Cerebral Venous Sinus Thrombosis in A Patient with Sjögren's Syndrome with Atypical Antibodies: A Case Report

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Abstract-

Background: Although Sjögren's syndrome has been known to complicate with white matter lesions, encephalopathy, or stroke, reports of cerebral venous sinus thrombosis due to Sjögren's syndrome with atypical antibodies are rare.

Case Report: A 50-year-old woman was admitted to our neurological ward with nausea and vomiting following acute onset of severe headache in the left occipital region. Brain computed tomography revealed no abnormalities. The patient was fully conscious, with normal cognitive functioning, but exhibited unsteady tandem gait. Both magnetic resonance venography and computed tomography venography suggested left transverse sinus blockage. Intravenous enoxaparin, followed by oral warfarin, was initiated as treatment for cerebral venous sinus thrombosis. After investigation, Sjögren's syndrome was diagnosed and lupus anticoagulant antibody test was positive. The patient was treated with hydroxychloroquine, and appeared fully recovered at the 6-month follow-up, with no clinical or radiological signs of relapse.

Conclusion: This case reports the relationship between cerebral venous sinus thrombosis and Sjögren's syndrome. It is necessary to screen autoimmune disorders in patients with cerebral venous sinus thrombosis that present with no common risk factors of venous thrombosis in order to prevent inappropriate management, and potentially adverse outcomes.

Key Words: antiphospholipid syndrome, coagulation disorder, autoimmune disease, Sjögren's syndrome

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INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltrates in the exocrine glands, specifically the salivary and lacrimal glands, with higher prevalence in women. The main symptoms of SS are xerostomia and xerophthalmia[(1)], but a variety of psychiatric and neurological complications of SS have also been described[(2)]. The reported prevalence of neurological involvement in SS is highly variable (8-70%)[(3,4)].

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The complication rate for the central nervous system (CNS) in SS patients has been reported to be from 1.5% to 36%[4], with a tendency to occur in later stages of the disease[5,6]. Although complications of the peripheral nervous system in SS patients are reportedly more common than those of the CNS, it is believed that the prevalence of CNS complications may be underestimated due to variability of presentation[7]. While diagnosis of SS is based primarily on clinical features and laboratory findings, some SS-associated magnetic resonance imaging (MRI) findings have also been described, such as small punctate white matter hyperintensities in the subcortical and periventricular areas[8].

Cerebral venous sinus thrombosis (CVST) is a local venous obstruction disorder that may cause focal neurological deficits, as well as generalized conditions related to increased cerebrospinal fluid pressure, secondary to blockage of major sinuses. CVST is often related to otomastoiditis, infections of the orbit and central face, neoplasm, pregnancy, puerperium, systemic diseases, dehydration, intracranial tumors, oral contraceptives, and coagulopathies[9]. It has been reported that CVST may be a clinical presentation for SS[10,11]. Primary SS with atypical antibodies, typical of other systemic autoimmune diseases, may share clinical findings due to immunological overlaps[12]. Furthermore, antiphospholipid (aPL) antibodies are the most frequently detected atypical antibodies (approximately 25%) in primary SS patients, and they are believed to be responsible for thromboembolic events in SS[12,13].

Here, we report a case of CVST in patient with SS with atypical antibodies, and discuss the possible pathophysiology.

CASE REPORT

A 50-year-old woman was admitted to our neurological ward with acute onset of severe headache in the left occipital area, associated with nausea, vomiting, and dizziness for 1 day. The condition persisted and could not be temporarily relieved using pain-killers. She had never experienced such symptoms before. Her past clinical history was unremarkable, except for hyperlipidemia. No other risk factors, such as hypertension, diabetes, smoking, contraceptive drug use, or family history of thrombosis were present. Moreover, during her initial neurological examination, the patient was fully conscious, presenting apparently normal cognitive function. No abnormalities or focal neurologic deficits were evident except for unsteady tandem gait. Furthermore, non-contrast brain computed tomography (CT) scan obtained in our emergency department revealed no abnormal findings, and brain magnetic resonance images (MRI) revealed normal grey and white matter, with no obvious lesions in the brain parenchyma. However, the left transverse sinus was not visible in the magnetic resonance venography images (Figure A), and seemed to be at least partially blocked in the CT venography (Figure B) with filling defect images (Figures C and D). Finally, T1-weighted post-contrast MRI showed a filling defect in the corresponding area (Figure E).

The patient was treated with injectable anticoagulant (enoxaparin; 0.5 mg/kg subcutaneously every 12 hours, and 1.0 mg/kg over 12 hours) followed by oral anticoagulant (warfarin, 5 mg daily), and was subjected to an extensive screening procedure for coagulation disorders including thrombophilias, protein C deficiency, protein S deficiency, antithrombin deficiency, activated protein C resistance, and homocysteine levels. Investigation regarding autoimmune diseases was performed including tests for aPL, antinuclear, anti-dsDNA, antineutrophil cytoplasmic, antimitochondrial, and anti-SS-related antigen A (anti-Ro/SSA) antibodies. The test for aPL antibodies included IgG and IgM anticardiolipin (aCL), IgG and IgM anti-β2 glycoprotein-1 (aβ2GPI), and lupus anticoagulant (LA) antibodies, which was in accordance with the guidelines of the International Society on Thrombosis and Haemostasis[14].

The patient was found to be positive for anti-Ro/SSA and anti-dsDNA antibodies, and elevated LA antibodies levels were also detected. Furthermore, the results of sialoscintigraphy, minor salivary gland biopsy, and Schirmer's test satisfied the American-European Consensus Group classification criteria for SS[15]. Hydroxychloroquine (200 mg daily, orally) was started for the treatment of SS. Moreover, the presentation of venous thrombosis, and the detection of LA activity (detected 12 weeks apart) met the revised Sapporo criteria for APS[16]. Consequently, the diagnosis of CVST in SS with atypical antibodies was set. At her 3-month follow-up appointment, she had no clinical

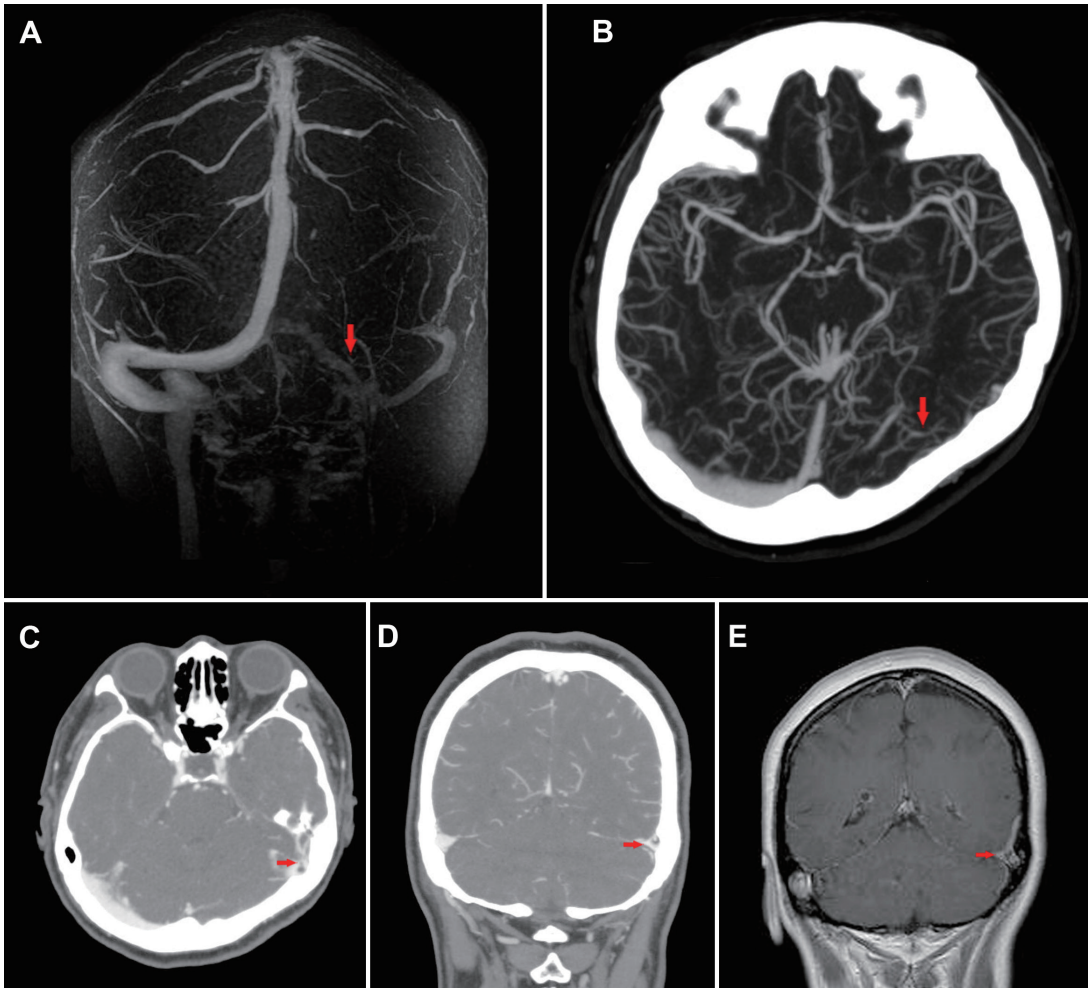

Figure 1. The patient's left transverse sinus was not visible on magnetic resonance venography (A, arrow). Computer tomography venography revealed patulous appearance (B, arrow), and filling defect (arrows in axial and coronal view, C and D) in the distal left transverse sinus, with partial thrombosis. The T1-weighted post-contrast magnetic resonance image showed a filling defect (E, arrow) in the corresponding area. No imaging modality suggested abnormalities of the grey or white matter, and no obvious parenchymal lesions were detected.

relapses, and appeared to be fully recovery. Further, T1-weighted post contrast MR image revealed full recovery without the previous filling defect in the corresponding area.

DISCUSSION

As compared with other subtypes of stroke, CVST occurs less frequently, and is more difficult to be diagnosed[17]. In recent years, with the widespread use of MRI and rising clinical awareness, CVST is being recognized more frequently[18]. Similar to other types of extracranial venous thromboses, there are multiple risk factors for CVST. Thus, a thorough investigation of additional potential causes should be carried out, even in cases when specific risk factors for CVST have already been identified in the patient.

The clinical presentation of CVST is highly variable. CVST onset may be acute, subacute, or chronic. Headache, which is the most frequent symptom of CVST, may arise gradually, acutely, or have a thunderclap onset and be accompanied by focal neurologic deficits (e.g. nystagmus,

dysphagia, hearing loss, cerebellar incoordination), focal or generalized seizures, or encephalopathy with altered mental status or coma[19]. In our patient, headache was the first symptom of CVST, followed by nausea, vomiting, and cerebellar incoordination.

Although SS is characterized mainly by lymphoid infiltration and functional deterioration of the exocrine glands, the disease often presents with extraglandular manifestations including neurological abnormalities. CNS complications include aseptic meningitis, myelitis, and vasculitis of the microcirculation associated with white matter lesions and encephalopathy[20]. Cases in which CNS presented with arterial stroke have also been reported[4,8,21]. Early diagnosis of SS is helpful for the prevention and management of disabilities related to CNS complications, but this is often challenging as various CNS symptoms typically precede the diagnosis of SS. The patient described in this work did not present the typical clinical symptoms of SS, namely xerostomia and xerophthalmia, even though sialo-scintigraphy, salivary gland biopsy, and Schirmer's test results were all positive.

In this case, in addition to the typical antibody of SS (anti-Ro/SSA), atypical antibodies (anti-dsDNA; aPL, LA) were also detected. It has been reported that the prevalence rates of anti-dsDNA and aPL antibodies in primary SS were 4-5% and 13%, respectively[12,13]. CVST has been reported in collagen vascular disorders with anti-dsDNA antibodies, suggesting an association between anti-dsDNA antibodies and CVST, especially in systemic lupus erythematosus[22,23]. The aPL antibodies, including LA and aCL antibodies, are a group of closely related immunoglobulins that interact with phospholipids. Patients with aPL antibodies are prone to undergo repeated episodes of thromboembolic events, such as cerebral infarction, deep venous thrombosis, and fetal loss[13,24]. Furthermore, aPL antibodies were previously detected in up to 53% of CVST patients[25], suggesting an association between aPL antibodies and CVST. In contrast, absence of aPL antibodies has also been reported in SS patients with thrombosis, suggesting that autoantibody-mediated vasculitis may be another possible mechanism leading to CVST[26]. Taken together, these previous reports imply that the possible causes of CVST in SS patients may be related to atypical antibodies including aPL or anti-ds DNA antibodies, or to SS-mediated vasculitis. Therefore, in this case report, based on the concomitant findings of atypical antibodies in SS, we speculate that atypical antibodies and SS may both contribute to CVST. Overall, the observations made in this case confirm the interconnection between the underlying mechanisms of atypical antibodies, SS, and CVST.

This case reports the relationship between CVST, SS, and atypical antibodies. We believe that it is necessary to screen autoimmune disorders in patients with cerebral venous sinus thrombosis that present with no common risk factors of venous thrombosis, or clinical symptoms for such systemic autoimmune diseases. Misdiagnosis of insidious autoimmune diseases may result in inappropriate choice of therapeutic strategy, ultimately affecting the clinical outcome.

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