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Leuprolide acetate pseudomenopause therapy as a cause of reversible cerebral vasoconstriction syndrome

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1. Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by thunderclap headache and radiological findings of multifocal reversible cerebral vasoconstriction, which usually resolve in 3 months [1]. Around 80% of cases occur in women and peak at age around 42 years [1].

Although the pathophysiology is not well understood, vasoactive drugs and postpartum vasculopathy are known to be common precipitating factors [1]. Abrupt decline in estrogen after delivery might trigger sudden vasoconstriction in the brain. Additional RCVS cases associated with probable estrogen reduction other than those following recent childbirth have also been reported [1]. Herein, we report a case of RCVS following pseudomenopause therapy with leuprolide acetate injection for uterine adenomyosis, and consider the mechanism, including estrogen reduction and incidence of RCVS.

2. Case report

A 42-year-old woman visited the department of gynecology in our hospital due to lower abdominal pain and menorrhagia. She had a past medical history of migraine. She was diagnosed with uterine adenomyosis, planned for hysterectomy, and received a subcutaneous leuprolide acetate injection once every 4 weeks in order to stop menstruation and shrink the volume of adenomyosis. This is referred to as pseudomenopause therapy.

Ten weeks later, after having received 3 times of subcutaneous 1.88 mg leuprolide acetate injection in total, she was admitted to the hospital and was scheduled for a total abdominal hysterectomy the following day. On the night of admission, soon after defecation, she felt a sudden crushing headache, which reached maximum intensity within a minute, and vomited multiple times. She described it is the most sharp and painful headache she ever had, and that it was totally different from an ordinary migraine attack. Her blood pressure, heart rate, and body temperature were 154/100 mmHg, 69 beats/min, and 35.8 °C, respectively. Head computed tomography (CT) showed a cortical subarachnoid hemorrhage (SAH) along the convexity, including the cerebral falx and left parietal region (Fig. 1A). Head magnetic resonance angiography (MRA) showed no cerebral aneurysm but did show multiple constrictions in the left anterior and bilateral posterior cerebral arteries (Fig. 1B, C). Blood testing showed low levels of estradiol, at < 10 ng/ml, and progesterone 0.24 ng/ml, but no other abnormal findings, including negative D-dimer, C-reactive protein, antinuclear antibody, anti-neutrophil cytoplasmic antibody, and anti SS-A and anti SS-B antibodies.

In view of the cortical SAH and cerebral artery vasoconstriction, we considered RCVS, primary angiitis of the central nervous system (PACNS), cerebral venous sinus thrombosis, and latent aneurysm rupture in the differential diagnosis. PACNS was unlikely because the characteristic features of thunderclap headache and convexity SAH were relatively uncommon in this syndrome. CT angiography and venography showed no findings of cerebral aneurysm or venous sinus thrombosis. Thus, we first considered RCVS and started continuous intravenous administration of 0–1.5 μg/kg/min of nicardipine and oral verapamil 120 mg per day. A nonsteroidal anti-inflammatory drug was prescribed per request. For a couple of days, she experienced severe

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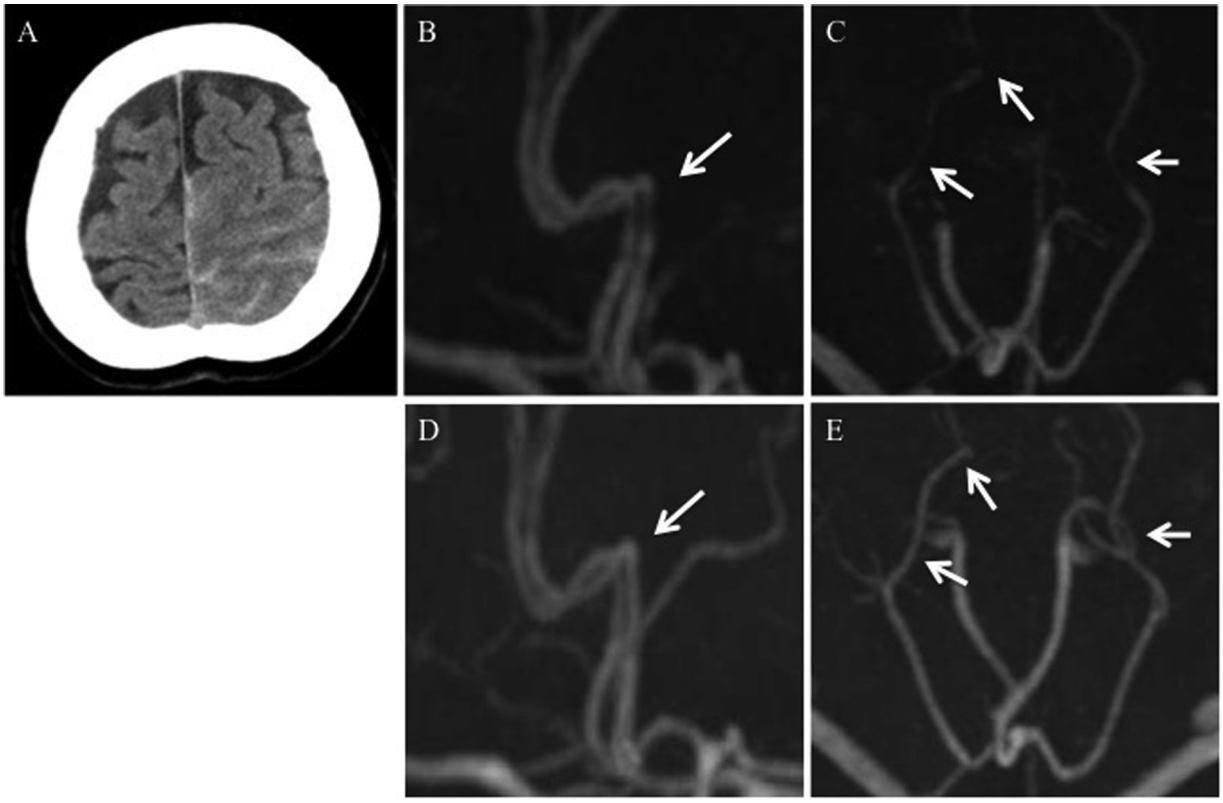

Fig. 1. Brain imaging findings. (A) Computed tomography showing cortical subarachnoid hemorrhage in cerebral falx and left parietal region. (B) Magnetic resonance angiography (MRA) showing no cerebral aneurysm and vascular constriction at the left anterior cerebral artery (arrow). (C) MRA showing multiple vascular constrictions at the bilateral posterior cerebral artery (arrows). (D and E) MRA 1 month after onset showing significant improvement of vasoconstrictions (arrows).

headache and nausea; however, the symptoms gradually improved. Ten days later, her headache attacks had resolved. One month later, MRA showed improvement of the vasoconstriction (Fig. 1D, E), which confirmed the diagnosis of RCVS, and the patient had no neurological deficit. The patient has had no recurrence for over half a year.

3. Discussion

The underlying cause was thought to be administration of leuprolide acetate for RCVS in this case. Leuprolide acetate is a gonadotropin-releasing hormone, which generally causes downregulation of the gonadotropin-releasing hormone receptor in the pituitary, thereby reducing gonadotropin release and leading reduced estrogen secretion from the ovary [2]. Based on this mechanism, leuprolide acetate can be used to treat estrogen-dependent gynecological diseases, including uterine fibroids and adenomyosis. Indeed, the patient's serum estrogen at RCVS onset was low. We considered 2 mechanisms for the association between estrogen decrease and cerebral vasospasm. First, estrogen is a vasodilator that acts on cerebral circulation, thus promoting the production of vasodilators, such as nitric oxide and prostacyclin [3]. Accordingly, reduction of estrogen may lead to cerebral vasoconstriction. It is known that the postpartum state is a major precipitant of RCVS [1], and that estrogen decreases rapidly in this state. Previous literature indicated that acute estrogen reduction due to factors other than the postpartum state, including oral contraceptive pill use, intrauterine insemination, and hysterectomy with bilateral salpingo-oophorectomy have also been shown to cause RCVS [1]. Second, estrogen affects cerebrovascular mitochondrial function by enhancing the capacity for oxidative phosphorylation, while at the same time decreasing the formation of reactive oxygen species [3]. Mitochondria play a notably important role in producing high levels of energy for the critical transporters of the blood-brain barrier (BBB). Therefore, loss of estrogen could eventually compromise the BBB. Recently, an association between BBB breakdown and RCVS has been reported [4]. Hence, mitochondrial dysfunction caused by estrogen reduction is possibly correlated with the BBB breakdown observed in RCVS. Based on the above, we suggest that a relatively acute drop in serum estrogen levels due to pseudomenopause therapy could have led to RCVS occurrence.

Migraine patients require careful evaluation to detect RCVS ictus. In migraineurs, a new-onset headache symptom of RCVS may be misdiagnosed as a severe migraine attack; thus, a careful interview is vital to elicit a pathognomonic thunderclap headache or neurological deficit. This patient complained of rapid-onset headache of unprecedented severity. Further, acute migraine treatment with triptans, ergots, and dihydroergotamine are major precipitants of RCVS or can exacerbate vasoconstriction when prescribed for unrecognized RCVS headache [5]. It is considered that migraine is a possible risk factor for intracranial hemorrhage in RCVS [1], as in this patient's clinical course.

4. Conclusion

We described a case of RCVS following pseudomenopause therapy. Given that estrogen is a cerebral vasodilator and plays a role in maintaining the BBB, we suggest a relationship between blood estrogen reduction and RCVS pathogenesis.

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Informed consent

Written informed consent was obtained from the patient.

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Declaration of Competing Interest

None.

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