Reversible Cerebral Vasoconstriction Syndrome Presenting as Subarachnoid Hemorrhage, Reversible Posterior Leukoencephalopathy, and Cerebral Infarction

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by acute severe headache with or without additional neurological symptoms and reversible cerebral vasoconstriction. Unruptured aneurysm has been reported in some cases with RCVS. We report a severe case of a 53-year-old woman with RCVS having an unruptured cerebral aneurysm and presenting as cortical subarachnoid hemorrhage, reversible posterior leukoencephalopathy syndrome, and cerebral infarction. She was successfully treated with corticosteroids and a calcium channel blocker and the aneurysm was clipped. Her various complications are due to the responsible vasoconstriction that started distally and progressed towards proximal arteries. This case demonstrates the spectrum of presentations of RCVS, a clinically complicated condition.

Key words: vasoconstriction, Call-Fleming syndrome, cortical subarachnoid hemorrhage, aneurysm, cerebral infarction, reversible posterior leukoencephalopathy syndrome


Introduction

Reversible cerebral vasoconstriction syndrome (RVCS) is characterized by the sudden onset of headache, with or without neurological deficits, associated with multifocal, reversible narrowing of cerebral arteries on angiography (1). It has been described under various names including Call-Fleming syndrome, benign angiopathy of the nervous system, and postpartum cerebral angiopathy (2-4). It may occur spontaneously or it may be provoked by various precipitating factors, the most common being postpartum and exposure to various vasoactive substances (1, 5). In a study of a large series of 67 patients with RCVS, various complications with different time courses were observed. Cortical subarachnoid hemorrhage (cSAH) (22%), intracerebral hemorrhage (6%), seizures (3%), and reversible posterior leukoencephalopathy syndrome (RPLS) (9%) were early complications, occurring mainly within the first week. Ischemic events, such as cerebral infarction (4%), occurred significantly later than hemorrhagic events, mainly during the second week (6). However, the combination of nonaneurysmal SAH and intracerebral lesions is not necessarily typical; these we know as severe manifestations of RCVS (7). In addition, unruptured aneurysms have been reported in some patients with RCVS, but no clear causal relationship has been documented (8-14). Here, we report on the case of a severe RVCS patient with an unruptured cerebral aneurysm and presenting with SAH, RPLS, and cerebral infarction.

Case Report

A 53-year-old woman with a history of hypertension was admitted to a nearby neurosurgical hospital because of a sudden-onset severe headache associated with nausea, reaching peak intensity within one minute. The headache occurred while walking. The headache was unusual for her, and there was no prior history of migraine or other thunder
Figure 1. (A) Non-enhanced CT image of the head of the patient shows minor subarachnoid hemorrhage (SAH) overlying the right superior frontal surface (white arrow). (B) Non-enhanced CT image of the head on day 6 shows hypodensity in the right predominant parieto-occipital lobes bilaterally (white arrowheads). (C) Non-enhanced CT image of the head on day 12 shows expansion of hypodense lesions (white arrowheads), and disappearance of cSAH seen on the earlier images. (D) Digital subtraction angiography (DSA) anteroposterior projections of the right carotid artery shows multifocal anterior and middle cerebral arterial segmental vasoconstriction (black arrows). (E) DSA lateral projection of the right carotid shows multifocal anterior and middle cerebral arterial segmental vasoconstriction (black arrows). (F) DSA anteroposterior projection of the left carotid shows segmental vasoconstriction (black arrows). (G) DSA lateral projection of the left carotid shows a 5 mm left internal carotid artery aneurysm (black arrowhead).

clap headache, and no history of vasoconstrictive drug use. On admission, she was alert. There were no focal neurologic signs. A rigidity of the neck with the Kernig sign was absent. Initially, a computed tomography (CT) image of the brain showed cSAH localized to a cortical sulcus in the right superior frontal lobe (Fig. 1A). Digital subtraction angiography (DSA) on the same day demonstrated an unruptured aneurysm (5 mm diameter) located on the ophthalmic segment of the left internal carotid artery (ICA). There was no extravasation of contrast from the aneurysm on DSA. DSA did not show typical segmental vasoconstriction in the anterior and posterior circulations. There was no sinus
thrombosis or arteriovenous malformation. During DSA, she had secondary generalized seizures. After intubation and ventilation, these seizures were suppressed by intravenous barbiturate administration. Two days after the onset of severe headache, the trachea was extubated with the patient awake. She had mild headaches, which gradually improved in two weeks. She had never developed severe and sudden headaches. She had never experienced recurrent seizures. A brain CT performed on day 6 showed hypodense lesions in both the parieto-occipital lobes, and then repeat brain CT on day 12 showed a gradual expansion of these lesions (Fig. 1B, 1C). The brain CT on day 12 showed the disappearance of small cSAH over the right superior frontal lobe (Fig. 1C). DSA was performed on day 13, which revealed multiple segments of irregularity consisting of narrowed areas of multiple branches of both internal carotid arteries and an unruptured saccular aneurysm of the left ICA (Fig. 1D-G). She was immediately referred to our hospital under suspicion of primary angiitis of the central nervous system (PACNS). On admission, her temperature was 36.5°C and her pulse was 109 beats per minute. Her blood pressure was 200/100 mmHg. On physical examination, the breath sounds were vesicular, and there were no rales or rhonchi. Cardiovascular examination revealed normal heart sounds, with no audible murmurs. Ophthalmologic examination excluded retinal vasculitis or inflammation. On neurologic examination, she was alert and oriented. There was no aphasia, agnosia, or apraxia. Motor examination revealed mild weakness (Medical Research Council [MRC] grade, 5-/5) of the distal part of the left upper extremity. A stiff neck and the Kernig sign were absent. The remaining neurological examination findings were normal. Routine hematological and biochemical test findings were entirely normal. The findings of coagulation function tests were normal. The anti-phospholipid antibodies, including the lupus anticoagulant and anti-cardiolipin antibodies were negative. The rheumatoid factor and anti-nuclear, anti-double stranded DNA, anti-SSA, anti-SSB, and anti-neutrophil cytoplasmic antibodies were negative. The level of the angiotensin-converting enzyme was within the normal range. Hepatitis B and C screening showed negative results. Cerebrospinal fluid (CSF) analysis showed no xanthochromia. CSF analysis also showed a protein level of 87 mg/dL, a glucose level of 64 mg/dL, and a leukocyte count of 1/μL. Electrocardiography showed a sinus rhythm at a rate of 106 beats per minute without specific ST-segment and T-wave abnormalities. Her transthoracic echocardiography on admission revealed no identifiable wall motion abnormality. Diltiazem infusion was initiated concurrently with hypervolemic therapy using 25% human albumin. Her blood pressure was maintained at approximately 140-180/80-100 mmHg. On day 14, she had severe weakness of the left upper extremity (MRC grade, 1/5). She also had weakness of the left lower extremity (MRC grade, 3-/5) and of the right lower extremity (MRC grade, 1/5). Babinski’s sign was present bilaterally. Computed tomography angiography (CTA) showed vasoconstrictions in the right anterior cerebral artery (ACA), the branches of both middle cerebral arteries (MCAs), and posterior circulation (Fig. 2). The segmental dilatations of the bilateral vertebral arteries were observed (Fig. 2). All spine MRI findings were normal. On day 17, her consciousness level gradually deteriorated (E3M6V5). Her blood pressure occasionally increased to approximately 190-200/100-110 mmHg from baselines of 140-180/80-100 mmHg. A portable electroencephalography showed normal findings. Brain MRI with fluid-attenuated inversion recovery imaging (FLAIR), performed on day 17 demonstrated hyperintense lesions in the bilateral parieto-occipital lobes and the frontal cortices and subcortices (Fig. 3A, 3B). Brain MRI with diffusion-weighted imaging (DWI) on day 17 demonstrated hyperintense lesions in the bilateral parieto-occipital lobes and the right frontal lobe, which are indicative of cytotoxic edema (Fig. 3C, 3D). Conversely, some of the right parieto-occipital hyperintense lesions on FLAIR images were hypointense, and the left frontal hyperintense lesion on FLAIR images was isointense on DWI, which are indicative of vasogenic edema (Fig. 3C, 3D). MRA showed poor vascularization of the bilateral anterior and posterior circulations, with partial dilatations of the bilateral vertebral arteries (Fig. 4A). Her symptoms gradually worsened and the probability of developing PACNS was found. She was started on intravenous methylprednisolone (three days, 1 g/day), followed by a tapering course of oral prednisolone. On day 24, her consciousness level improved (E4M6V5). On day 25, diltiazem infusion was stopped and then she received oral amlopidine (5 mg/day). Her blood pressure decreased to approximately 120-150/60-90 mmHg and did not exceed 160/100 mmHg. The FLAIR hyperintense lesions in the bilateral frontal and parieto-occipital lobes on day 17 became less hyperintense on FLAIR images on day 29 (Fig. 3E, 3F). MRA on day 29 showed partial resolution of cerebral arterial narrowing (Fig. 4B). We diagnosed her as having RCVS.
on the basis of the vasoconstriction with reversibility in addition to the rapid development of symptoms, CSF results, and brain imaging findings. On day 33, ophthalmologic examination disclosed right inferior quadrantanopia. On day 51, her only abnormalities were right inferior quadrantanopia and mild paraparesis. There has been no aphasia, agnosia, or apraxia throughout her clinical course. She was transferred to a rehabilitation hospital. The surgical treatment of the unruptured aneurysm was deferred because of the fear of further aggravation of cerebral infarcts due to vasospasm in addition to her disagreement to the obliteration of the aneurysm. When she was discharged from the rehabilitation hospital, she was able to walk without assistance. Thirty months after the onset, a follow-up MRI with FLAIR showed chronic infarctions in the right frontal and bilateral parieto-occipital lobes (Fig. 3G, 3H) (15). The FLAIR hyperintense lesions in the left frontal lobe and part of the right parieto-occipital lobe, which are considered indicative of vasogenic edema were reversible. The decreased hyperintensity in the right frontal lobe and bilateral parieto-occipital lobes on day 29 was a fogging effect rather than simply a reduction in the amount of swelling (Fig. 3E, 3F) (16). Her MRA findings were normal excluding the unruptured aneurysm of the left ICA, which is consistent with the diagnosis of RCVS (Fig. 4C). Forty-two months after the onset, the aneurysm was successfully clipped. Using an operating microscope during surgery, we found no evidence of recent or past bleeding around the aneurysm.

**Discussion**

RCVS is characterized pathophysiologically by a prolonged but reversible vasoconstriction of (mostly) medium- and large-sized cerebral arteries that constitute the anterior circulation and posterior circulation. Patients with RCVS are typically women between the ages of 20 and 50 years (1). The common clinical presentation is hyperacute severe headache, often called a “thunderclap headache” with or without focal neurological deficits or seizures. However, the differentiation between RCVS and vasculitis such as PACNS by MRI and angiography is sometimes difficult, as in the present case (17). Therefore, the diagnosis of RCVS should be made on the basis of the timely demonstration of complete or near-complete reversibility of vasoconstriction within 3 months, in addition to the typical clinical findings and results of adjunctive studies, such as CSF examination (1). We diagnosed her as having RCVS on the basis of severe, acute headache with typical neurologic symptoms, near-normal

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**Figure 3.** Brain magnetic resonance imaging (MRI) FLAIR and diffusion-weighted sequences. (A and B) The MR images on day 17 show multiple cortical and subcortical hyperintense lesions in bilateral parietal, occipital, and frontal regions. (C and D) The diffusion-weighted images on day 17 at similar levels show hyperintense lesions in the right frontal lobe and bilateral parieto-occipital lobes, consistent with cytotoxic edema (large arrows). There are hypointense and isointense lesions (arrowheads), which were hyperintense on FLAIR images, consistent with vasogenic edema. (E and F) The MR image on day 29 shows a lower hyperintensity in the bilateral frontal and parieto-occipital lobes. (G and H) The MR image 30 months later shows chronic infarctions in the right frontal lobe and bilateral parieto-occipital lobes, which is consistent with encephalomalacia (arrows) and gliosis (dotted arrows).
CSF findings, and typical vasoconstriction with reversibility, whose complete resolution was slow.

SAH is not infrequently encountered in RCVS, perhaps 1 in 4 cases, and has already been reported in several isolated RCVS cases (9, 18-25). Differentiating SAH due to RCVS from that due to other causes, particularly aneurysmal SAH, is crucial. SAH due to RCVS does not correlate with the site and severity of vasoconstriction in contrast with aneurysmal SAH, which does correlate with the site and severity of vasoconstriction. In RCVS, subarachnoid blood typically overlies the cortical surface and is usually minimal or moderate in amount, whereas the vasoconstriction is widespread and multifocal, affecting medium- and large-sized arteries remote from the site of bleeding (11, 26). In contrast, the blood in aneurysmal SAH tends to be more prominent near the ruptured aneurysm where it directly triggers the vasoconstriction, which is thus not multifocal but affects only one or two medium-sized arteries close to the site of bleeding. In addition, there is a strong relationship between the amount of cisternal blood seen on the initial CT images, and the risk of development of vasoconstriction; for uncertain reasons, the presence of a large amount of blood in the lateral ventricles adds to this risk (27). The amount of SAH was minimal in this patient; the possibility of minor leaking of blood from the left IC aneurysm is also considered as a differential diagnosis (28). However, the localized subarachnoid blood in the right frontal lesion in this patient was clearly remote from the left IC aneurysm. Moreover, it appears extremely unlikely that small localized bleeding at the surface of the brain could explain the subsequent diffuse vasoconstriction in this patient (29). It has been considered that cSAH in RCVS is due to the rupture of small pial vessels caused by a sudden increase in blood pressure, combined with the failure of cerebrovascular autoregulatory mechanisms (30).

Thus, it is highly likely that cSAH in the present case was caused by a distal cerebral vasculature but not from the left IC aneurysm. The findings of this patient support the underlying mechanism of RCVS: that is, an abnormal process initially affects very small cerebral arteries (7). This mechanism can also explain why the first angiography of the pre-
sent patient did not show typical vasoconstrictions; it was performed too early to detect typical vasoconstriction in the medium- and large-sized arteries (26).

The subsequent radiological abnormalities in the present case are unique. It is highly likely that the parenchymal lesions revealed by the series of CT and MRI were consistent with RPLS with cerebral infarction. Both vasogenic edema and cytotoxic edema, clearly differentiated by FLAIR and DWI, were observed in the parenchymal lesions of this patient, although ADC maps were not obtained. The lesions in the left frontal lobe and right parieto-occipital lobe showing reversibility on FLAIR images and iso- or hypointensity on DWI had features of RPLS. On the other hand, the lesions in the right frontal lobe and bilateral parieto-occipital lobes showing hyperintensities on DWI had features of infarction. RPLS is characterized by usually reversible, posterior-predominant white and gray matter lesions (vasogenic edema) on brain MRI (31). Interestingly, similar features exist between RPLS and RCVS patients (24). Clinical features such as sudden-onset headaches, seizures, and visual deficits are common in patients with RPLS and RCVS. The pathological features of RPLS and RCVS partially overlap including disturbances in cerebral vascular tone. The pathological features of RPLS have been related to endothelial dysfunction and failure of cerebral autoregulation involving distal arteries and capillaries, whereas patients with RCVS have a more proximal cerebral vasoconstriction (24). RPLS was found in 9% of the patients with RCVS reported by Ducros and coworkers (6, 7) and several other cases have been reported (24, 25, 32-34). In the present patient, the posterior dominant hypodense lesions were observed by CT of the head. It is considered that parenchymal lesions involving RPLS appeared to develop 6 days after the onset of severe headache. The exact pathophysiology of RPLS is unknown, but three theories are debated (31). First, the current more widely accepted theory suggests that severe arterial hypertension leads to a failure of autoregulation, subsequently causing hyperperfusion with endothelial injury/vasogenic edema. Second, the earlier original theory suggests hypertension or rapid blood pressure changes lead to cerebral vasoconstriction, ischemia, and subsequent brain edema. Third, a more recent theory is that T cell activation, endothelial cell activation, and inflammatory cytokine responses may trigger cerebral vasoconstriction leading to hyperperfusion and brain edema. As the trigger of RPLS in this patient, it is possible that vasoconstriction and hyperperfusion caused brain ischemia and subsequent brain edema. In addition, the efficacy of steroid pulse therapy with a calcium channel blocker for reducing edema suggests that the third theory is also reasonable. One of the features of the present patient is cerebral infarctions in the right frontal lobe and bilateral parieto-occipital lobes. Cerebral infarction has also been reported in RCVS cases, which occurs later, mainly during the second week (6). However, the complicated clinical course of having cSAH, RPLS, and infarction, as seen in the present case is rare. To the best of our knowledge, only two cases have been reported (7, 25). There are at least two potential mechanisms for the subsequent bilateral, posterior-predominant infarctions in this patient. In the areas of massive edema, increased tissue pressure eventually impairs the microcirculation and leads to infarction (35). In RCVS, the underlying disturbance in the control of cerebral vascular tone first involves small distal arteries responsible for PRLS, and then progresses toward medium- and large-sized arteries responsible for infarctions (6). The most plausible mechanism in this patient is that severely decreased cerebral blood flow due to vasoconstriction of medium- and large-sized arteries led to irreversible changes. Although some of the brain parenchymal lesions of this patient were irreversible, the expansion of the parenchymal lesions owing to vasoconstriction was markedly inhibited by the treatment with methylprednisolone pulse and a calcium channel blocker (36, 37). However, randomized controlled trials do not yet exist, and further studies will be necessary to establish the standard treatment for RCVS.

It is unclear whether the unruptured aneurysms are incidental findings or whether they are indicative of an underlying abnormality in vessel tone (23). According to a study of a large French series, unruptured aneurysms were recognized in 6% of RCVS patients, which is not much more frequent than in the general population (26). The prevailing view is that these unruptured aneurysms are incidental (36).

In conclusion, the development of cSAH, RPLS, and cerebral infarction with different time courses in the present patient were caused by the responsible vasoconstriction of RCVS, which started distally and progressed towards proximal arteries. To the best of our knowledge, this is the first report of a case of RCVS in which the unruptured aneurysm was successfully treated after the remarkable recovery from a serious and complicated clinical course.

The authors state that they have no Conflict of Interest (COI).

References

7. Ducros A, Fieidler U, Porcher R, Boukobza M, Stapf C, Bousser MG. Hemorrhagic manifestations of reversible cerebral vasocon-