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Cerebral Sinus Venous Thrombosis in Systemic Lupus Erythematosus

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ABSTRACT

Introduction: Cerebral sinus venous thrombosis (CSVT) is a major cause of stroke in young patients. The incidence of CSVT ranging from 1-12 cases per 1 million adults per year. Autoimmune diseases such as Systemic Lupus Erythematosus (SLE) can cause CSVT. The incidence of CSVT involvement in SLE is 1%. It is characterized by thrombosis in the sinuses and veins, which causes various symptoms, such as headache, seizures, motor weakness, and decreased consciousness. **Cases:** We report a case of a 20-year-old woman with SLE who complained of seizures accompanied by weakness on both sides of the body and a history of headaches. There is an increase in D-dimer, with positive ANA and anti-ds-DNA tests. A non-contrast CT scan of the head showed a lobar venous infarct with hyperdense lesions, a head non-contrast MRI/MRV revealed a dural sinus thrombosis with a deep cortical/subcortical venous infarct, no bleeding was seen. Patients were given Fondaparinux sodium therapy for 5 days, followed by Warfarin sodium for 3-12 months with a target INR of 2.0-3.0, and control SLE by administering immunosuppressants gave better outcomes for patients. **Conclusion:** The diagnosis of CSVT in this patient was based on clinical suspicion and imaging confirmation, and elevation of D-dimer. Non-contrast CT of the head as an initial examination often shows normal imaging. Still, there is also an image of a hyperdense lesion that usually causes an incorrect diagnosis, resulting in delays in therapy. Anticoagulation in CSVT should still be given even if there is bleeding.

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INTRODUCTION

Cerebral sinus venous thrombosis is an uncommon form of stroke, usually affecting young people. Although the introduction of CSVT has progressed in recent years, diagnosis and treatment are still tricky because of the diversity of underlying risk factors, non-specific symptoms, and lack of uniformity in treatment.^{1,2,3}

Cerebral sinus venous thrombosis is estimated to occur in 1-12 people per 1 million population per year. Approximately 3-8% of the patients with CSVT have thrombosis of the deep cerebral veins or profunda cerebral veins in the basal vein (vein of Rosenthal), internal cerebral vein (internal vein), and the great vein of Galen, caused by thrombosis in that area.^{1,3,4}

Cerebral sinus venous thrombosis has certain risk factors such as gender, pregnancy, postpartum period, and infectious diseases. Other risk factors include oral contraceptives, genetic and acquired prothrombotic states, malignancies, autoimmune and inflammatory disease.^{5,6}

Cerebral sinus venous thrombosis is a rare complication of SLE. In such patients, the thrombotic risk is strongly associated with the presence of antiphospholipid antibodies (aPL) and lupus anticoagulant (LA). Because SLE is rarely cited as a risk factor for CSVT, little is known about its frequency as to the underlying etiology, clinical characteristics, response to treatment, or long-term outcome.^{5,7,8}

CASE

A 20-year-old, unmarried woman was admitted one week earlier in Internal Medicine with severe SLE with hematologic manifestations, lupus nephritis, and mucocutaneous symptoms. She was consulted to the neurology department because of tonic-clonic seizure, frequency one time, duration less than 5 minutes; prior seizure, the patient was alert, but the patient was conscious during the seizure. Then there is weakness on both sides of the body and numbness/tingling in socks and gloves. The patient previously had a history of headaches, especially on the right side of the head. The characteristics of headache were throbbing, mild to moderate intensity. Severe headache since \pm 3 days ago. There was no history of hypertension and history of diabetes mellitus or infection.

On physical examination, the patient was conscious, quadriparous with strength in both arms 4 and legs 3, increased muscle tone and physiological reflexes, negative pathological reflexes, and socks and gloves type hypesthesia. Blood examination showed increased levels of D-dimer (7.84 mg/L), ANA test (1/3200), Anti ds-DNA (1632.67 IU/ml), and a

positive Coombs test.

A non-contrast head CT scan showed a lobar venous infarct with hyperdense lesions, suggesting subarachnoid hemorrhage. On head non-contrast MRI/MRV, the result showed dural sinus thrombosis with deep cortical/subcortical venous infarct; no bleeding was seen. The results of electroencephalography obtained background abnormalities.

The patient was given Fondaparinux sodium 2.5 mg once daily subcutaneously for five days, followed by oral anticoagulant Warfarin sodium 2 mg once daily for 3-12 months (guideline of anticoagulant, target INR 2.0-3.0), to control the seizures given Phenytoin 100 mg three times daily, and controlling SLE by administering Mycophenolate Mofetil 500 mg twice daily, Hydroxychloroquine 200 mg once daily, Cyclosporin 25 mg once daily, Atorvastatin 20 mg once daily.

DISCUSSION

In this case report, we discuss a 20-year-old woman with SLE who was treated in the neurology department of RSMH who had a seizure. Seizures began with headaches that got worse and were followed by weakness of both arms and legs after the seizure. The first thing to think about in this patient is an acute intracranial condition from the anamnesis. A chronic condition should be suspected regarding prior recurrent headaches, especially in the progressive form of headache. However, the headache felt by the patient is diffuse and progressive, so vascular causes. The seizures may be due to processes in the cortical/subcortical.

On physical examination, there was central spastic weakness. The history and physical examination, results lead to an acute intracranial process that vascular abnormalities cause. Follow-up examinations are then carried out and looking for other risk factors. There is an increase in D-dimer with ANA and anti-double standardised DNA (+) tests. Diagnostic investigations included a non-contrast CT scan of the head with the impression of a lobar vein infarct accompanied by hyperdense lesions, suspicious of subarachnoid hemorrhage (Figure 1). However, there were no signs of meningeal stimulation on physical examination, and a picture of infarction appeared in the lobar vein. Therefore, a follow-up CT venography was planned because patients with SLE were afraid of being allergic to contrast. An MRI/MRV without contrast was performed to confirm the diagnosis of an infarct in the vein and rule out cerebral hemorrhage.

From the non-contrast head MRI, the lesion was mild hypointense/isointense on T1 against gray-white matter (Figure 2a) to hyperintense/mild hyperintense/isointense on T2 (Figure 2b),

hyperintense on FLAIR (Figure 3a) in the deep cortical/subcortical frontoparietal lobe bilateral and right temporal, the DWI does not show a restricted water restricted area (Figure 3b).

Magnetic resonance venography results showed decreased flow with constriction of the superior sagittal sinus, superficial cerebral vein, deep cerebral vein, internal cerebral vein, a great cerebral vein of Galen, straight sinus, cavernous sinus, sinus confluence, sinus transversus, sigmoid sinus, jugular bulb. The superior sagittal sinus shows multiple filling defects with abnormal intensity (Figure 4).

Cerebral sinus venous thrombosis is a rare SLE disorder, an overlapping manifestation of neuropsychiatric lupus (NPSLE) and vascular disease.^{9,10} Enforcement of NPSLE in SLE patients can use the Bortoluzzi algorithm.^{9,11} In this patient, clinical symptoms of neurology appeared > 6 months after diagnosis of SLE, so it can be concluded that symptoms appear concomitant (2 points). However, in this patient, there were no Ainala criteria. Ainala's criteria consist of: (1) isolated headache (2) anxiety (3) mild depression (mood disturbance but does not meet the criteria for a major episode resembling depression) (4) presence of mild cognitive impairment (3 of 8 cognitive domain disorders) (5) presence of polyneuropathy not confirmed by electrophysiology.

There were symptoms of polyneuropathy in this patient, but the TCNS score of 3 (no neuropathy). Therefore, Ainala's criteria are met in this case (0 points). The patient was found to have confounding factors, namely CVD (dyslipidemia, hypercoagulability), seizures (stroke) (0 points), and the favorite factors are headache (no familiar history, abnormal neuroimaging) then (2 points). In addition, to establish the diagnosis of NPSLE, it is crucial to determine SLE activity, and the MEX-SLEDAI criteria can be used.^{9,12} Based on the MEX-SLEDAI criteria, this patient scored 19 points. According to the MEX-SLEDAI criteria, patients with a score of < 2 had mild SLE disease activity. Then, patients with a score of 2-5 had moderate SLE disease activity. Meanwhile, patients with a score > 5 had severe SLE disease activity. So this patient has severe SLE activity, and the total of all points based on this Bortoluzzi algorithm is 4 points. Therefore, the diagnosis of NPSLE has not been established.

Cases of CSVT in SLE patients are very rare. Several mechanisms play a role in the development of CSVT in SLE. The complex interaction between endothelial cells and LA will trigger the inhibition of proteins C and S responsible for the occurrence of thrombosis. Autoantibodies attack the negatively charged surface of phospholipids, thereby triggering platelet activation to form a thrombus. Impaired fibrinolysis, antithrombin III, hyperfibrinogenemia, or

changes in coagulation may also lead to thrombosis.^{12,13}

The endothelial injury also plays a role as a cause of immune complex induced vasculitis, which eventually leads to CSVT. Inflammation can reduce fibrinolytic activity through upregulation of plasminogen activator inhibitor (PAI) formation.¹³ Headache, seizures, and motor deficits in patients are the most common symptoms of CSVT, which indicate an increase in intracranial pressure. Clinical manifestations also depend on the location of the thrombosis. The superior sagittal sinus is the most involved location, which can cause headaches, increased intracranial pressure, and papilledema. Motor deficits that are sometimes accompanied by seizures may also occur. Cortical involvement may cause contralateral motor weakness. The picture of infarction on MRI/MRV of the patient is due to thrombosis in the deep cerebral venous system (internal cerebral vein, Galen's vein, straight sinus).^{1,14}

Thrombosis in the dural vein causes clinical manifestations such as seizures, headache, loss of consciousness, and others. Thrombosis in the dural vein can cause blood formation in the sinus venosus of the brain that prevents blood from flowing to the brain. Several clinical features can differentiate CSVT from other cerebrovascular diseases. Focal seizures or generalized seizures are common in CSVT patients (40%).^{1,5} Several other clinical features related to the anatomic location of cerebral venous drainage occur due to bilateral brain involvement but are very rare.^{1,3} The use of antiepileptic drugs (given antiepileptic drug Phenytoin 100 mg three times daily and an EEG has been done) in acute CSVT patients with supratentorial lesions and seizures can prevent recurrent seizures, so the patient is considered an acute symptomatic seizure.

D-dimer is a product of fibrin degradation. Elevated levels of D-dimer represent the level of activation of the fibrinolytic and coagulation systems. Anatomical extension of sinus thrombosis may be related to D-dimer levels. However, normal D-dimer levels can also be found in patients with CSVT. D-dimer levels can decrease at the onset of the attack, and this shows that in acute and chronic conditions, they tend to have negative D-dimer levels.^{1,5}

Antiphospholipid syndrome (APS), also known as Hughes syndrome, is a pathological autoimmune condition in which the accumulation of blood clots by antiphospholipid antibodies occurs. This disease is a disorder of thrombosis, recurrent abortion, or both accompanied by persistently elevated antiphospholipid antibodies, such as anticardiolipin antibodies (ACA) or LA. This APS event will worsen the outcome of SLE.^{1,13}

Radiologic features often found in CSVT are bleeding (84.3%) and non-bleeding (15.7%). Computed tomography without contrast often shows a normal

picture, but there is also a picture of CSVT. Variations in the anatomic features of the sinus venosus make the role of CT in diagnosing CSVT less sensitive. Abnormal non-contrast head CT scans are found in only 30% of patients. The primary sign of acute CSVT on a non-contrast head CT scan is a hyperdense lesion filling the dural vein or sinus (1/3 cases). Thrombosis in the posterior part of the superior sagittal sinus may occur.^{1,14,15}

In the patient, the results of a non-contrast head CT scan were in the form of a hyperdense picture similar to bleeding, but the MRI/MRV did not show bleeding (indicating deep vein thrombosis). Computed tomography and MRI help evaluate patients with CSVT. However, the diagnosis of CSVT also cannot be ruled out even though the image is not found on MRI and CT scans. Magnetic resonance venography or computed tomography venography (MRV/CTV) may be performed if the CT/MRI image does not support the direction of CSVT. Computed tomography venography is preferable for subacute or chronic onset because of the varying density of sinus thrombosis. Cerebral vein images can be seen from MRV, while sinus images are better seen through DSA. The MRI/MRV image in the acute phase (0-5 days) is isointense on T1, hypointense on T2 due to an increase in deoxyhemoglobin in the blood cells in the thrombus. In the subacute phase (6-15 days), T1 and T2 are hyperintense due to methemoglobin in the thrombus. In the chronic phase (>15 days), isointense at T1, isointense/hyperintense at T2.^{1,15}

The medical therapy used in this patient was Fondaparinux sodium 2.5 mg once daily subcutaneously administered for 5 days. Fondaparinux sodium is an LMWH (Low Molecular Weight Heparin) group that tends to be safe to give to patients with a low risk of heparin-induced thrombocytopenia and osteoporosis. Then, oral anticoagulant therapy for 12 months because unprovoked CSVT with a target INR of 2.0 to 3.0.^{1,5} Warfarin sodium is given after the use of fondaparinux sodium. Warfarin sodium administration should be continued for 3-12 months while maintaining an INR of 2.0 to 3.0 to prevent recurrent CSVT and other venous thromboembolic events.^{1,3} For the control and therapy, gave Cyclosporin 25 mg once daily, Mycophenolate mofetil 500 mg twice daily, and Hydroxychloroquine 200 mg once daily, which was continued after inpatient treatment with Warfarin sodium 2 mg once daily.

The prognosis for this patient is low risk of poor outcome. There was an improvement in the National Institutes of Health Stroke Scale (NIHSS) score (10→2), Modified Rankin Scale (mRS) (4→1) when discharged from the hospital, and an improvement in motor strength from the beginning of admission (3→4+), as well as a decrease in value of D-dimer

(2.86 mg/L). Outcome improvement may be due to the patient's young age, female gender, no loss of consciousness/severe neurological deficit, and other risk factors (cancer, CNS infection, hereditary thrombophilia). Several factors associated with a poor prognosis are based on demographics (age >37 years, male gender), clinical symptoms (coma, neurological deficit, poor NIHSS score, decreased consciousness, hemiparesis, seizures), neuroimaging (intracerebral hemorrhage, involvement of the brain), straight sinus, deep venous sinus thrombosis, venous infarction), and risk factors (cancer, CNS infection, hereditary coagulopathy).^{1,3,5}

Complete recovery was found in 79% of patients. In a prospective study, it was found that the mortality rate was around 9.4%. Mortality in CSVT with SLE is 30-50%. However, neuroimaging and LMWH can be reduced the mortality rate to 11.8%. Complete or partial improvement was observed in survivors (76.5%), no relapse or poor outcome with permanent neurologic deficits during the 3-year follow-up.^{1,3,5}

CONCLUSION

Cerebral sinus venous thrombosis is characterized by thrombosis in either the sinus, dural or superficial veins which can cause various symptoms, including headache, seizures, motor weakness, and loss of consciousness. The thrombosis in this patient suggests a pre-established systemic or autoimmune disorder. Cerebral sinus venous thrombosis in SLE may be caused by various factors, including vasculitis and antiphospholipid syndrome. Subcutaneous anticoagulation followed by oral anticoagulation and controlling Systemic Lupus Erythematosus with immunosuppressant drugs or hydroxychloroquine may provide a better outcome in these patients.

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ATTACHMENT

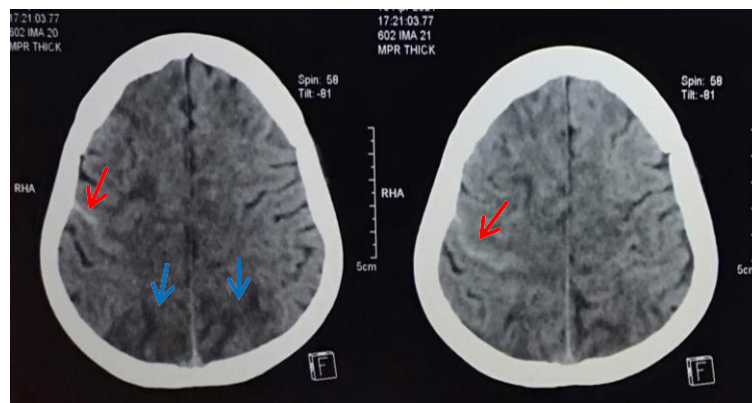


Figure 1. Non-contrast computed tomography head scan showed hyperattenuation in right temporal lobe (red arrows) and venous lobarinfarct in parietal lobe (blue arrows).

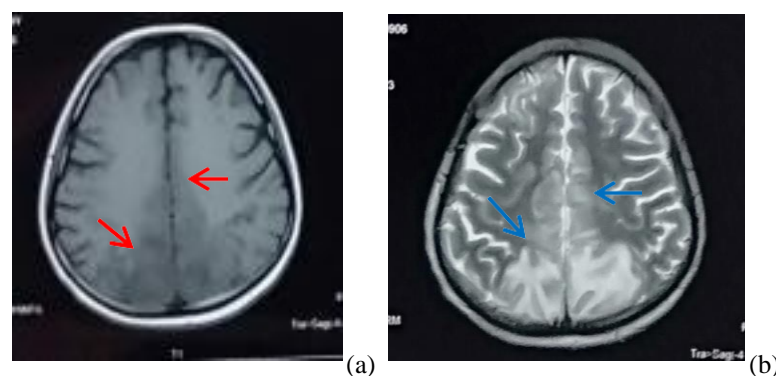


Figure 2. Non-contrast head MRI, mild hypointense/isointense on T1 (a - red arrows) against gray white matter, and hyperintense/mildhyperintense/isointense on T2 (b - blue arrows) showing high-intensity bland venous infarct in frontoparietal lobe bilateral.

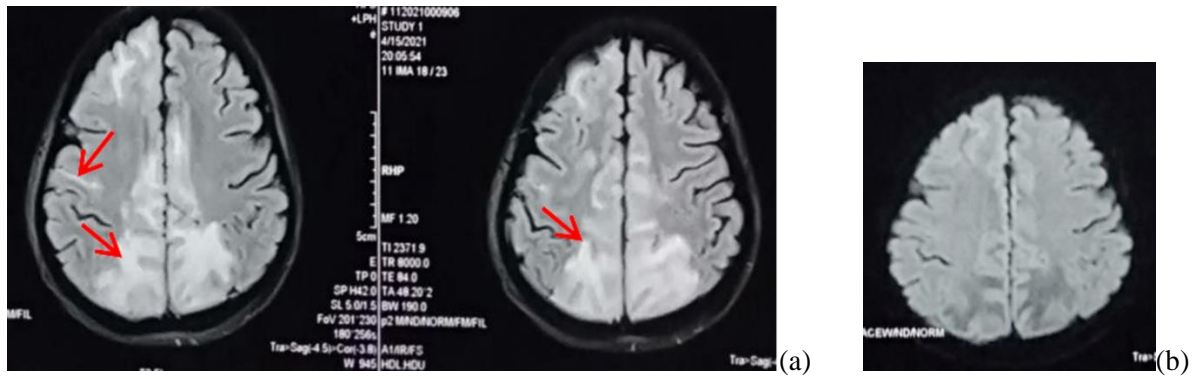


Figure 3. Non-contrast head MRI, hyperintense on FLAIR in the deep cortical/subcortical frontoparietal lobe bilateral and right temporal(a – red arrows). DWI does not show a water restricted area (b)

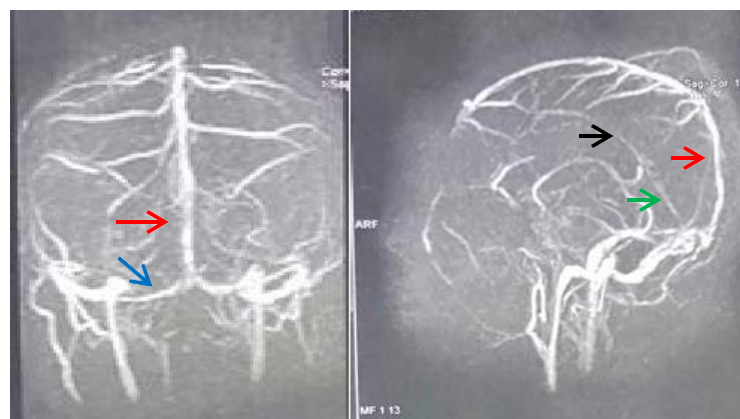


Figure 4. Non-contrast head MRV results showed decreased flow with constriction of the superior sagittal sinus (red arrows), transversusinus (blue arrow), inferior sagittal sinus (black arrow), and straight sinus (green arrow)