Hematol Oncol Stem Cell Ther (2016) 9, 36–38

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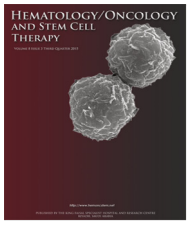

LETTER TO EDITOR

Cyclosporine-related brainstem atypical posterior reversible leukoencephalopathy syndrome following hematopoietic stem cell transplant

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Received 18 February 2015; accepted 11 April 2015
Available online 28 April 2015

Posterior reversible leukoencephalopathy syndrome (PRES) is a rare and severe complication of calcineurin inhibitor neurotoxicity, especially following high risk procedures, such as hematopoietic stem cell transplantation (HSCT). We report an isolated brainstem localization of PRES in a 23-year-old patient who, two days following cyclosporine (CsA) administration, manifested gradual symptoms that included hypertension, vomiting, vertigo, tremor, nystagmus, and visual disturbance. Radiologic magnetic resonance imaging (MRI) showed two bilateral punctiform, increased signals on T2 with fluid attenuation inversion recovery (FLAIR) in the pons. The patient's symptoms, as well as MRI signs, were resolved when the cyclosporine treatment was discontinued.

Posterior reversible leukoencephalopathy syndrome (PRES) is a rare clinical and radiological inflammatory complication, involving the central nervous system and the impairment of the blood brain barrier. Clinical symptoms may include headache, vomiting, mental confusion, seizures, coma, cortical blindness and other neurological disorders [1]. These symptoms have been reported in patients with severe hypertension, eclampsia, hemolytic uremic syndrome, and are also associated with neurotoxic drugs such as cyclosporine (CsA) and tacrolimus. Radiologic magnetic resonance imaging (MRI) is the gold standard diagnostic test for the posterior regions of the parietal, temporal and occipital lobes, which are the classic locations for PRES [2].

We report an atypical case of PRES with isolated brainstem localization, related to CsA, in a 23-year-old male patient who had a sibling-matched bone marrow transplant for severe aplastic anemia. The conditioning regimen consisted of cyclophosphamide (200 mg/kg, i.v.) and rabbit anti-thymocyte globulin (rATG) (12 mg/kg, i.v.). To prevent cytokine release syndrome related to rATG, antihistaminic and methyl prednisone (2 mg/kg/day, i.v.) was administered over five days. Prophylaxis of graft versus host disease (GVHD) consisted of post-graft CsA (Sandimmun®) administered at a dose of 3 mg/kg/day by continuous infusion started at day 1 before graft, with a maintained therapeutic range between 200–400 ng/ml, and methotrexate. Acyclovir was also prescribed to prevent Herpes simplex virus (HSV).

On day 1 post transplant (two days after CsA administration), the patient experienced an inexplicably high level of

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http://dx.doi.org/10.1016/j.hemonc.2015.04.005

blood pressure (180/110 mmHg), vertigo, and nausea. On physical examination there were cutaneous and mucous paleness, regular respiratory rhythm with an oxygen saturation of 99% while inhaling ambient air. Cardiac auscultation revealed regular tachycardia (100 beats per minute) without extraneous sounds. Neurological examination showed normal strength sensation as well as normal gait and coordination. Peripheral blood count showed neutropenia (100/μl), anemia (9.6 g/dl), and thrombocytopenia (77,000/μl). Serum creatinine level, serum sodium concentration, AST, and ALT were normal. Serum cholesterol was low at 0.93 g/l and serum CsA was within therapeutic range (218 ng/ml). Other laboratory tests were normal. Mean arterial blood was maintained below 100 mmHg through continual infusion of nicardipine.

Twenty days later, the patient developed vomiting, vertigo, and visual disturbance. Physical examination showed bilaterally decreased vision, asymmetry of the pupils, nystagmus, tremor, and imbalance in resting state. The patient was apyretic, with normal blood pressure (110/70 mmHg). The fundus examination, fluorescence angiography and visual field tests found papilledema with retinal hemorrhages and visual disturbances; and a diagnosis of bilateral edematous optic neuropathy was made (Fig. 1). MRI showed two bilateral punctiform and increased signals on T2, together with fluid attenuation inversion recovery (FLAIR) in the pons (Fig. 2a), which confirmed diagnosis of isolated brainstem localization of an atypical PRES. Residual CsA was in the upper limit of the therapeutic range (384 ng/ml). We discontinued cyclosporine, replacing it on the same day with tacrolimus (Prograf®). An additional continuous infusion of magnesium (4 mg/24Hr. i.v.) was administered. Blood cryptococcus antigen by enzyme immunoassay test was negative.

Forty-eight hours later, the patient's vertigo and ability to see color started to improve. Complete resolution of neurologic signs was achieved two weeks after the onset of the symptoms with disappearance of the brainstem lesions in brain MRI control (Fig. 2b). The fluorescence angiography and the visual field tests revealed a remarkable decrease of inflammatory optic signs and improvement of visual acuity. Engraftment was achieved successfully at day 33. With a follow up of 15 months, patient is alive with no further complications.

Bone marrow transplant offers a curative treatment for young patients with acquired severe aplastic anemia when human leukocyte antigen (HLA) identical sibling donor is available. Calcineurin inhibitors such as CsA are considered the standard GVHD prophylaxes. However, among their side effects, neurological toxicity can cause serious complications such as PRES. Siegal et al. recently reported an incidence rate of 7% among 302 consecutive recipients who underwent HSCT for malignant and non-malignant hematologic diseases, with a significant inferior survival rate at one year in PRES versus no PRES groups (27% vs 63%, respectively) [3].

Vasogenic edema, which predominantly affects the white matter of cerebral hemispheres, especially posterior regions, occurs due to the differences in sympathetic innervations between the anterior and posterior circulation. The posterior region of the brain is the classic location of PRES because it is more vulnerable to the excessive perfusion pressure that is associated with systemic hypertension [4].

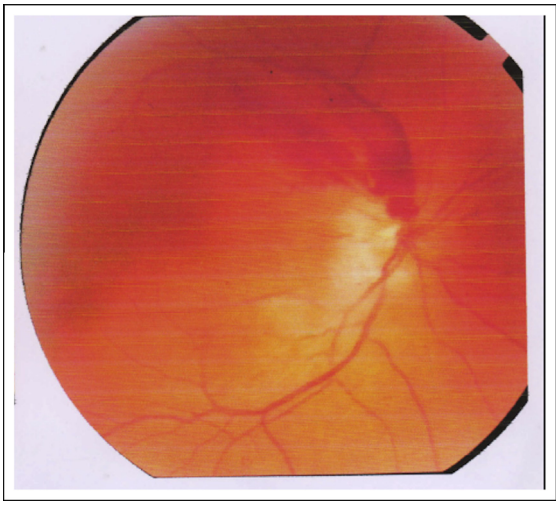

Figure 1 Retinal angiography on diagnosis. Right eye.

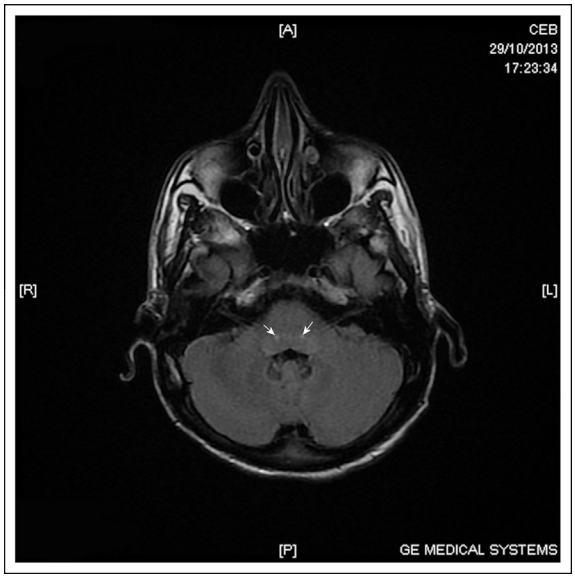

Figure 2a MRI showing two bilateral punctiform (arrows) increased signal on T2 together with fluid attenuation inversion recovery (FLAIR) in the pons.

In our case, MRI showed that the brainstem was predominantly involved, whereas the occipital lobes were spared. Mechanisms of brainstem involvement have been postulated by Doi et al. Extensive fluid leakage in the brainstem may spare the parietal and occipital regions in the distal portion of the vertebra-basilar artery system, or relatively rich sympathetic nerve innervations may occur in the parieto-occipital region, which is mainly supplied via the posterior communicating artery from the anterior circulation [5].

CsA is known to be highly lipophilic, with about 80% plasma binding to high and low-density lipoprotein. In contrast, a low rate of serum cholesterol can result in increased unbound CsA, which may cause neurotoxicity, fluid retention, and which has a direct toxic effect on the vascular endothelium, resulting in the release of endothelin

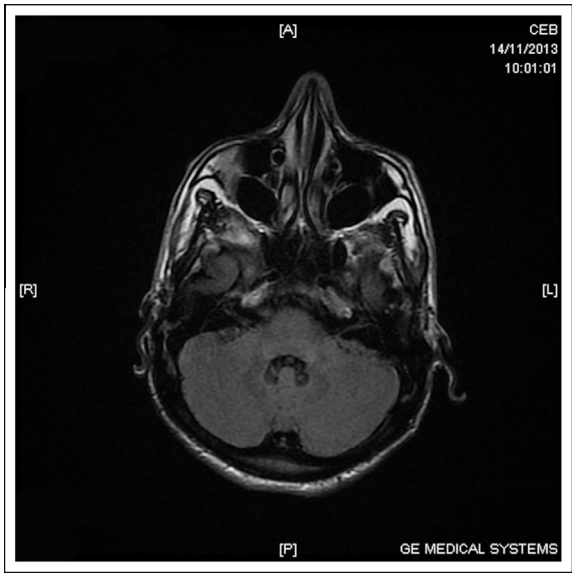

Figure 2b MRI on day 16 showing improvement.

prostacyclin and thromboxane A2 and, consequently, apoptosis on brain capillary endothelial cells.

Our patient was at high risk for the development of neurotoxicity for two reasons: first, he had a low rate of cholesterol; and second, a high-dose of methyl prednisone used to prevent cytokine release syndrome may have potentiated the neurotoxic effect of CsA [6]. Other risk factors described in the literature include low magnesium, aluminum overloads, or the association of CsA with voriconazole.

The distribution of lesions in bilaterally symmetric brainstem is an uncommon localization of PRES. In this case, we suspected secondary to CsA neurotoxicity because of the rapid improvement after the discontinuation of cyclosporine.

Conclusion

PRES is typically reversible but unless recognized early and treated appropriately permanent brain injury may ensue. It is very important to identify and prevent this complication in high-risk HSCT patients; we also support the recommendation of an appropriate prophylaxis for PRES.

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