Cerebral Venous Sinus Thrombosis On Systemic Lupus Erythematosus And Multiple Sclerosis: A Case Report And Literature Review

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Abstract

Background: Both multiple sclerosis (MS) and systemic lupus erythematous (SLE) are autoimmune diseases and cerebral venous sinus thrombosis (CVST) is coincidence regarding hypercoagulable condition of both diseases. The presence of both diseases in the same patient is rare, which suggests a relative incompatibility between these diseases.

Case presentation: We report a female case with Systemic Lupus Erythematosus history, aged 27 years, with blurred vision, diplopia, severe headache, numbness and progressive right hemiparesis in 2 weeks. There was ovoid lesion in bilateral juxtacortical parietal and occipital lobe with neuritis optic in magnetic resonance imaging supporting demyelination process. There was narrowing caliber at left transversus and right sigmoid sinus in magnetic resonance venography. She showed improvement in vision, numbness, headache and motor strength in right extremities after receiving pulse dose of corticosteroid for three days.

Conclusion: The distinction between MS and SLE with CVST is a diagnostic challenge for the neurologist, and the presence of both diseases should be considered in patients with clinical neurologic manifestations of MS who present with typical systemic manifestations of SLE and CVST.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is systemic in nature affecting the joints and several other organs including the skin, heart, lungs, kidneys and nervous system.[1,2] The involvement of the central, peripheral, and autonomic nervous systems and psychiatric disorders in SLE is termed 'neuropsychiatric lupus' (NPSLE).[3,4] Neuropsychiatric symptoms can also be one of the early manifestations of SLE. Research says that up to 40% of these symptoms appear during the first year after a diagnosis of SLE is made.[5] The most common manifestation of SLE with Central Nervous System (CNS) involvement is headache, followed by mood disturbances and cognitive dysfunction, stroke and seizures.[5,6] In some cases, NPSLE is a direct manifestation of SLE whereas in others, the occurrence of demyelinating events may reflect a comorbid autoimmune condition, such as Neuromyelitis Optic Spectrum Disorder (NMOSD) or Multiple Sclerosis.[7,8] Multiple sclerosis (MS) is a chronic inflammatory process that occurs in the central nervous system, which involves the structure of neurons in the brain and spinal cord. This inflammatory process results in disruption of the damage to the axon's protective layer, namely myelin which protects axons and nerves in the central nervous system.[4]

We discuss a case report of SLE and relaps-remitting MS (RRMS) with Cerebral Venous Sinus Thrombosis (CVST). Written informed consent to publish case details and any accompanying images was provided by the patient. Dr. Hasan Sadikin General Hospital Bandung Human Research Ethics Committee approved this consent process.

CASE PRESENTATION

A 27-year-old female admits to the emergency unit with blurred vision, diplopia, severe headache, numbness and progressive right hemiparesis in 2 weeks. She had history of Systemic Lupus Erythematosus has been recorded 5 years ago, and had routine medication before admission was mycophenolate sodium 360 mg every 8 hours and folic acid

5mg once daily.

On examination: Fully alert and normal vital sign. Low visus on both eyes (20/200) with positive Relative Afferent Pupillary Defect (RAPD) and right abducen cranial nerve palsy. Right facial and hypoglossal nerve palsy, hemiparesis and hemihypestesia on right extremities.

Laboratory tests:

WBCs 9.69 × 103/μL, RBC 4.18 × 103/ μL, hemoglobin 10.60 (low) g/dL, platelet count 333× 103/μL, neutrophils 94% (high), lymphocytes 5% (low), eosinophil 0%, basophil 5% and monocyte 1% (normal values: WBCs 4–10 × 103/μL, hemoglobin 12–15 g/dL, platelets count 140–450 × 103/μL, neutrophil 40–75%, lymphocytes 20–45%, monocytes 2–10%, eosinophils 2–6%, and basophils 0–1%). Prothrombin Time (PT) 13.30 seconds, aPTT 25.40 seconds, International Normalized Ratio (INR) 1.23 (high). Human Immunodeficiency Virus (HIV) antigen was non-reactive. All electrolytes were normal limit. Liver and renal functions within normal limit. There was ovoid lesion in bilateral juxtacortical parietal and occipital lobe with neuritis optic in magnetic resonance imaging supporting demyelination process (Figure 1). Magnetic resonance venography showed narrowing caliber at left transversus and right sigmoid sinus (Figure 2). She was treated with intravenous metilprednisolone 500mg twice daily for three days, mycophenolate sodium 720 mg every 8 hours, warfarin 3 mg once daily, Mecobalamin 500mg every 8 hours, and Pregabalin 75mg twice daily for neuropathic pain symptoms.

Figure 1

Magnetic Resonance Imaging. Ovoid lesions in the juxtacortical bilateral parietal lobes, bilateral occipital lobes, and bilateral optic neuritis are supporting of demyelinating disease in SLE.

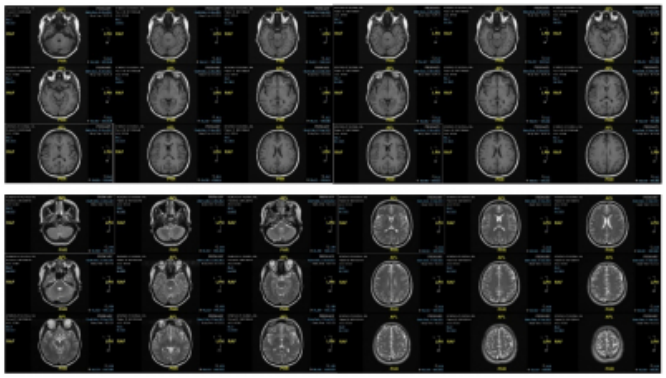
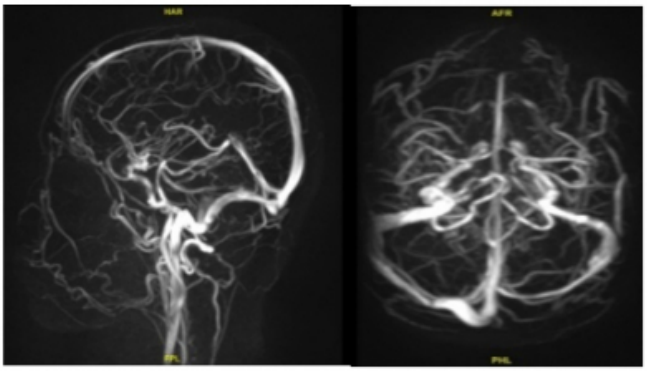


Figure 2

Magnetic Resonance Venography There was a reduction in the caliber of the left transverse sinus and the right sigmoid sinus.



After 7 days of hospitalization, she had improved the right limb's motor strength (walking with assistance), vision, headache, numbness and pain.

DISCUSSION

The most common manifestation of SLE with Central Nervous System (CNS) involvement is headache, followed by mood disturbances and cognitive dysfunction, stroke and seizures.[4,5] The mechanism of the pathogenesis of headache in NPSLE is not completely clear, there are several possible causes. Many autoantibodies have been detected in plasma samples of SLE patients and have been associated with NPSLE. Some of them are anti-ribosomal-P, anti-DNA/NR2, anti-DNA (16-1 idiotype), antiphospholipid (aPL), anticardiolipin (aCL) and Gamma Ammino Butyric Acid (GABA) antibodies.[3,5,6] It is hypothesized that auto-antibodies or pro-inflammatory cytokines circulating across the blood brain barrier (BBB) and entering the brain induce neurotoxicity.[4] Hawro et al reported that in NPSLE patients, the presence of autoantibodies to 2GPI was significantly associated with headache, ischemia, stroke and seizures.[4,12] The mechanisms that may be involved in the pathogenesis of the neuropsychiatric manifestations of SLE including headache in SLE patients are complex.[12,14] Several studies suggest that there are several factors such as genetics, vascular damage and occlusion, BBB dysfunction, nerve damage mediated by autoantibodies or inflammatory mediators including cytokines, and also direct neuronal cell death.[4] Two relevant pathogenetic pathways have been identified, namely the vascular-ischemic mechanism which is generally induced by aPL, immune complexes, and agglutination involving large and small blood vessels, which are considered to be more often responsible for the onset of

focal neuropsychiatric symptoms.[11] The second is an inflammatory neurotoxic process whose mechanism is predominantly mediated by complement activation, increased BBB permeability, migrating intrathecal autoantibodies and local production of immune complexes and pro-inflammatory cytokines and other inflammatory mediators, which may lead to diffuse neuropsychiatric manifestations. consider the causes of infection, especially herpes virus infection which can occur as a result of SLE immunosuppression.[3,6]

Multiple sclerosis (MS) is a chronic inflammatory process that occurs in the central nervous system, which involves the structure of neurons in the brain and spinal cord. This inflammatory process results in impaired damage to the axon's protective layer, namely myelin that protects axons and nerves in the central nervous system.[5,9,10] This disease is often diagnosed between the ages of 20 and 45 years. This disease is more common in women than men with a ratio of 2:1.5 The diagnosis of MS is made by clinical symptoms and imaging with magnetic resonance imaging (MRI) of the head and spine. In this patient, there were complaints of difficulty walking caused by balance disorders, progressively occurring 3 months of SMRS and had been experienced several times with recovery between these complaints.10 In addition, the results of the physical examination found focal neurological deficits that marked the upper motor neuron (UMN) lesion.[12,17]

The current diagnostic criteria for MS are McDonald's criteria, which are assessed based on clinical, radiographic, and laboratory aspects. The McDonald's criteria were created in 2001, revised in 2005, 2010 , 2016 and most recently in 2017.[6] A diagnosis of multiple sclerosis can be made if one of the five categories of criteria is met, depending on how many clinical attacks have occurred and not based solely on the clinical picture radiology (MRI) or serology alone.[9]

The common clinical features for optic neuropathy are visual loss, visual field scotoma and dyschromatopsia. Pain is a variable picture which, if present, indicates an inflammatory process. A relative afferent pupillary defect (RAPD) is a necessary clinical finding for the diagnosis of unilateral optic neuropathy. The term "Typical optic neuritis" (ON) has been widely used to designate unilateral ON which presents in young patients with an acute or subacute presentation, pain that worsens with eye movement and has a generally good prognosis. Typical optic neuritis is most often caused by disorders that are idiopathic or Multiple Sclerosis (MS). The term “atypical optic neuritis” refers to severe bilateral visual loss (to no light perception), painlessness, bleeding into the optic disc or retina, macular exudate, or uveitis. This patient is more directed to atypical optic neuritis characterized by the age of the patient between 15-45 years, complaints of blurry vision in both eyes, no pain in eye movement. Headaches can occur due to stimulation and sensitization of pain-sensitive structures in the head.[11] Secondary headaches can occur due to neurological manifestations of immunological/autoimmune disorders, both those involving the central nervous system (CNS) such as Multiple Sclerosis (MS) and systemic ones such as Systemic Lupus Erythematosus (SLE).[11,12,14] There are several epidemiological similarities between immunological or autoimmune diseases and the incidence of primary headaches, one of which is gender, namely women and young age. Headaches in MS most closely resemble migraine-type headaches.[14] Neuroinflammatory events involving activation of microglia and astrocytes also occur during the process of cortical spreading depression (CSD) which is the same pathophysiology of migraine with aura (MA).[12,13] Several preclinical studies have revealed that CSD not only induces glial cell activation but also increases the expression of pro-inflammatory cytokines, adhesion and chemokines as well as the expression of toll-like receptors (TLR3 and TLR4). Pre-clinical models of migraine pathophysiology suggest that activation of the trigemino-vascular system is the key to localized neurogenic inflammation involving the dural and wattle vessels. This causes several processes such as extravasation of plasma proteins due to increased meningeal vascular permeability and activation of immune cells, namely mast cells and macrophages.[12-14]

Mast cell activation will trigger the formation of several pain mediators such as serotonin, histamine, heparin, proteases and arachidonic acid products, pro-inflammatory cytokines and chemokines that are involved in trigeminal peripheral sensitization.[15] The C fibers of the trigeminal nerve will release calcitonin gene-related peptide (CGRP) which interacts with its own receptor on the dural vessels. This interaction will activate adenylate cyclase which causes dilation of blood vessels so that it will trigger pain.16 Astrocytes and glial cells also have CGRP receptors. The interaction of CGRP with its receptors on astrocytes and glia cells will induce the release of several pro-inflammatory cytokines such as tumor necrosis factor (TNF)- and

interleukin (IL)-1ß which dramatically amplify trigeminal nociception. Headaches, especially migraine with MS, are decreased CSF serotonin levels, sympathetic hypofunction, and vitamin D deficiency.[17] In addition, there are theories that explain the relationship between the location of MS lesions and the type of head that occurs. Patients with demyelinating lesions in the midbrain or periaqueductal gray matter (PAG) area will experience a fourfold increase in migraine-like headaches, compared with MS patients without lesions in this area. This finding may be explained by the role attributed to PAG in the pathophysiology of migraine.[18] The location of cervical demyelinization especially in the upper cervical area is associated with tension-type headache (TTH). Demyelination lesions of the pons in the trigeminal nerve root entry zone can cause headaches of the trigeminal neuralgia type.[14,17]

In this patient there is thrombosis in the vein (CVST) which can be caused by hypercoagulable conditions and result in headache. This hypercoagulable state may be associated with SLE in this patient. Several mechanisms play a role in the development of CVST in SLE.[26] The complex interaction between endothelial cells and Lupus Antibody (LA) will trigger inhibition of proteins C and S which are responsible for the occurrence of thrombosis.[26] Autoantibodies attack the negatively charged surface of phospholipids, thereby triggering platelet activation to form a thrombus. Impaired fibrinolysis, antithrombin III, hyperfibrinemia, or changes in coagulation may also lead to thrombosis.[14,15,26] The presence of optic neuropathy and MRI images in the form of ovoid lesions with hyperintense T2 in the parietal and occipital subcortical areas accompanied by bilateral optic neuritis images suggest a demyelination process (multiple sclerosis) which is still possible to diagnose in comparison with SLE lesions.[19-21]

There is controversy over the pathogenesis of MS and CVST involving autoimmunity.[15] Currently, there are two theories that are believed to play a role in the pathophysiology of MS and CVST:

a. The association between MS plaques and adjacent parenchymal vessels is associated with an inflammatory process, particularly lymphocytic infiltration around small or medium-sized veins. This inflammatory process is not only limited to demyelinating plaques but also affects the white and gray matter that usually appears and the meninges.[15,18]

b. Several immunological mechanisms lead to inflammation of the blood vessel walls and an increase in the permeability of the blood-brain barrier. In addition, perivascular leukocyte accumulation is associated with increased serum protein deposition. In addition, in some cases, changes in acute vascular conditions can occur consisting of intraluminal platelet aggregation and thrombosis and can cause total thrombotic venous or venular occlusion. In some cases, a severe inflammatory reaction has been observed in association with the veins.[18,26]

Demyelination disease is defined as the Neuropsychiatric SLE/NPSLE syndrome in the ACR nomenclature.[7] In some cases, NPSLE is a direct manifestation of SLE whereas in others, the occurrence of demyelinating events may reflect a comorbid autoimmune condition, such as NMOSD or MS.[7,9] In addition, optic neuropathy in SLE can also be caused by an ischemic process. Fluorescein angiography can help differentiate between some cases of optic neuritis and ischemic optic neuropathy, which often results from thrombosis or vasculitis.[9,12] It is also important to consider the cause of infection, particularly herpes virus infection, which can occur as a result of SLE immunosuppression.[17,18]

In MS, the immunosuppressants MMF, azathioprine, methotrexate and cyclophosphamide have been studied; however, their efficacy is not yet well established. A retrospective study has shown that 55% of patients had no evidence of disease activity when followed up with cyclophosphamide as induction therapy.[24,25] Another retrospective study showed that MMF reduced annualized relapse rate and EDSS remained stable between initiation and one year after the beginning of MMF.[30] A multicenter, randomized, non-inferiority trial has shown that efficacy with azathioprine was not inferior to that of IFN beta for patients with Relaps-Remitting Multiple Sclerosis (RRMS).[29-30] However, it is necessary that the efficacy of these drugs be demonstrated in phase III clinical trials and, if possible, be compared with disease-modifying therapies (DMTs).[24,25] Adrenocorticotropic (ACTH) hormone gel was approved by the United States Food and Drug Administration as a treatment for relapsing MS in 1978 and a treatment option for SLE in 1952.[30,31] ACTH has anti-inflammatory and immunomodulatory effects due to activation of central and peripheral melanocortin receptors.[31] In MS, a systematic review demonstrated that ACTH or corticosteroids were effective over the short term in improving symptoms, thus favoring recovery.[31] Regarding to SLE patients with moderate or severe active SLE, an open-

label study showed that ACTH gel may provide significant disease activity reduction.[30,31]

However, there is controversy regarding the administration of high-dose steroids in CVST patients. The use of steroids is associated with coagulation status so that it can affect the CVST condition. Patients with chronic inflammatory disease are at risk for venous thromboembolism (VTE).[26] The risk of developing VTE is related to an exacerbation of the disease usually treated with corticosteroids.[27] When corticosteroids induce a procoagulant state, patients with exacerbations and receiving corticosteroid therapy have a very high risk of developing VTE. Hypercoagulability induced by steroid therapy is associated with elevated factors VII, VIII, and XI. There are studies that show an increase in FVIII levels after short-term administration of high-dose dexamethasone in healthy men, which is in line with observations in patients with Cushing's syndrome. However, other non-genomic studies have shown that high doses of acute glucocorticoids increase activation of endothelial nitric oxide synthase (eNOS), which may inhibit VWF secretion. While endothelial dysfunction and increased oxidative stress and chronic insulin resistance associated with excess glucocorticoid in the long term have been reported to increase plasma VWF levels. It is also explained that the long-term use of oral corticosteroids allows for an increase in factors II, V, VII, IX, X, XII and fibrinogen which further induces a hypercoagulable state.[22,23,26,27]

In addition, the presence of steroid therapy in MS can interact with anticoagulant therapy, namely warfarin which is used as CVST therapy.[23] There are studies showing a supratherapeutic effect of INR in individuals taking warfarin and steroids. The exact mechanism of interaction between warfarin and oral corticosteroids is not clearly known, but it is thought to be related to the process of both drugs in the liver. Methylprednisolone, prednisone, and warfarin are metabolized in the liver via the CYP3A4 isoenzyme pathway.[27] Inhibition of warfarin metabolism potentially occurs as a result of competitive binding to CYP3A4. In addition to the CYP3A4 pathway, warfarin is also a substrate for the CYP1A2, 2D6, and 2C9 isoenzymes pathways. However, there is another influence, namely genetic deficiency of the cytochrome P450 isoenzyme that causes various compensatory warfarin metabolism through different isoenzyme pathways. Kaufman says another possible theory of warfarin's effect with steroids is related to serum pH. The use of steroids will increase the serum pH which can cause the binding of warfarin to protein to decrease so that it will increase the free warfarin level in the blood. In this patient was treated with intravenous metilprednisolone 500mg twice daily for three days, mycophenolate sodium 720 mg every 8 hours, warfarin 3 mg once daily, Mecobalamin 500mg every 8 hours, and Pregabalin 75mg twice daily for neuropathic pain symptoms.

After 7 days of hospitalization, she had improved the right limb's motor strength (walking with assistance), vision, headache, numbness and pain. It needs to be watched out for related to the possibility of bleeding side effects from warfarin use.[26,27]

Limitation of Study

This article had several limitations. We did not assess the panel of pro-inflammatory assay in this patient.

CONCLUSION

The distinction between MS and SLE with cerebral venous sinus thrombosis is a diagnostic challenge for the neurologist, and the presence of both diseases should be considered in patients with clinical neurologic manifestations of MS who present with typical systemic manifestations of SLE.

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