[CASE REPORT]

Posterior Reversible Encephalopathy Syndrome and Reversible Cerebral Vasoconstriction Syndrome after Rapid Blood Transfusion

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Abstract:
We herein report a case of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) that occurred immediately after blood transfusion. A 64-year-old Japanese woman was diagnosed with liver cirrhosis due to hepatitis B 2 years ago. She was admitted to our hospital with hemorrhagic shock due to esophageal variceal rupture. She was hospitalized with rapid blood pumping transfusion, after which consciousness disorder appeared, and her blood pressure suddenly increased. Magnetic resonance imaging revealed PRES and RCVS. We speculated that hypoalbuminemia and blood transfusion might have been involved in the development of PRES and RCVS.

Key words: posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, blood transfusion, magnetic resonance imaging, hypoalbuminemia

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Introduction
Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological entity that presents with acute neurological symptoms, such as headache, encephalopathy, seizures and blood pressure fluctuations (1). Brain magnetic resonance imaging (MRI) usually reveals vasogenic edema predominantly involving the bilateral parieto-occipital regions. Various factors can be triggered to result in the development of PRES, such as hypertension, renal failure, sepsis and immunosuppressive therapy.

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by thunderclap headache and reversible constriction of the cerebral arteries (2). RCVS and PRES share many clinicoradiographic features, suggesting similar pathophysiological mechanisms (2).

We herein report a case of PRES and RCVS that occurred immediately after blood transfusion for hemorrhagic shock.

Case Report
A 64-year-old Japanese woman had been diagnosed with chronic hepatitis B 7 years ago. The abdominal echogenic findings from two years ago indicated liver surface blunting and irregularity, portal vein dilation and a small amount of ascites. She was diagnosed with liver cirrhosis at that time. She was admitted to our hospital with hemorrhagic shock due to esophageal variceal rupture. On arrival, her consciousness was clear, her blood pressure was 82/47 mmHg, and her heart rate was 86 beats per minute. Her hemoglobin level was 8.8 g/dL, platelet count was 10.1×10⁴/μL, prothrombin time% was 65.3%, total bilirubin was 0.5 mg/dL, ammonia was 79 μg/mL, aspartate aminotransferase was 40 U/L, alanine aminotransferase 25 U/L, and albumin was 2.9 g/dL. Her liver cirrhosis was classified as Child-Pugh A.

However, after emergent endoscopic varicocele ligation, her blood pressure decreased to 58/21 mmHg, and her heart rate increased to 111 beats per minute, and she entered a coma. At that time, her disturbance of consciousness was thought to have been caused by hemorrhagic shock. She re-
ceived transfusion of 6 units of blood for 5 minutes. Her blood pressure increased to 169/72 mmHg at 1 hour after the transfusion; however, she remained in a coma. She was continuously administered high-dose albumin (37.5 g) for 3 hours and 12 units of fresh-frozen plasma (FFP) for 12 hours. Her blood pressure increased significantly to 222/86 mmHg the next day. Nicardipin, a calcium antagonist, was started (continuous intravenous infusion of nicardipin 2 mg/h), but the reduction in her blood pressure was insufficient. Four days after the consciousness disorder appeared, abnormal lesions in the bilateral cerebral hemisphere (Fig. 1A) were found on head computed tomography along with severe quadriplegia. Brain MRI demonstrated high intensities on fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 1B) of the bilateral frontotemporal and parieto-occipital lobes. Increased apparent diffusion coefficient (ADC)-map changes were observed in the bilateral frontotemporal and parieto-occipital lobes (white arrowheads) with decreasing changes linearly covering subcortical lesions in the right frontal lobe, the left frontal lobe and the left parietal lobe (red arrowheads) on the fourth day of admission (Fig. 1C). On diffusion-weighted imaging (DWI) (Fig. 1D), areas of hyperintensity were noted in the bilateral frontotemporal and parieto-occipital lobes with areas of low intensity around the subcortical lesion in the right frontal lobe and the left parietal lobe (arrowheads). MRI perfusion with arterial spin labeling (ASL) clearly demonstrated hyperperfusion in the area corresponding to the same sites on DWI (Fig. 1E). MR angiography showed bilateral middle cerebral artery (M1) (Fig. 2A; arrowheads), bilateral posterior cerebral artery (P2) (Fig. 2C; arrowheads) and bilateral anterior cerebral artery (A2 and A3) stenoses (Fig. 2E; arrowheads). A cerebrospinal fluid examination indicated significant albuminocytologic dissociation, with a protein concentration of 433 mg/dL, but the reduction in her blood pressure was insufficient. Electroencephalography (EEG) indicated right-dominant diffuse high-amplitude sharp waves (Fig. 3A). Based on these EEG findings and the findings of hyperperfusion on ASL in the area corresponding to the same sites on DWI, she was diagnosed with PRES combined with non-convulsive status epilepticus after transfusion and was administered the intravenous levetiracetam (1,000 mg/day).

Her blood pressure normalized after several hours of strict anti-hypertensive treatment (continuous intravenous infusion of nicardipin 5 mg/h). Her consciousness level improved to normal seven days after transfusion. All of the cerebral vessel constriction sites on MR angiography were also improved on the 14th day of admission (Fig. 2B, D and F). Reversible constriction in M1-P2 is known to be common in RCVS and to be associated with the highest risk of PRES (3). It was suspected that RCVS had also been complicated at the time. The ADC-map abnormalities (Fig. 1F) and DWI findings showed a reducing trend, while the hypointense lesions on DWI disappeared (Fig. 1G) on the 20th day of admission. ASL signals (Fig. 1H) and abnormal waves of electroencephalography (Fig. 3B) normalized on the 20th day of admission. The ADC-map changes (Fig. 1I) and DWI findings (Fig. 1J) were alleviated; however, a wide range of high-intensity areas remained on FLAIR imaging on the 48th day of admission (Fig. 1K). Severe quadriplegia persisted even at 12 months after the onset of PRES and RCVS.

Discussion

We encountered a case of PRES and RCVS that developed after rapid aggressive blood transfusion. While there have been several reports of PRES and/or RCVS after transfusion in patients with chronic anemia (4-6), the mechanisms underlying the development of PRES and RCVS remain unclear. Most reports have suggested that a rapid increase in the hematocrit level and viscosity after transfusion may have overloaded the mechanisms of cerebral autoregulation, leading to hyperperfusion (4, 5). Many of the previous patients in question developed PRES and/or RCVS at one to two weeks after transfusion for chronic anemia (4, 5). However, PRES developed within one hour from transfusion and a large amount of FFP for severe hemorrhagic shock caused by bleeding from the rupture of esophageal varix in the present case. Zhao et al. described two cases of PRES that developed several days after transfusion for chronic anemia, with PRES occurring only two hours after the last transfusion (6). The authors speculated that the pathophysiology was similar to that of transfusion-related acute lung injury, which is defined clinically as acute noncardiogenic pulmonary edema occurring within six hours after transfusion (6). In transfusion-related acute lung injury, the first event is a clinical disorder that causes activation of the pulmonary endothelium, leading to the sequestration and priming of neutrophils in the lung; hemorrhagic shock may therefore have been the first event in the present case. Blood product transfusion, which is the second event, then activates the primed neutrophils, causing endothelial damage and disrupting the blood-brain barrier, which leads to vasogenic edema (7). The brain would be the only target organ, rather than the lung in the present case.

However, the present case had liver cirrhosis. There have been few reported cases of PRES complicated with liver cirrhosis (8, 9). In both of the reported cases, hyperammonemia was seen in the acute phase. Ammonia reaching the astrocytes is detoxified by glutamine synthetase in the presence of glutamate to form glutamine (10). Glutamine overproduction promotes the swelling of astrocytes, which results in cerebral edema, inducing intracranial pressure. Hyperammonemia has been implicated in the dysregulation of the cerebral blood flow and consequent cerebral vasodilation causing vasogenic edema. Cirrhosis may be accompanied by astrocyte swelling and low-grade cytotoxic cerebral edema, which is associated with the degree of hyperammonemia (11). However, the ammonia level was normal in the present case. The cause of PRES and the association with
Figure 1. Head computed tomography scan 4 days after admission and brain magnetic resonance images 4, 20 and 48 days after admission. (A) Low densities in the right dominant bilateral cerebral hemisphere were found on head computed tomography on the fourth day of admission. (B) Fluid-attenuated inversion recovery (FLAIR) imaging showed high intensities in the bilateral frontotemporal and parieto-occipital lobes on the fourth day of admission. (C) Increased apparent diffusion coefficient-map (ADC) -map changes were observed in the bilateral frontotemporal and parieto-occipital lobes (white arrowheads) with decreasing changes linearly covering subcortical lesions in the right frontal lobe, the left frontal lobe and the left parietal lobe (red arrowheads) on the fourth day of admission. (D) Diffusion-weighted imaging (DWI) showed areas of hyperintensity in the bilateral frontotemporal and parieto-occipital lobes with areas of low intensity around the subcortical lesion in the right frontal lobe and the left parietal lobe (arrowheads). (E) MRI perfusion with arterial spin labeling (ASL) clearly demonstrated hyperperfusion in the area corresponding to the same sites on DWI. The ADC-map abnormalities (F) and DWI findings (G) showed a reducing trend, while the hypointense lesions on DWI disappeared on the 20th day of admission. (H) The ASL signals normalized on the 20th day of admission. The ADC-map changes (I) and DWI findings (J) were alleviated; however, a wide range of high-intensity areas remained on FLAIR imaging on the 48th day of admission (K). FLAIR: Fluid-attenuated inversion recovery, ADC: Apparent diffusion coefficient, DWI: Diffusion-weighted imaging, ASL: Arterial spin labeling
hyperammonemia is unclear.

In addition, hypoalbuminemia was thought to have occurred due to the inhibition of protein synthesis accompanying liver cirrhosis. The presence of vasogenic edema in PRES was significantly associated with decreased serum albumin levels in the present patient. Albumin is a main contributor to the colloid osmotic pressure, reducing the perfusion pressure, which results in retention of fluid in the vessel. Albumin protects vascular endothelial cells from oxidative stress and damage (12). In patients with pediatric nephrotic syndrome with low levels of serum albumin who develop PRES, PRES rapidly abated after the substitution of albumin (13). The present patient was administered a large amount of albumin and FFP after blood transfusion. Kozar et al. showed that FFP decreased endothelial inflammation and hyperpermeability after hemorrhagic shock in in vitro endothelial studies (14), and the early administration of plasma is an important component of damage control resus-

Figure 2. Brain magnetic resonance (MR) angiography findings 4 and 14 days after admission. MR angiography showed bilateral middle cerebral artery (M1) (A; arrowheads), bilateral posterior cerebral artery (P2) (C; arrowheads) and bilateral anterior cerebral artery (A2 and A3) stenoses (E; arrowheads). All of the cerebral vessel constriction sites on MR angiography were also improved on the 14th day of admission (B, D and F; arrowheads). MR: Magnetic resonance
citation, as it improves the outcome in trauma patients with significant hemorrhaging (15). In patients with liver cirrhosis, the transfusion of a large amount of albumin and FFP over a short period may dramatically change the colloid osmotic pressure, and an unusual water volume may be retained in the blood vessels. Hypoalbuminemia due to liver cirrhosis may therefore have been the trigger for the onset of PRES in the present case. Taken together, the amount of FFP, albumin usage and the transfusion time may be key points for preventing the occurrence of PRES.

Furthermore, regarding the MRI findings in the acute phase of present case, for the most part, the abnormal lesions showed vasogenic edema. However, there were some areas that seemed to show cytotoxic edema, and both coexisted. Vasogenic edema is considered to be the main cause of PRES, which results from the impaired autoregulation of the cerebral blood flow and endothelial cell dysfunction. However, in a recent study, DWI of 50 patients with PRES revealed vasogenic edema in 6.9% and cytotoxic edema in 9.1% of the patients. Complete resolution was observed in the patients with cytotoxic edema (16). The presence of restricted diffusion is generally associated with irreversible brain damage and suggests a poor prognosis. Ishikura et al. described the case of two children with PRES who showed hyperintensity on DWI with restricted ADC values; both cases made a full clinical and radiological recovery. The author indicated that cytotoxic edema infrequently coexists with vasogenic edema and is regarded as a severe or advanced lesion due to PRES (17). In another PRES case, epileptic ictal hyperfusion in the areas corresponding to the areas of cortical hyperintensity on DWI with mild restricted ADC values was observed on MRI (ASL perfusion imaging) (18). These findings suggest that acute symptomatic partial epilepsy developed around the epileptogenic PRES lesions before the manifestation of secondary generalized seizure. In the ictal phase, MRI can show transient cerebral lesions with restricted diffusion of early reversible cytotoxic edema. In the present case, most areas of hyperfusion depicted on ASL coincided with the lesions on DWI that showed restricted ADC values and improved in the recovery phase. These transient changes with restricted diffusion of early reversible cytotoxic edema and with hyperperfusion on ASL may have been due to the disruption of the blood-brain barrier after blood transfusion or/and cortical neuronal hyperactivity after non-convulsive status epilepticus as a secondary phenomenon in the present case.

The diagnostic criteria for RCVS were applied in the present case (2), and our patient met almost all of the criteria.
except for the appearance of acute severe headache. In three large case series for RCVS, normal initial CT or MRI findings, any abnormal CT or MRI findings, cerebral infarction and PRES were reported in 55%-88%, 12%-81%, 8%-39% and 9%-38% (19-21). In the present case, the parenchymal lesions were not present in all regions corresponding to the areas of diffuse vascular stenosis, but there was no contradiction in the appearance of brain lesions in RCVS as mentioned above. However, there is also a possibility that such findings have been missed merely due to the time of performing MRI. Indeed, RCVS is known to be seen only in the peripheral blood vessels at the early stage of onset and then gradually shifts to the proximal vessels (2). The numbers of involved first segments (anterior cerebral artery A1, middle cerebral artery M1, posterior cerebral artery P1 and the basilar artery; total 7), second segments (anterior cerebral artery A2, middle cerebral artery M2, posterior cerebral artery P2; total 6) and all arterial segments (total 13) were significantly higher in patients with PRES than those without in RCVS, (3). Furthermore, the sensitivity of indirect findings have been missed merely due to the time of per-
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ripheral vascular stenosis may therefore have been undetectable by MR angiography at the time of the assessment in the present case but may have been detected if cerebral catheter angiography had been performed at an early stage of onset.

In conclusion, we encountered a patient in whom PRES and RCVS developed after rapid blood transfusion. A rapid increase in the hematocrit level and viscosity as well as a pathophysiology similar to transfusion-related acute lung injury might have appeared after transfusion induction the development of PRES and RCVS, with a low level of serum albumin due to liver cirrhosis as the trigger.

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

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