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Sjögren Syndrome Associated Cerebral Venous Sinus Thrombosis with Presenting as Convexal Subarachnoid Hemorrhage: A Case Report

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Abstract

Cerebral Venous Sinus Thrombosis (CVST) is an uncommon cerebrovascular disease caused by cerebral venous sinus blockage, leading to increased intracranial pressure, venous infarction, or bleeding. Among the patients, convexal Subarachnoid Hemorrhage (cSAH) caused by CVST is relatively rare, accounting for only 0.5% to 0.8% [1] of all CVST patients. Convexal SAH is a subtype of non-aneurysmal SAH, characterized by the limitation of bleeding in one or several convex cortical sulci. The pathogenesis of CVST is challenging to find but valuable for subsequent treatment. We report a patient with CVST caused by primary Sjögren Syndrome (pSS) and secondary "Non-criteria" antiphospholipid syndrome, whose first manifestation was cSAH. After diagnosis, the patient was given long-term anticoagulation to treat CVST and "Non-criteria" antiphospholipid syndrome. The case aims to discuss the diagnosis, pathogenesis, personalized treatment plan, and the risk of recurrence.

Keywords: Cerebral venous sinus thrombosis; Sjögren syndrome; Convexsal subarachnoid hemorrhage

Introduction

Cerebral venous thrombosis accounts for 0.5% of all types of strokes [2], with the estimated annual incidence of 3 to 4 cases per 100,000 populations [3]. The common cause of CVST included infections, dehydration, pregnancy, trauma, and inherited hematopathy, and the autoimmune disease, but more than 12.5% of cases remained idiopathic [4]. The Sjögren syndrome-associated CVST or "Non-criteria" antiphospholipid syndrome-associated CVST is scarcely reported [5]. It reminds us of the importance of seeking etiologies for afterward therapeutic anticoagulation. It also illustrates that the CVST as the cause of cSAH can be vital for subsequent anticoagulant therapy, which contradicts in SAH of other reasons.

Case Presentation

A 32-year-old Asian female presented with sudden headache with extremities spasms and loss of consciousness lasting for hours with nausea, vomiting, blurred vision, diplopia, aconuresis, and left extremities numbness for more than eleven days. The patient denied dysphasia, dysphagia, photophobia, gait disturbance, or sensory loss. Mild xerostomia and saprodontia were also spotted *via* inquiry of history. The patient had diabetes but denied hypertension or hyperlipidemia, thrombophilia, malignancy, or dehydration. She also denied usage of oral contraceptives or repetitive miscarriages. On admission, her vital signs, including blood pressure, heart rates, and respiration were stable with a Glasgow Coma Scale of 15/15. Central nervous examination revealed left extremities weakness with muscle strength grade 4 and mild ataxia on the left side. The cranial nerves, sensory functions, and deep reflexes were normal. Meningeal irritation signs and nuchal rigidity were negative.

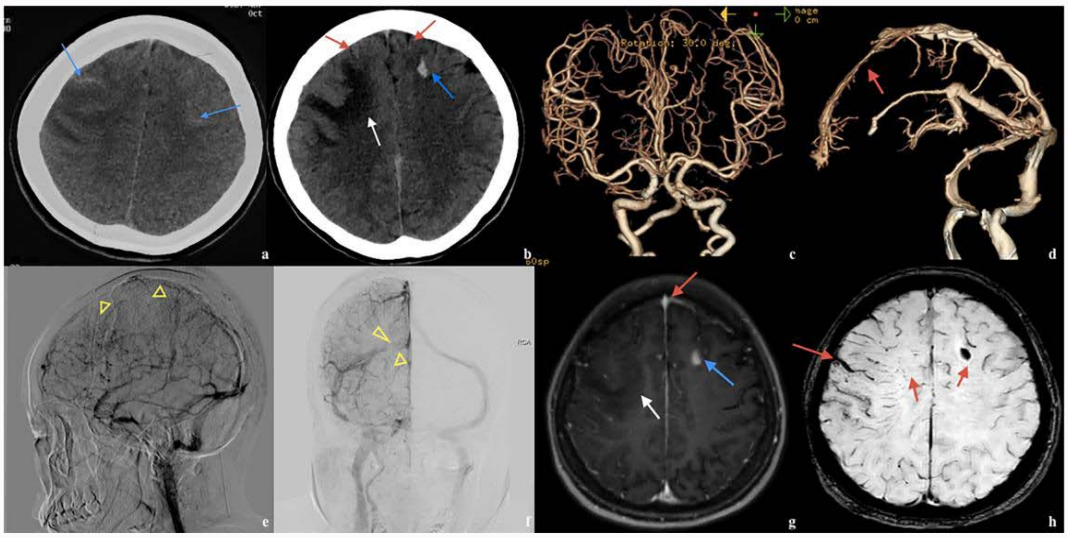

Figure 1: (a) axial non-enhanced CT on day 2 shows the convexal SAH in the frontoparietal sulcus (blue arrow), (b) axial non-enhanced CT on day 8 shows the convexal SAH in the frontoparietal sulcus (red arrow), parenchymal hemorrhage (blue arrow), cortical edema (white arrow) (c,d). The computed tomography arteriology shows no aneurysm or stenosis, computed tomography venography shows the filling defect in the Superior Sagittal Sinus (SSS). (e,f) DSA shows the filling-defect in SSS and right Transverse Sinus (TS), which confirmed CVST (yellow triangle). (g) Axial T1 shows the hyperintensity in SSS (red arrow), parenchymal hemorrhage (blue arrow), hypointensity, which means cortical edema (white arrow) (h). The SWI shows microbleeding (short red arrow) and dilation of cortical vein in the right frontal lobe (long red arrow).

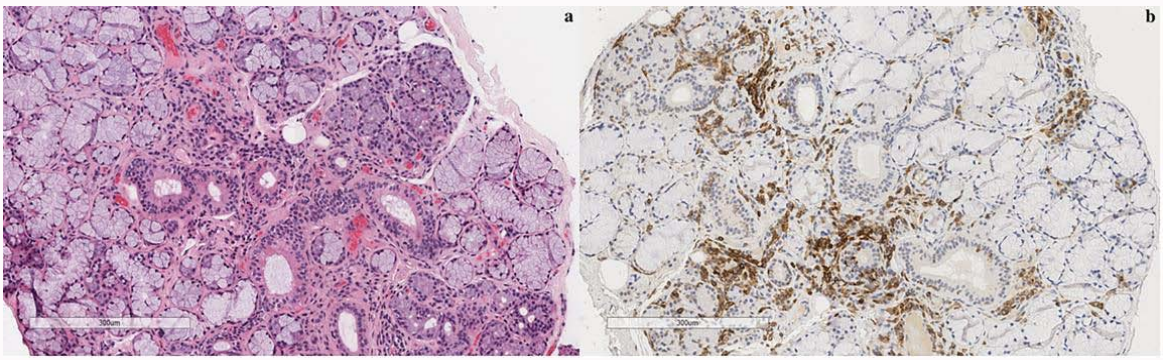

Figure 2: Histology of the labial gland. Pathology result of the 4mm2 labial salivary gland biopsy, stained with H&E, lymphocyte infiltrate with one focus >50 lymphocytes (x100) (A). Immunohistochemical stain: Leukocyte common antigen (+) (x100) (B). A diagnosis of Sjögren syndrome can be made.

Emergency Brain Non-Enhanced CT (NECT) showed linear hyperdensity in bilateral frontal lobe sulcus on day 2. Subsequent NECT on day 8 revealed subcortical edema and parenchymal hemorrhage (Figure 1a, 1b), and Computed tomography angiography detected no aneurysm or stenosis while computed tomography venography showed filling defect in the Superior Sagittal Sinus (SSS) and right Transverse Sinus (TS) (Figure 1c, 1d). DSA was made to rule out aneurysmal SAH and show the filling defect in SSS and right TS (Figure 1e, 1f).

Blood tests showed elevated estimated sedimentary rate of 100 mm/h, elevated C reactive protein was 16.99 mg/L, autoantibody spectrums revealed anti-SS-related antigen A (anti-Ro/SSA) antibodies (+++), anti-SS antigen B (anti-SSB) antibodies (+++), anti-Ro-52 (+++), Antinuclear Antibodies (ANA) 1:3200 and anti-nuclear RNP/Sm antibodies (-). The antiphospholipid antibody test showed positive IgA Anti-β2 glycoprotein I antibody (IgA anti-β2GPI antibody) (54.11 RU/ml) positive, negative IgG and IgM anti-β2GPI, and negative anti-cardiolipin. A 12 weeks reexamination also revealed positive IgA anti-β2GPI (40.77 RU/ml) with the negative IgG and IgM. The Anti-Neutrophil Cytoplasmic Antibody (ANCA), complement, Immunoglobulin G and Immunoglobulin G subtype 4, rheumatoid factor were normal. The prothrombin time, partial thromboplastin time, and International Normalized Ratio (INR) were within normal ranges (11.4s, 29.6s, and 0.99s). The activity of Protein S is 39.9% (63.50% to 149.00%), antithrombin III is 63% (83.00% to 128%), and coagulation factor VIII is 191% (50% to 150%). The thyroid functions test showed the thyroxine 36.88 nmol/L (69.97 to 152.52), Thyroid Stimulating Hormone 18.08 ulu/mL (3.28 to 6.47), anti-thyroglobulin and anti-thyroid peroxidase antibody were strongly positive, which indicated the Hashimoto thyroiditis. The liver function tests with liver and gall ultrasounds and urinalysis were normal. The labial gland biopsy showed that the cluster of lymphocytes infiltrates the small salivary gland tissue of 4 mm^2; Leukocyte Common Antigen (LCA) highlights the lymphocyte (+), which confirmed a diagnosis of Sjögren syndrome (Figure 2).

The Low Weight Molecular Heparin (LMWH) was given after CVST was diagnosed and warfarin was delivered four days later, bridging with LMWH. The clinician adjusted warfarin dose to maintain the INR of the patient at 2 to 3 in 12 weeks.

Discussion

In CVST-associated SAH, nearly 90% of patients first appeared as sudden and thunderclap-like headaches [6] that mimic the aneurysmal SAH. The seizure occurs in 35% to 90% in 2 case series [7,8] as in our case. The mechanism may be the stimulation of the convexal cerebral cortex caused by cSAH, leading to abnormal cortical discharge. The NECT is often the preliminary examination for SAH for its high sensitivity but a suboptimal tool for CVST. A case series revealed that the circumscribed convexity SAH localized to the dural sinuses or cortical veins with sparing of the basal cisterns might point to an underlying CVST [9]. Compared with NECT, the MRI is more sensitive as 21/22 was spotted by the MRI FLAIR sequence in that case series [8]. Digital subtraction Angiography is the "gold standard" for the diagnosis [10], which can show the filling defect and blood drainage of the venous and venous sinus. Different hypothesizes can explain the causal relationship between CVST and SAH. Sinus thrombosis increases the adjacent venous pressure, causing the dilation and rupture of cortical veins [11]. The occlusion of the cerebral vein also leads to venous infarction presenting as elevated intracranial pressure, brain tissue edema, and brain infarction [12].

The patients also complained of xerostomia and xerophthalmia with anti-Ro/SSA and anti-Ro/SSB positive. The labial glands biopsy confirmed the diagnosis of Sjögren syndrome [13]. Among SS patients, the common neurological manifestations are peripheral neuropathy, autonomic nervous disease, and myelitis [13]. To our knowledge, there are only five Sjögren syndrome-induced CVST reported in literature, and none of them had secondary cSAH [5]. A theory declared that the pSS-induced autoimmune vasculitis could cause the vasculitic necrosis and leads to thrombosis [14], may explain the etiology.

The IgA anti-β2GPI antibody-positive on day 1 and 12 weeks with the sinus thrombosis, the "non-criteria antiphospholipid syndrome "or" Seronegative Antiphospholipid Syndrome (SNAPS)" can be diagnosed [15,16]. Though the Sapporo standard did not include IgA anti-β2GPI antibody [17], it certainly strongly correlates with thrombosis events and recurrent miscarriage [15]. IgA aβ2GPI positivity alone is associated with an increased risk of arteriovenous and venous thrombosis and all types of thrombosis [18].

Since the concurrence of Sjögren syndrome and APS and the presence of anti-SSA, we believed the APS has occurred secondary to Sjögren syndrome [19]. Secondary APS can occur in nearly 3% to 4% pSS patients [20]. Antiphospholipid syndrome can lead to thrombosis by affecting coagulation via increasing the expression of thromboxane A2 [23] and tissue factor [24] or activating the classic complement pathway [25]. The APL-associated CVST presenting as cSAH has been reported in many cases [21]. In conclusion, The SS that caused the seronegative APS that leads to the CVST and associated cSAH.

The thyroid dysfunction is the third most relevant risk factor for CVST [1], and Grave's disease-associated CVST presenting as cSAH cases were reported [7,8]. Hashimoto thyroiditis-related CVST was also revealed [22]. In general, hyperthyroidism leads to thrombosis due to the endothelial activation and decreased fibrinolytic activity [23], while the hypothyroidism is often associated with bleeding. Hashimoto thyroiditis relates with APS antibodies present, but no relations of HT with a thrombotic manifestation of APS [24]. Our patients presented anti-thyroglobulin and anti-thyroid peroxidase antibody, thus, multiple factors may contribute to the onset of CVST, and including SS associated vasculitis, hypercoagulable state stemmed from anti-phospholipid antibody syndrome and autoimmune thyroiditis.

The therapeutic dose of LMWH was given after CVST was confirmed by MRV and DSA [25] to prevent the potential of elevated intracranial pressure and herniation. Warfarin was given for long-term anticoagulation in the heparin bridging phase to prevent CVST recurrence, affecting 2 to 7 percent of patients [1]. As for this case, since the CVST was caused by Sjögren-induced APS, the priority is the APS treatment which mainly includes antiplatelet, anticoagulant, and immunomodulatory therapy [26]. The standard treatment for APS in the first venous thrombotic event is an oral vitamin K antagonist with a target INR of 2 to 3 [27]. Due to the high recurrence rate of thrombotic events in APS, a lifetime anticoagulant is recommended. New anticoagulants lack evidence of efficacy in the APS treatment [28]. APS also requires immunomodulatory therapy, especially in patients secondary to other rheumatic immune system diseases. Glucocorticoids and immunosuppressants shall be considered for the management of pSS, but there is no specific treatment so far due to lack of data on efficacy and safety trials. Hydroxychloroquine, methotrexate, azathioprine, and cyclophosphamide can be used with ESSDAI taken [29].

The prognosis of CVST is favorable, with more than 80% good outcomes, but the prognosis of CVST-related SAH depends on early diagnosis and treatment. In 2 cases series [6,7], the mortality rates are 2/10 and 1/22, though the sample size limited, we can conclude that the cSAH was not related to bad outcomes, the occurrence of parenchymal infarcts, raised intracranial pressure, and extensive deep venous thrombosis may worsen outcome. As for the prognosis of APS, a large cohort study [30] confirms that APS patients who survive their first episode are still at risk for recurrent events. Because warfarin and aspirin reduces but do not eliminate the risk of recurrent thromboembolic or obstetric complications, which can sometimes be fatal. So a regular follow-up visit is needed to evaluate the coagulation status and succeeding treatment.

Conclusion

Cerebral venous thrombosis should be considered when convexal subarachnoid hemorrhage patients presented with neurological deteriorations and new onsets of headache and seizure. In this case, the Sjögren syndrome and secondary antiphospholipid caused hypercoagulation and leading to thrombosis in venous sinuses, presenting as the convexal subarachnoid hemorrhage. The CTV, MRV, or DSA should be used to confirm the presence of CVST therefore make a precise therapeutic regime. Finding immunological etiology behind it also matters for a following rational and sound treatment plan.

Authors Contribution

Administration support: XZ, RJ, YJ. (2) Collection data and biopsy results: ZJ, GD, FM. (3) Manuscript writing and revising: All authors. (4) Final approval of manuscripts: All authors.

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