antithrombotic agents should be carried out with caution.

Immunosuppressive agents may be of benefit for the treatment of immune activity, as evidenced in our case and in three other cases in the literature review. But it is still unclear whether immunosuppressant agents are of benefit for moyamoya disease.¹⁵ Maintenance stability of stable blood pressure is important in treating moyamoya disease because of frangible moyamoya vessels, and hemodynamic instability may be fatal to the patient, as seen in our case. Surgical treatment modalities have been used to manage the hemorrhagic and ischemic consequences of moyamoya disease. Ventricular drainage and hematoma evacuation are often used for hemorrhagic cases. In ischemic moyamoya disease, surgical methods have been used to restore and maintain adequate cerebral perfusion.

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Conflict of interest

None declared.

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