Cerebral Infarction and Cortical Subarachnoid Hemorrhage Preceded Vascular Contraction in Reversible Cerebral Vasoconstriction Syndrome Patient with Hidden Breast Cancer

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Abstract

Thunderclap headaches, stroke, seizures, and cortical subarachnoid hemorrhage can all reveal reversible cerebral vasoconstriction syndrome (RCVS). Most parenchymal brain lesions occur simultaneously and sequentially with cerebral vasoconstriction in RCVS patients. Therefore, it is not easy to suspect RCVS in patients with only parenchymal brain lesions without vasoconstriction even if they present with a typical thunderclap headache. Furthermore, RCVS should be differentiated from central nervous system vasculitis. However, it is especially difficult to distinguish RCVS from the cerebral involvement of multisystem vasculitis when there is a positive result in the serologic test for autoantibodies. We report a case of RCVS with hidden breast cancer in which ischemic stroke and cortical subarachnoid hemorrhage were observed earlier than vasoconstriction, and there were positive autoantibodies.

Keywords: Autoantibody, cerebrovascular accident, malignancy, reversible cerebral vasoconstriction syndrome

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by the sudden onset of a thunderclap-like headache (TCH), with or without focal neurological deficits and seizures.[1,2] Reversible segmental cerebral artery vasoconstriction on angiography is the essential component for diagnosing RCVS. And ultimately, 81% of patients with RCVS develop brain lesions including posterior reversible encephalopathy syndrome (9%–14%), brain edema (38%), ischemic strokes (4%–54%), cortical subarachnoid hemorrhage (SAH; up to 34%), intracerebral hemorrhage (up to 20%), or subdural hemorrhage (2%).[3,4] Vasoconstrictions might not be evident during the early stage of RCVS, and TCH can be the only symptom or sign during the first stage. In contrast, most brain lesions (especially, ischemia) occur simultaneously and sequentially with cerebral vasoconstriction. We report a case of an RCVS patient complicated by ischemic stroke and cortical SAH before definite cerebral vasoconstriction and founded hidden malignancy.

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Case Report

A 50-year-old woman had a severe headache with nausea and vomiting 2 days before admission. A brain computed tomography that was taken at the external hospital showed no demonstrable abnormal brain parenchymal lesion. She experienced a severe headache once again during her sleep on the day when she visited our hospital. She underwent a brain MRI and cerebrospinal fluid (CSF) study. Diffusion-weighted images showed tiny high-signal intensity spots at the right caudate head and low-signal intensity at the apparent diffusion coefficient, and she was diagnosed with an acute ischemic stroke [Figure 1a]. The fluid-attenuation inversion recovery image showed subtle high density in the right temporal-occipital sulcus [Figure 1c], and a low-density lesion

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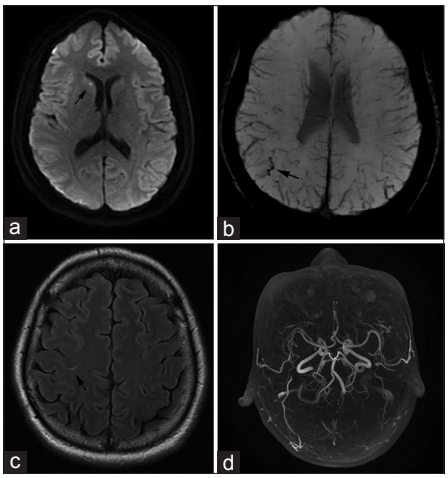

Figure 1: Initial magnetic resonance imaging and magnetic resonance angiography. (a) The axial diffusion-weighted image showed hyperintensity at the right caudate head caused by acute infarction. (b) The serpentine high-signal intensity in the pre- and post-central gyrus was observed in fluid-attenuated inversion recovery, and (c) a low-signal intensity was observed in the susceptibility-weighted imaging, which was a specific finding of cortical subarachnoid hemorrhage. (d) Magnetic resonance angiography showed normal cerebral arteries

along the sulcus was observed with susceptibility-weighted imaging in a similar position [Figure 1b], so it was diagnosed as cortical SAH. Although there were no abnormalities on the initial magnetic resonance angiography (MRA) [Figure 1d], the patient was clinically suspected to have RCVS or central nervous system (CNS) vasculitis. The CSF study, performed while our patient was being treated with simple analgesics, revealed zero white blood cells, two red blood cells, CSF protein 27 mg/dL, and CSF glucose 58 mg/dL. Xanthochromia and microbiology studies were negative.

She was treated with nimodipine from the 1st day of hospitalization after performing autoantibodies and immunologic studies. Anti-Sjögren's syndrome A (SSA)/SSB, antinuclear antibody (ANA), and perinuclear antineutrophil cytoplasmic antibody (P-ANCA) were detected, but clinically, there was no suspicion of rheumatic and organ-specific autoimmune diseases (ADs). The frequency and intensity of a headache were significantly reduced, while we continued to treat the patient with nimodipine. An MRA on 5 days after admission revealed multifocal narrowing of intracranial arteries (both middle cerebral artery, anterior cerebral artery, and posterior cerebral artery) [Figure 2a]. Narrowing of blood vessels was still observed in the MRA taken on the 15th day of symptom onset [Figure 2b]. We maintained nimodipine for 2 months. Breast cancer (invasive ductal carcinoma type) was found and treated during the workup to find the reason why the autoantibody test was positive. A follow-up MRA performed 2 months later showed that previously narrowed vessels had been fully improved [Figure 2c]. The patient did not report any recurrence of symptoms for an 8-month follow-up.

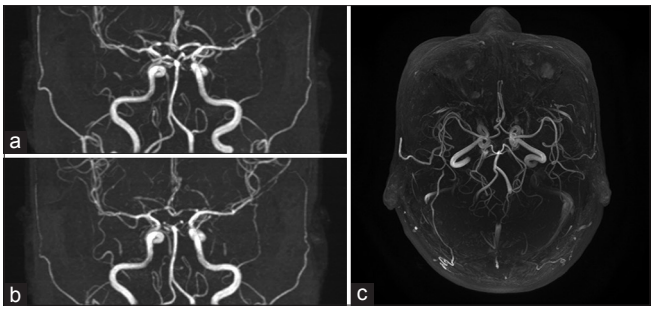

Figure 2: (a) The multifocal stenosis of intracerebral arteries (both middle cerebral artery, anterior cerebral artery, posterior cerebral artery) was observed on the magnetic resonance angiography performed 5 days later. Stenosis progressed compared with the previous study. (b) The stenosis of both middle cerebral arteries was improved, but both anterior cerebral arteries and posterior cerebral arteries still deteriorated compared with the previous study on magnetic resonance angiography performed on the 13th day after stroke onset. (c) The multifocal narrowing of the intracerebral arteries, which were observed in the previous studies, is no longer seen on magnetic resonance angiography performed 2 months after the stroke onset

Discussion

A thunderclap headache is defined as an explosive, severe, and unexpected headache with peak intensity at the time of onset. When a headache of this type occurs, the diseases that need to be distinguished are idiopathic benign recurrent headache disorder, SAH, cerebral venous thrombosis, dissection, pituitary apoplexy, spontaneous intracranial hypotension, and hypertensive encephalopathy.[5] In addition, RCVS should be differentiated as in our case.

RCVS is characterized by a thunderclap headache combined with reversible segmental vascular constriction and was proposed as a unifying term in 2007 by a panel of experts.[6] Other characteristic findings of RCVS are normal or almost normal CSF analytical findings and angiographic reversibility within 12 weeks of onset.[7] The diagnosis of primary (isolated) vasculitis of the CNS, which should be distinguished from RCVS, is particularly difficult. The multisystem diseases that can cause cerebral vasculitis are rather stereotypes. Serologic tests are usually abnormal among patients with cerebral involvement of multisystem vasculitis but usually normal among those with isolated vasculitis of the CNS. Moreover, findings on examination of the CSF include lymphocytosis, increased protein, elevated inflammatory markers, and normal glucose in a patient with vasculitis. When the disease is diagnosed as vasculitis, we should use steroids. Conversely, the use of steroids in RCVS is even more cautious because there is a trend that is associated with poor prognosis of the disease.[4]

In our case, RCVS was suspected due to ischemic stroke and cortical SAH after a characteristic thunderclap headache. Cortical SAH along convexity frequently occurs in RCVS patient aged 60 years or younger.[4,8] Cortical bleedings could result from rupture or reperfusion injuries affecting small

arteries of the leptomeninges as an ongoing process of the illness and are unlikely to account for the diffuse cerebral vasoconstriction and dilatation.[4] However, SAH found in patients with RCVS is usually easy to distinguish from aneurysmal SAH, which is not related to small cortical bleeding and causes a localized vasospasm near the ruptured aneurysm.

Initial MRA was confusing in that it did not show vasoconstriction. However, reversibility of vasoconstriction was confirmed by serial follow-up MRA after the use of nimodipine. Nimodipine, verapamil, and magnesium sulfate are used for 4–12 weeks to relieve arterial narrowing, which is the idea that complete or substantial normalization of arteries was shown by follow-up indirect or direct angiography within 12 weeks of clinical onset.[6,9] In our case, the follow-up MRA was performed 2 months after the onset of a headache, and the nimodipine was stopped after confirming normalization of vascular contraction.

Another confounding factor for this case was the serologic test results. In this patient, anti-SSA/SSB, ANA, and P-ANCAs were detected. Systemic vasculitis includes an acute inflammatory response with raised erythrocyte sedimentation rate and increased values of C-reactive protein in the laboratory test and represents various nonspecific systemic manifestations which include fever, night sweats, malaise, weight loss, arthralgia, and myalgia.[10,11] In primary angiitis of the CNS, serum findings usually are normal, but CSF analysis manifests inflammatory findings. These include a mild lymphomonocytic pleocytosis or protein elevation in more than 90% of patients.[11] However, in our case, there was no suspicion of systemic vasculitis or rheumatic disease, and normal findings were observed in the CSF study. Hence, we suggest that RCVS is more preferential than vasculitis.

Finally, breast cancer was observed later in our case. In some patients, vasculitis that can occur during or before cancers that have shown autoantibodies in malignancies strongly suggests that cancer sera exhibit immunologic features that are common in rheumatic ADs.[12] Malignancies associated with vasculitis were predominantly hematologic, including myelodysplastic syndromes and lymphoid malignancies, followed by solid tumors.[13] In the study for the relationship between vasculitis and malignancy,[13] 24 cases (36.9%) of solid tumors with vasculitis were found in total 60 patients, and only two patients (3.1%) were diagnosed as breast cancer with vasculitis. Moreover, in the biological test, ANCA was observed in 20.4%, ANA in 14%, and rheumatoid factor in 6.7%.[13] In another study, the ANA blood concentration was significantly increased in all breast cancer patients (0.7–1.8 U/ml) compared with control group (0.3–0.6 U/ml), irrespective of the grade or stage.[14] We think that the positive autoantibody of our patient may be associated with breast cancer. However, considering the clinical course, imaging findings, and result of CSF and serologic test of the patient, it is thought to be a reasonable finding for RCVS rather than cancer-related vasculitis. The patient had a dramatic response to nimodipine and did not report any recurrence of symptoms for an 8-month follow-up.

Conclusion

RCVS should be considered for an acute stroke patient with a thunderclap headache even if the initial MRA is observed as normal. As in our case, we should always be concerned about the presence of an underlying malignancy in patients with RCVS, especially when the patient has a positive result for an autoantibodies test which is not related to vasculitis or rheumatic disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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