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Intrauterine Fetal Demise Followed by CVT in a Woman with SLE and Secondary APS

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We recently encountered a rare case of systemic lupus erythematosus (SLE) with secondary antiphospholipid syndrome (APS) presenting with cerebral venous thrombosis (CVT). A 24-year-old woman with a history of recent fetal loss experienced an intractable headache, followed by right hemiparesis and hypoesthesia over her limbs with the exception of her left lower extremity. Head CT and MRI with magnetic resonance venography (MRV) demonstrated CVT. Early diagnosis and aggressive therapy of CVT are of prime importance for achieving a favorable outcome. We present this rare case to emphasize that CVT is often multifactorial. Further investigations and the clinical symptoms of the patient proved the diagnosis of SLE with secondary APS.

Key words: systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), cerebral venous thrombosis (CVT), magnetic resonance venography (MRV)

INTRODUCTION

Cerebral venous thrombosis (CVT), an infrequent stroke type responsible for less than 1% of all strokes in adults, is often described as having an unpredictable outcome[1-2]. Diverse conditions can cause or predispose to CVT. Although pregnancy and peurperium may cause CVT in young women, it is crucial to regard it as a risk factor rather than a cause because it is commonly found together with other conditions, such as systemic lupus erythematosus (SLE) with secondary antiphospholipid syndrome (APS), Behçet's disease, and congenital thrombophilia. CVT is an uncommon cerebrovascular complication in SLE with secondary APS[3]. The diagnostic criteria of APS include the presence of both (1) thrombosis or recurrent, unexplained fetal loss and (2) anticardiolipin antibodies (IgG or IgM isotype) of medium to high titers or lupus anticoagulants on at least two occasions at least eight weeks apart[4]. APS can occur in association with other autoimmune disease (secondary APS), most frequently SLE, or as an isolated disorder (primary APS)[5]. In this article, we report a case of intrauterine fetal demise (IUFD) followed by CVT in a patient with SLE complicated by APS. CVT is often multifactorial and identification of a risk factor or even of a cause of CVT should not deter a search for other causes because delayed treatment may lead to a poor clinical outcome.

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CASE REPORT

A 24-year-old woman with a history of IUFD diagnosed at 32 weeks gestational age developed a headache about two days after the termination of the pregnancy. The headache was mostly diffuse, progressive, and permanent: it was not fully relieved by analgesics and was so severe that it woke her from sleep. She was taken to the hospital about two weeks after the termination of the pregnancy because she complained of worsening headache, double vision and a sudden onset of numbness and weakness of her right limbs.

On physical examination, temperature was 37.5°C, pulse was 80, and respiration rate was 20. The blood pressure was 120/70 mm Hg. The neurological examination showed a normal mental status and mild dysarthria. The cranial nerve examination revealed bilateral papilledema and right

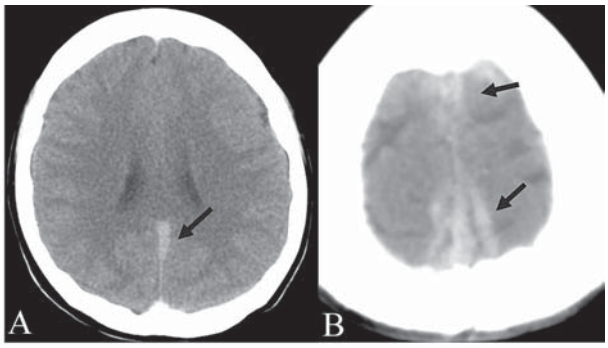

Fig. 1 Unenhanced cranial CT scans disclosed cerebral venous thrombosis. (A) Abnormal high density was noted in part of the straight sinus (arrow). (B) The cord sign was demonstrated in the superior sagittal sinus and some cortical veins (arrow).

facial palsy of a central type. In addition, she was unable to abduct her right eye and had diplopia. Sensation was intact except for the extinction of pinprick sensation in the right limbs on simultaneous bilateral stimulation. Motor strength was Medical Research Council grade 2/5 in the muscles of the right upper limb, 3/5 in the muscles of the right lower limb and 5/5 in the muscles of the left limbs. The plantar response was extensor on the right.

Noncontrast head CT revealed abnormal high density in part of the straight sinus, the superior sagittal sinus, and some cortical veins (Fig. 1). This phenomenon is indicative of the "cord sign", demonstrating CVT. Cerebral MRI with magnetic resonance venography (MRV) disclosed a lack of filling of the left transverse sinus (Fig. 2A). A filling defect of the thrombosed superior sagittal sinus (SSS) (Fig. 2B) was seen as the "empty delta sign". MRV demonstrated inadequate or totally absent flow signals in the SSS, and downstream in the sinus confluence and bilateral transverse/sigmoid sinuses (Fig. 2C, 2D). The patient was started on subcutaneous low-molecular-weight heparin (Nadroparin calcium 3800 IU) every 12 hours for one week).

Laboratory tests were performed. The complete blood count was normal except the platelet count was 142,000 per cubic millimeter (normal range, 150,000 to 400,000 per cubic millimeter). The prothrombin time was 12.7 seconds (control, 11.2 seconds); the partial thromboplastin time was 25 seconds (control, 30 seconds); international normalized ratio (INR) was 1.26. The concentrations of creatine kinase, aspartate amino-transferase, alanine aminotransferase, urea nitrogen, creatinine, glucose, uric acid, phosphorus and total protein were normal. The urine was positive for protein (+) and occult blood (+++); the

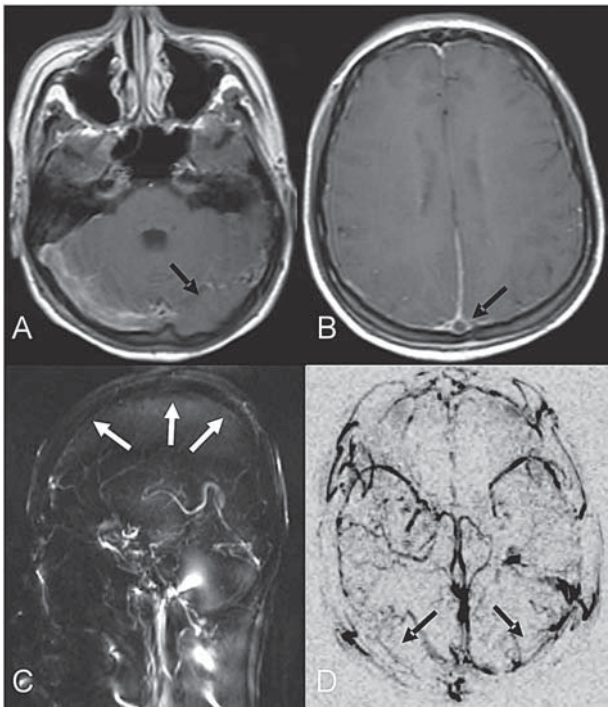

Fig. 2 (A) Gadolinium-enhanced T1-weighted MRI revealed a lack of filling of the left transverse sinus (arrow). (B) A filling defect of the thrombosed SSS (arrow) gives the "empty delta sign". (C) and (D) MR venography demonstrated an inadequate or totally absent flow signal in the superior sagittal sinus (white arrow), and downstream in the sinus confluence and bilateral transverse/sigmoid sinuses (black arrow).

sediment contained 40-50 red cells, 1-3 white cells, no casts per low-power field and no bacteria per high-power field.

Young stroke studies were further surveyed. She was found to have a diagnosis of SLE based on (1) photosensitivity; (2) bilateral arthritis of the knee joints; (3) antinuclear antibodies, with a high ANA titer of 1 in 640, with a homogeneous pattern; and (4) immunologic disorder, with an anti-dsDNA concentration of 191 IU per milliliter (normal range, 0-30 IU/ml). Furthermore, she met the diagnostic criteria of secondary APS, including the presence of SLE, CVT, unexplained fetal loss, and the presence of lupus anticoagulants on at least two occasions at least 8 weeks apart[4-5]. Tests for lupus anticoagulants were positive at titers of 1.5 (normal range, 0-1.2) on the second hospital day and 1.27 about half a year later. Tests for anticardiolipin antibodies, anti-Ro antibodies, anti-La antibodies, anti-Sm antibodies, anti-RNP antibodies and VDRL were all negative. The concentration of complement component 3

was 75.8 mg per deciliter (normal range, 79-152 mg/dl) and the concentration of complement component 4 was 11.5 mg per deciliter (normal range, 16-38 mg/dl). Intravenous methylprednisolone pulse therapy (1.0 g/day for three consecutive days) was commenced in combination with hydroxychloroquine (200 mg/day). Anticoagulation was changed from low-molecular-weight heparin (LMWH) to oral warfarin (2.5 mg/day). The INR was adjusted to between 2 and 3 (therapeutic range). There was a marked improvement of neurological symptoms with the disappearance of thrombus in a follow-up MRI on the fifteenth hospital day. Veins and sinuses detectable by means of Doppler duplex sonography from transtemporal, transnuchal, and transorbital approaches were within normal flow velocities. Her headache and motor strength gradually improved about one week after admission. By the time of discharge from hospital (on the seventeenth hospital day), her motor strength improved to 4/5 in the left extremities. At outpatient follow-up two months after discharge, she remained well, without recurrence of headache or neurological deficit.

DISCUSSION

The diagnosis of CVT may be very difficult due to its large spectrum of clinical manifestations and the multiple associated conditions and etiologies[3]. The symptoms and clinical course of CVT vary from headache (most common), intracranial hypertension without focal signs, altered mental status, seizures, focal neurologic deficits, and even death[6]. We present a patient with CVT as the initial manifestation of SLE with secondary APS after IUFD. The patient initially encountered a severe persistent headache, which was not responsive to analgesics and then rapidly developed neurological signs. Therefore, we emphasize that CVT should be considered in any patient with persistent headache that is unresponsive to analgesics, with or without neurologic signs, especially in women with IUFD. This rare case was diagnosed as CVT by the finding of the "cord sign" on unenhanced brain CT. The "cord sign", presenting in up to 24.5% of cases, consists of a hyperdense line over one of the hemispheres on unenhanced CT, representing fresh thrombus in the superficial cerebral vein, and is more specific than other signs[7]. The most sensitive examination technique for CVT is MRI in combination with MRV[8]. T1-weighted and T2-weighted MRI will also show a hyperdense signal from the thrombosed sinuses.

APS, also known as Hughes syndrome, was first used to denote the clinical association between antiphospholipid antibodies (aPLs) and a syndrome of hypercoagulability[9]. The most commonly detected subgroups of antiphospholipid antibodies are lupus anticoagulant antibodies, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies. APS can occur in association with other autoimmune disease (secondary APS), most frequently SLE, or as an isolated disorder (primary APS)[5]. APS is found in about 40% of patients with SLE with central nervous system involvement and correlates strongly with the formation of thrombus[10]. Thrombosis is a major risk factor in patients with SLE with secondary APS. Thrombosis may affect the mother, both in the venous and arterial beds, and have a role in pregnancy loss[11]. However, it is rare that CVT is the initial manifestation of SLE with secondary APS after IUFD. The prevalences of CVT and fetal loss were 0.7% and 8.3% respectively in APS patients[12]. In this case, the underlying cause of the IUFD followed by CVT was SLE with secondary APS. Thrombosis, the main complication of APS, can affect any size vessel and the consistent histopathological lesion is a bland thrombus without inflammation[13]. A broad spectrum of clinical features that includes peripheral venous and arterial thrombosis, obstetric manifestations and pregnancy morbidity, skin disease, cardiac and pulmonary manifestations, renal involvement, hematological manifestations, and neurological disorders can be seen in patients with APS[12]. The importance of cerebral disease in patients with APS is now becoming a new chapter in neurology[14]. Neurological involvement in APS includes cerebral ischemia (arterial and venous), headache, dementia, cognitive dysfunction, psychosis, depression, transverse myelitis, multiple sclerosis-like disease, chorea, and seizures[14]. The mechanisms of the cerebral involvement in APS are not completely understood, although animal models are providing important insights into some of the underlying mechanisms for CNS dysfunction[15-17]. Interestingly, although the mechanism of neurological involvement in APS is considered primarily thrombotic[18], there is an increasing body of evidence that supports the hypothesis that aPLs may also have more direct pathogenic effects[19]. It has been shown that aPLs bind neurons, glial cells, and myelin and disrupt their function. aPLs may also interfere with endothelial cells and promote their procoagulant activity[14].

Treatment of CVT in patients with SLE with secondary APS has included corticosteroid, immunosuppressant and anticoagulant therapies[2,3,20]. Long-term treatment for CVT has not been standardized; however, many authorities favor long-term anticoagulation therapy with warfarin to prevent thrombotic events, especially in those at risk of further thrombotic episodes such as with SLE with second-

ary APS[11]. The prognosis of treated SLE and secondary APS patients with CVT is usually favorable if treatment is started as early as possible. Early diagnosis and therapy that is more intensive may prevent associated complications. We chose a combination of anticoagulant (LMWH followed by oral warfarin), corticosteroid, and hydroxychloroquine as a therapeutic regimen that led to a favorable outcome.

In conclusion, we emphasize that headache should not be ignored in young women during pregnancy or after fetal loss. It is rare that CVT is the initial manifestation of SLE with secondary APS after IUFD. However, because CVT is often multifactorial, identification of other recognized causes or predisposing conditions, such as the SLE with secondary APS in our patient, should progress without delay. Early suspicion and diagnosis are essential because delayed treatment may lead to a poor clinical outcome.

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