Posterior Reversible Encephalopathy Syndrome in a Normotensive Child after Allogeneic Hematopoietic Stem Cell Transplantation

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Posterior reversible encephalopathy syndrome (PRES) is an uncommon clinicoradiological syndrome that is characterized by acute neurological symptoms such as headache, convulsion, visual disturbance, and altered consciousness (1). The characteristic magnetic resonance (MR) finding is vasogenic edema, predominantly in the subcortical areas of the posterior parietal and occipital lobes on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (2). Hypertension, toxemia of pregnancy (preeclampsia and eclampsia), sepsis, autoimmune conditions, and exposure to immunosuppressive/cytotoxic drugs are all risk factors for PRES and can predispose the individual who has one of them to the syndrome (3).

Cyclosporine (CsA) is a calcineurin inhibitor and potent immunosuppressive agent used for prophylaxis against cellular rejection after transplantation. Despite its proven efficacy in preventing acute rejection episodes, CsA may cause PRES in up to 7% of the patients that undergo hematopoietic stem cell transplantation (HSCT) (4).

Herein, we describe a rare case of PRES induced by CsA after an allogeneic HSCT from a sibling donor.

Case report

The patient was a 10-year-old child who presented at our hospital (March 2017) with relapsed acute lymphoblastic leukemia (ALL), and because there was a sibling donor, we decided to perform an allogenic HSCT. Adhering to the ALL-REZ BFM 2002 protocol, on day −1, CsA was started at a dose of 3 mg/kg/day for graft-versus-host disease (GVHD) prophylaxis. At 42 days post-transplant, the patient presented with a headache, altered mental function (he was disoriented and could not follow simple commands), incoherent speech, visual disturbance (blurry, reduced vision and diplopia), and 5 consecutive acute generalized tonic-clonic convulsions. He had no history of hypertension or of renal or cardiac disease. Brain MR images revealed hyperintense signals in the bilateral fronto-parietal and occipital lobes on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (Figure 1). However, there were no lesions on the diffusion-weighted images. Electroencephalography demonstrated non-specific slow wave changes (Figure 2). The diagnosis of PRES was made based on the convulsions and the brain MRI findings, and the patient was treated with phenytoin (loaded at a dose of 20 mg/kg and continued with 5 mg/kg) and methylprednisolone (30 mg/day for 3 days). However, the patient had another convulsion after 1 week. Therefore, we changed CsA to mycophenolate mofetil (MMF) (600 mg/m2). After this change, his complaints disappeared and the clinical findings improved dramatically on the 11th day. Four weeks later, the brain MR examination showed that the abnormal signal intensity lesions had disappeared (Figure 1).
Discussion

The calcineurin inhibitor CsA is employed frequently in immunosuppressive therapy (often following an HSCT procedure) as a means of preventing GVHD; it is also a commonly implicated risk factor for PRES (5). However, at both therapeutic and supratherapeutic levels, CsA has been linked to severe neurological complications, including disorientation, confusion, convulsion, and visual impairment (from therapy onset) (6). Our patient presented with similar findings.

While there were no specific diagnostic criteria supporting the diagnosis of PRES, brain MR imaging and clinical signs upheld that conclusion (7). Common causes of PRES include hypertension, preeclampsia, eclampsia, chemotherapy, treatment with immunosuppressive agents, connective tissue disease, transplantation, infection, and renal disease (8). We excluded these factors in the differential diagnosis. Moreover, when the treatment was switched from CsA to MMF, the patient's symptoms gradually improved, disappearing on the 11th day. Four weeks later, the brain MR images showed that the lesions with abnormal signal intensity had disappeared (T2-weighted and FLAIR sequences). In the end, the combination of the clinical signs and the MR/CT images seemed to confirm the diagnosis of PRES.

The pathophysiology of PRES is not yet well understood. Currently, the most widely accepted theory suggests that severe hypertension that cannot be controlled by the autoregulatory mechanism causes hyperperfusion with endothelial injury and vasogenic edema (9). Severe hypertension was detected in 80% of the cases of PRES that have appeared in the literature up to now, which datum confirms the theory propounded earlier (10).

According to another theory, an immunological mechanism that is triggered by immunosuppressive/cytotoxic drugs causes endothelial damage and the release of proinflammatory cytokines, resulting, finally, in blood–brain barrier disruption and vasogenic edema. The mechanism described in this second theory is considered to be the primary one in normotensive cases with PRES (11). In our case, mean systolic blood pressure ranged from 100 to 115 mmHG and the mean diastolic blood pressure ranged from 60 to 73 mmhg; moreover, our patient had no transient hypertension at any point during his follow-up.

As articulated above, CsA is a calcineurin inhibitor that is widely used in HSCT and organ transplant procedures to prevent rejection. It is metabolized by the hepatic cytochrome P450 system, specifically CYP3A4 and CYP3A5, and there is large interindividual variability.
in CsA pharmacokinetics (12). It has been shown that CsA-associated toxicity could result even when CsA levels are within the therapeutic range (39–48%) (4). Our patient’s blood CsA level never exceeded 187 ng/ml during the follow-up, and similar observations have been made by Chang et al., Minn et al., and Palmer et al (13,14,15). We speculate that blood CsA level is a poor indicator of CsA toxicity and that further studies are needed to predict the adverse conditions related to CsA toxicity.

CsA is an important drug widely used for immunomodulation in stem cell transplants, and, as turned out to be the case in our patient, PRES should be considered in all transplant patients receiving CsA, because it is a reversible disease if recognized early enough and correctly managed.

References