Isolated Posterior Fossa Involvement in Posterior Reversible Encephalopathy Syndrome

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SUMMARY – *Posterior reversible encephalopathy syndrome (PRES) is characterized by reversible vasogenic edema affecting the subcortical white matter of bilateral occipital and parietal lobes. We describe a case of isolated posterior fossa involvement of PRES which occurred during remission induction chemotherapy for T-cell acute lymphoblastic leukemia. Both the brainstem and cerebellum were extensively involved, but the supratentorial structures were completely spared. The follow-up magnetic resonance images revealed reversibility of most lesions. The knowledge of atypical radiological features of PRES is essential for prompt diagnosis.*

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity associated with various conditions such as eclampsia, severe hypertension and cytotoxic medications¹. Clinical manifestations include sudden onset of headache, seizures, hypertension, altered mental status, visual disturbances, vomiting, nausea and focal neurological signs. Radiologically, PRES is characterized by reversible vasogenic edema affecting the subcortical white matter of bilateral occipital and parietal lobes. The diagnosis is based on the clinical and radiological features, reversibility of the lesions, association with conditions known to induce PRES, and exclusion of other conditions which can present with similar features. The diagnosis is achieved without difficulty if these features are fulfilled, but can be challenging if presented with atypical features. Herein we describe a case of isolated posterior fossa involvement in PRES which occurred during remission induction chemotherapy for T-cell acute lymphoblastic leukemia (T-ALL).

Case Report

A ten-year-old girl undergoing remission induction chemotherapy for T-ALL – consisting of four doses of intravenous vincristine (1.5 mg/ m²) and daunorubicin (30 mg/ m²) administered every week, eight doses of intramuscular L-asparaginase (5000 units/ m²) administered every third day, daily oral dexamethasone (10 mg/m²/ day for three weeks and tapered thereafter), and a single dose of intrathecal cytarabine (30 mg), methotrexate (12 mg) and prednisolone (10 mg) administered on day five – complained of headache on the 22nd day after initiation of therapy. The symptom waned soon after, but redeveloped on the following morning with increasing intensity and in association with vomiting. She had never had previous hypertensive episodes. On examination, she was drowsy. Blood pressure was elevated (141/105 mmHg; 99th percentile = 127/86 mmHg). She was afebrile, and her heart rate was 63 beats/minute. The laboratory findings were unremarkable except the abnormal hematological profile consistent with T-ALL. Induction chemotherapy was withheld,

and she was treated with oral amlodipine (2.5 mg). Cranial computed tomography (CT) (Figure 1A) revealed marked swelling of the pons and bilateral cerebellum and patchy areas of low density in these structures and the midbrain. The clinicians in charge were concerned by the possibility of venous infarction as a complication of L-asparaginase, and proceeded to cranial magnetic resonance imaging (MRI) examination. As in CT, marked swelling of the pons and bilateral cerebellar hemispheres was observed on MRI (Figure 1B-G). Patchy areas of signal abnormalities were observed in these structures and the midbrain. The lesions were hyperintense on the T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. A small hypointense focus was observed within the right cerebellar lesion, thought to be punctate hemorrhage. On the T1-weighted images, the lesions were hypo- to isointense. On the gadolinium-enhanced T1-weighted images, some areas of patchy enhancement were observed within the cerebellar lesions. On the diffusion-weighted images (DWI; $b = 1000 \text{ s mm}^{-2}$), most lesions were isointense with increased apparent diffusion coefficient (ADC) values, indicating vasogenic edema. However, there were some hyperintense areas with decreased ADC values, indicative of cytotoxic edema. Normal flow voids were identified in the venous sinuses on T2WI, FLAIR images and DWI, and there was no filling defect within these sinuses on the gadolinium-enhanced T1-weighted images. Of note, there were no supratentorial abnormalities. Three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) revealed well-developed bilateral posterior communicating arteries (PComA). From these imaging findings and the clinical features, the presumptive diagnosis of PRES was made.

The patient responded well to withdrawal of the chemotherapy and antihypertensive therapy. Her consciousness improved and blood pressure returned to normal within a few hours. Induction chemotherapy was resumed on the following day, under careful monitoring of the vital signs and blood pressure. The symptoms did not recur, and the chemotherapy was successfully completed.

The MRI repeated six and 14 days later showed resolution of mass effect and diminution of the lesions and areas with contrast enhancement. The diagnosis of PRES was thus confirmed. The MRI repeated seven weeks later (Figure 2) showed further lesion diminution.

However, some lesions which appeared hyperintense on the initial DWI with ADC decrease persisted. The 3D-TOF-MRA showed diminution in caliber of the left PComA (almost invisible on the maximum intensity projection images) – suggesting dilatation of the artery at the initial MRA. The MRI and 3D-TOF-MRA repeated seven weeks later (Figure 2) also revealed features suggestive of thrombosis or stenosis of the right sigmoid sinus and internal jugular vein. However, there were no obvious clinical symptoms related to this event. The lack of MRI and MRA features suggestive of venous sinus thrombosis or stenosis at the initial presentation (Figure 1) and two consecutive follow-up scans (six and 14 days after the initial MRI) did not raise the suspicion that the posterior fossa lesions were related to venous sinus thrombosis or stenosis. PRES and venous sinus thrombosis/ stenosis were considered separate clinical events. No further work-up such as time-resolved CT angiography (4D-CTA) was performed². The follow-up MRI scans acquired one and 6.5 months after the thrombotic event revealed resolution of hyperintensity within the right sigmoid sinus and internal jugular vein.

Discussion

The parietooccipital region is the most frequently involved site in PRES. The incidence of observing PRES lesions in this region is as high as 98.7%³. PRES may also involve other brain structures such as the frontal and temporal lobes, thalamus, cerebellum, brainstem and basal ganglia; but with decreasing frequency and often together with the parietooccipital lesions. Isolated involvement of one or more of these structures without involvement of the parietooccipital region is uncommon. Isolated and extensive involvement of the posterior fossa structures is rarer. To our knowledge, there have been only two adult case reports in English literature on the isolated involvement of PRES lesions in both the brainstem and cerebellum with completely spared supratentorial structures (although the lesions are mainly located in one or more posterior fossa structures in some reported cases of the brainstem variant of PRES, the abnormalities are also observed in the supratentorial structures)^{4,5}. In both cases, poorly controlled preexisting hypertension seems to have triggered PRES. This would be the first report on the MRI findings of isolated and extensive involvement of the pos-

Figure 1 CT and MRI findings on the day of clinical presentation. The axial non contrast-enhanced CT (A) shows marked swelling of the pons and bilateral cerebellum and obliteration of the fourth ventricle. Low-density areas are seen in these structures. The axial FLAIR image (B) shows widespread areas of heterogeneous hyperintensity at the cerebellar vermis, bilateral cerebellar hemispheres and pons. These areas are hypo-to isointense on the axial pre-contrast-enhanced T1-weighted image (C). On contrast administration, some cerebellar lesions show a moderate degree of patchy enhancement (D). On the axial DWI (E), most lesions are isointense, but there are some patchy hyperintense areas in the bilateral cerebellar hemispheres and pons (not shown). The ADC map (F) shows increased ADC values in most cerebellar lesions. The lesions which are hyperintense on the DWI show decreased ADC values, suggestive of cytotoxic edema. The maximum intensity projection (MIP) of 3D-TOF-MRA (G) reveals a well-developed bilateral PComA.

Figure 2 Findings of the follow-up MRI performed 7 weeks after onset. The axial FLAIR image (A) shows a disappearance of mass effect and most of the lesions. However, some lesions which showed hyperintensity on the initial DWI still persist (arrows). The left PComA is not observable on the MIP of 3D-TOF-MRA (B). The FLAIR image (A) shows hyperintensity of the right sigmoid sinus, and the MIP of the 3D-TOF-MRA (B) shows hyperintensity of the right sigmoid sinus and internal jugular vein – suggestive of venous sinus thrombosis or stenosis.

terior fossa structures by PRES in the pediatric population and in the setting of remission induction chemotherapy for ALL.

The exact mechanisms underlying selective vulnerability of the posterior fossa structures in this case are not understood. Taken together the observation of transient elevation of blood

pressure during the episode in this case and the history of poorly controlled hypertension in the previous reports, hypertension may have implicated in the development of PRES with isolated posterior fossa involvement. Rapid and severe elevation in blood pressure may have impaired the autoregulatory function in the posterior

fossa vasculature, leading to increased capillary filtration pressure and vasogenic edema. It has been reported that mild hypertension induces edema predominantly in the supratentorial white matter, whereas severe hypertension induces vasogenic edema in the infratentorial structures, basal ganglia and thalamus⁶. As the latter structures are supplied by small arteries originating directly from larger trunks such as the MCA and the BA or its branches, these structures might be exposed to high perfusion pressure and vasogenic edema driven by it. Sparing of the basal ganglia may be related to the rich sympathetic innervation of the arteries supplying the structure. Sparing of the thalamus is yet to be explained. Doi et al. have proposed that sparing of the distal vertebrobasilar system may be due to excessive fluid leakage in the posterior fossa structures and/ or the potentially protective effect of collateral sympathetic innervation to the parietooccipital region through a dominant PComA⁷. In this case, the initial MRA demonstrated a fetal origin of the right PCA and dilated left PComA. While the right PComA may have enriched sympathetic innervation to protect the right parietooccipital region from high perfusion pressure, the observation of dilated left PComA is thought to be less likely explained by the latter phenomenon alone (Constriction or spasm of the PComA – as a protective or autoregulatory response to high perfusion pressure, instead of dilatation as in this case, is expected to be observed if the PComA serves as a source of protective collateral sympathetic innervation). Individual variation in the pattern of sympathetic innervation of the vessels of the vertebrobasilar circulation might play a role.

Considering normal blood pressure before initiation of the therapy and absence of other causes which could induce hypertension, remission induction chemotherapy is thought to be the trigger for hypertension in the present case. Among several agents used in remission induction chemotherapy, dexamethasone has been known to induce acute hypertension possibly through increased sensitivity of the sympathetic nervous system, enhanced vascular responses to other constrictor neurotransmitters and hormones, and a diminished endothelium-dependent vasodilatation mediated by nitric oxide, prostacyclin or the endothelium-derived hyperpolarizing factor⁸. Evidence has

also suggested that L-asparaginase may also trigger hypertension by the same or similar mechanisms inducing its thrombotic side effect⁹. Although long term or high dose intravenous or oral administration of prednisolone has been reported to induce hypertension, it is not known if a single intrathecal dose of prednisolone used for induction chemotherapy would induce severe hypertension.

While hypertension could induce PRES, it could also be a manifestation of PRES. In this setting, one or more agents used in remission induction chemotherapy could be the trigger for PRES. Some pharmacological agents such as cytarabine, methotrexate and L-asparaginase have been proposed to induce PRES, possibly through their direct cytotoxic effects on the vascular endothelium^{10,11}. Vascular endothelial injury can lead to extravasation of the intravascular fluid and a decrease in normal vascular tone, followed by vasospasm and ischemia.

A few reports which attempt to correlate clinical severity or reversibility of PRES lesions with lesion distribution suggest a poor outcome with brainstem involvement¹². However, the findings of others and the present case revealed a complete reversibility of the brainstem lesions¹³. In this case, there was a small area of cytotoxic edema in the pontine lesion which disappeared on follow-up – suggesting potential reversibility of the lesions with cytotoxic edema. Some cerebellar lesions with cytotoxic edema persisted. These could be irreversible lesions, but upon lack of residual neurological deficit, the prognosis of this case is considered good. However, extensive involvement of the cerebellum can result in obstructive hydrocephalus and tonsillar herniation, if attempts at timely intervention fail⁵.

In conclusion, we described a rare case of PRES with isolated and extensive involvement of the posterior fossa structures, which occurred during induction chemotherapy for T-ALL. Isolated involvement of the posterior fossa structures can occur during chemotherapy and without the presence of preexisting hypertension. As PRES lesions are potentially reversible upon timely management, early recognition is important. Knowledge of atypical features and a high index of suspicion would be invaluable for early diagnosis. This report also highlights the potential reversibility of brainstem lesions and the lesions with cytotoxic edema.

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