Implication of Cyclosporine in the Development of Reversible Posterior Encephalopathy Syndrome in Three Patients with Allogeneic Bone Marrow Transplants: Is MRI Apparent Diffusion Coefficient of Prognostic and Therapeutic Value?

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Abstract

The Posterior Reversible Encephalopathy Syndrome (PRES) is a serious complication of treatment with cyclosporine with an incidence of 8% in patients with bone marrow transplantation. PRES is a hypertensive encephalopathy with a various clinical presentations (twitching, convulsions, blindness and coma). Cyclosporine is an immunosuppressant used in the prevention of graft rejection in solid organ transplantation and prevention of Graft Versus Host Disease (GVH) during allogeneic bone marrow transplantation. We present 3 cases of patients that we have took care in our unit who presented severe neurological complications in the aftermath of their bone marrow transplant and after receiving cyclosporine.

Imaging performed by emergency, using MRI and measurement of Apparent Diffusion Coefficient (ADC) is an important consideration during the management of these patients. In case of a high ADC, reflecting vasogenic edema, patients might have a favorable prognosis and the use of corticosteroids may decrease edema while a decreased ADC may represent an irreversible damage with a poor outcome.

Early and appropriate care of PRES, taking in account ADC index, may improve prognosis of this potentially mortal syndrome.

INTRODUCTION

The Posterior Reversible Encephalopathy Syndrome (PRES) is defined both clinically and radiologically. Its neurological symptomatology is diverse: focal deficits, headache, seizures, confusion, and visual disturbances. Imagery shows bilateral multifocal lesions which predominate in the posterior areas of the brain. The physiopathology of this syndrome is not well understood and its etiology is most likely multifactorial. We report three cases of severe neurological toxicity in allografted patients in order to sensitize practitioners to the importance of early patient care in order to improve its prognosis.

MATERIALS/SUBJECTS

Case 1

A 53 year old patient with a history of ophthalmic zona and chronic renal failure (Cockroft clearance of 40ml/min) was hospitalized for an allograft of geno-identical peripheral stem cells in the context of a relapsing IgG Kappa myeloma in partial remission. He had benefited from first line therapy with three VAD type chemotherapies (adriblastine, oncovin, dectancyl) as well as an autograft conditioned with melphalan 200mg/m2 eight years prior. He was treated with three cycles of bortézomib.
a relapse six years later to which he only partially responded and subsequently developed an invalidating peripheral neuropathy. He later received six rounds of doxorubicin + cyclophosphamide to which he did not respond, and six VMCP/VBAP chemotherapies which he partially responded to.

The patient was conditioned with fludarabine 30mg/m2x3 and cyclophosphamide 750mg/m2*-3 for his allograft. Prevention of Graft Versus Host Disease (GVHD) with cyclosporin was initiated day 1 post-graft. Arterial hypertension was noted with a systolic pressure reaching 180 mmHg and a diastolic pressure reaching 90mmHg which warranted treatment with amlodipine. Cyclosporinemia remained therapeutic between 150-200µg/L. However, cyclosporine was stopped at day 15 post-graft due to the development of acute renal failure with a serum creatinine at 260µmol/L. A relay was achieved with prednisone 1g/2 days until day 28 post-graft at which point he became febrile due to a central catheter infection which necessitated its removal.

Neurological decline with temporo-spatial disorientation and a lower limb pyramidal syndrome warranted re-hospitalization at day 25 post-graft. He was transferred to the intensive care unit after he fell into a coma with a Glasgow score of 7 at day 30 post-graft. Physical examination revealed a left areactive mydriasis, a tetrapyramidal syndrome with spastic hypertonia of the four limbs, and an absence of meningeal signs.

An urgent head Computed Tomography (CT) was ordered and was found to be normal. A cervical spine magnetic resonance imaging (MRI) revealed compression of vertebrae without spinal damage. The head MRI performed at day 25 post-graft was normal. Lumbar puncture revealed hyperproteininemia at 0.58g/L and was negative for bacteria, viruses (PCR HS, JC, and BK virus) and parasites (Cryptococcus and toxoplasmosis). Direct cytological examination of cerebrospinal fluid (CSF) showed eight red blood cells (RBCs) and no white blood cells (WBCs). No plasmocytes were isolated after centrifugation. An EEG showed no evidence of epileptic foci. The fundoscopic exam was normal. Magnesemia was normal as well (0.97mmol/L). (Normal [0.53–1.11]).

Another head CT was ordered at day 35 post-graft and was normal. However, a head MRI showed supratentorial white-matter hypersignals in T2 and diffusion sequences predominating at the contact of the ependymal barrier (Figure 1). The Apparent Diffusion Coefficient (ADC) was low at 0.52.10⁻³ mm²/s whereas the contralateral ADC was measured at 0.8 , a decrease of 35% compared to the value in healthy zone.

The diagnosis of reversible posterior encephalopathy was evoked following these findings. The patient was treated by high dose corticotherapy and intravenous immunoglobulin (IVIG) but unfortunately continued degrading neurologically. He slipped into a coma and died 65 days post-graft.

Case 2

A 61 year old woman with a history of IgA Kappa myeloma diagnosed in 1996 and initially treated in 2001 with a VAD-type chemotherapy as well as a double bone marrow autograft relapsed in 2009 and was then treated with bortezomib. She developed a peripheral neuropathy secondary to this treatment.

She was later hospitalized for a mini-allograft of geno-identical peripheral stem cells conditioned with fludarabine 30mg/m2x3 and cyclophosphamide 750mg/m2x3 for a second complete remission of an IgA kappa myeloma.

Graft Versus Host Disease (GVHD) prevention consisted of antilymphocyte serum (3mg/kg), cyclosporin, and methotrexate at day 1, 3, 6, and 11. The patient developed acute renal failure (creatinine 246µmol/L) at day 2 post-graft secondary to an episode of acute urinary retention which necessitated temporary cessation of cyclosporin therapy.

The patient presented with tremors and myodonus of the four limbs at onset of treatment with cyclosporin, necessitating initiation of anti-epileptic treatment with levetiracetam 500mgtwice a day. A head CT performed at day 8 post-graft was normal. Furthermore, the patient maintained a systolic arterial pressure of 170 mmHg which necessitated treatment with intravenous nicardipine, as well as a hypomagnesemia (0.2mmol/L) which necessitated daily intravenous repletion. At day 40 post-graft, two episodes of generalized tonic-clonic seizures were observed. An emergency CT was ordered and was found to be normal.

The head-MRI completed at day 45 post-graft showed disseminated oedematous-looking biparietal and bioccipital hypersignals in T2 phase, in favor of PRES (Figure 2). However, the ADC was measured with a value of 1.28x10⁻³ mm²/s whereas in healthy zone ADC was 0.68x10⁻³ mm²/s, an increase of 89%. Multiple attempts to complete a lumbar puncture failed. Given the persistence of aplasia at day 30 post-graft, it was decided to reinject autologous peripheral stem cells.

A head MRI performed at day 90 post-graft showed a significant decrease of the hypersignals initially noted (Figure 3). Antiepileptic treatment was continued without recurrence of seizures.

There was significant neurological improvement, including a disappearance of the confusional syndrome, after initiation of corticotherapy. Nonetheless, the patient died three months post allograft from multi-organ failure in the context of an infectious pneumonia.

Case 3

A 54 year-old female patient was hospitalized for a pheno-
identical bone marrow transplant in the context of an acute lymphoblastic leukemia with translocation (9;22) and m-bcr transcript in complete remission after conventional treatment. The patient had a myelo-ablative conditioning treatment consisting of total body irradiation 8Gy and cyclophosphamide (80mg/kg). GVHD prevention was achieved with cyclosporine initiated at day 1 post-graft plus methotrexate at day 1, 3, and 6 post-graft, and was well tolerated. During the course of hospitalization the patient presented with facial cellulitis secondary to a bite she inflicted herself. A head-CT ordered to evaluate this infection showed bi-frontal subdural hematomas most likely linked to intracranial hypotension from repeated lumbar punctures. Serum levels of cyclosporine were supra-therapeutic with maximal values at 242mg/L. The patient did not develop arterial hypertension no hypo or hypermagnesemia, and renal function remained normal throughout the course of hospitalisation.

She was hospitalised at day 90 post-graft for severe neurological disturbances: temporo-spatial disorientation, gait disturbances, and obtundation. Lumbar puncture showed elevated proteins in CSF with sterile cultures. An emergency head-MRI performed at day 90 post-graft evidenced multiple diffuse hemispheric hypersignals in cerebral and cerebellar regions cortico-subcortical and present in the white matter in FLAIR, diffusion and T2 sequences consistent with posterior reversible posterior encephalopathy (Figure 4). The apparent diffusion coefficient was measured with a value of $1.18 \times 10^{-3}$ mm$^2$/s, whereas in healthy zone, its value was $0.67 \times 10^{-3}$ mm$^2$/s, an increase of 76%.

In this context, urgent care consisted of cessation of cyclosporine and initiation of corticotherapy with dexamethasone (20mg/day) for four days. There was notable clinical improvement after 48 hours of corticotherapy. A head MRI performed one month later showed a complete regression of the hypersignals (Figure 5, Table 1).

**DISCUSSION**

The precise etiology of PRES is unknown. However, multiple predisposing factors have been identified, the most important of which being rapid onset or uncontrolled arterial hypertension. Other promoting factors include: renal failure, eclampsia, treatment with a calcineurine inhibitor (cyclosporine) [1], hypercholesterolemia, hypomagnesemia [2], and concomitant use of corticosteroids [3].

The physiopathology of PRES is not well understood. Nonetheless, it has been hypothesized that an important dysregulation of arterial blood pressure or sudden onset arterial hypertension may lead to decreased permeability of the blood brain barrier and ultimately cause cerebral hyperperfusion in the context of an overload of cerebral perfusion pressure autoregulation mechanisms [4,5]. This hypothesis remains controversial [6], since recent evidence suggests vasospasm linked to arterial pressure variations may cause localised ischemia and vasogenic oedema leading to cerebral sequellae [4,6]. Others evoke endothelial dysfunction in the context of an immunological disorder (auto-immune disease, immunosuppressive treatment, sepsis, eclampsia) which may alter blood brain barrier permeability and cause localized cerebral oedema. Arterial pressure variations are not incriminated in this proposed
etiological mechanism, which is thought to be implicated in 20-30% of PRES cases [6]. These three proposed mechanisms are ultimately responsible for vasogenic oedema of cerebral white matter which leads to the recognized clinical and radiological manifestations of PRES [7]. Altered vasoregulation secondary to diminished parasympathetic innervations of blood vessels in posterior regions of the brain explains the more frequent posterior localisation in this syndrome.

Cyclosporine is an immunosuppressive agent used after organ transplantation as well as in the prevention of GVHD [8]. Its lipophilic nature allows it to easily cross the blood brain barrier. Both hypercholesterolemia and hepatic failure increase its diffusion into the brain. Multiple neurological side effects have been noted with cyclosporine [9-12]: tremors, paresthesias, seizures, encephalopathy, visual disturbances, and cortical blindness [13]. PRES is a potentially life-threatening complication of treatment with cyclosporine, with an incidence of 0.49% after solid-organ transplant [6], and of 5-8% after bone marrow allograft [6].

Cyclosporine can induce endothelial dysfunction, lead to vasoconstriction (increase of endothelin and thromboxane, decrease in nitric oxide and prostacycline), and increase parasympathetic activation [5]. Its toxicity is increased by hypercholesterolemia and hepatic failure [8]. Supratherapeutic cyclosporinemia is a known neurological risk factor; however, no link between cyclosporinemia and development of encephalopathy has been demonstrated [13, 14].

Rapid diagnostic evaluation with an emergency head MRI is warranted in allograft patients with suspected PRES [6]. Though CT is more readily available, its clinical use is limited to ruling out a cerebral hemorrhagic event in a patient population likely to be thrombopenic. The sensitivity of CT for diagnosis of PRES is low, with identification of PRES lesions in less than 50% of cases [2]. Head MRI is the gold standard and shows in T2, diffusion, and T2-FLAIR sequences characteristic hyperintense cortico subcortical signals in the occipital and fronto-parietal cortex [4,6]. Measurement of the ADC is imperative. A diminished ADC is linked to cytotoxic oedema, the most common example of which is acute phase ischemia. A diminished ADC is of poor prognosis since it reflect probably irreversible. An increased ADC is linked to a vasogenic edema and/or to demyelinating lesions [15,16].

Differential diagnosis of neurological abnormalities in allograft patients must include infectious etiologies. Lumbar puncture with exhaustive bacteriological, virological, and parasitological investigations must be completed. Transcranial doppler can also be of interest in the evaluation of such patients [14], showing increased velocities in cerebral arteries (middle, posterior, and less often anterior cerebral arteries) [14].

Appropriate care of allograft patients consists of:

- Continuous monitoring of blood pressure (which necessitates hospitalisation in an intensive care unit) and initiation of antihypertensive treatment when Blood Pressure (BP) is greater than 180mmHg. Trinitrine is contraindicated since cases of exacerbation of PRES have been described with this drug. Calcium channel blockers are to be favored for control of BP.

- Magnesium supplementation [2], (which has a calcium channel blocking effect) has a vasodilating antihypertensive effect as well as a preventative and curative effect on cerebral vasospasm [5]

- Cessation of cyclosporine [5]

Once cyclosporine treatment has been stopped, relay with corticosteroids is warranted to maintain immunosuppression, with the added benefit of favoring a reduction in vasogenic oedema [2] (when the ADC is elevated). However, when the ADC is low, cerebral lesions secondary to oedema are irreversible. In such cases, corticosteroids are not efficacious. It is important to note that corticosteroids are not indicated even in PRES since they may in fact be deleterious.

We observed a significant and rapid clinical improvement in two of three cases with elevated ADC after initiation of systemic corticotherapy.

As its name indicates, PRES is supposed to be reversible. A complete radiological (MRI) regression of lesions was observed

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Table 1: Cf. JSM Clin Case Rep 2(6): 1066 (2014)
in two of our patients (cases 2 and 3) (Figure 3, 5). Furthermore, there was no relapse of convulsions and cessation of anti-epileptic therapy was possible some time after initial presentation. PRES has a favorable prognosis in the short term, though it may be fatal in some cases [7]. Relapse rate is approximately 8%. Clinical recuperation is faster than regression of MRI lesions [7].

CONCLUSION

PRES is a severe complication of cyclosporine treatment. Allograft patients are at high risk not only because of immunosuppressive treatment but also because of concomitant use of corticosteroids and presence of immunological disorders after transplant. MRI is the gold standard for diagnosis of PRES and must be performed early in the course of the disease. Calculation of the ADC is essential since it has a prognosis value [6]: patients with a lowered ADC have a poor prognosis with consequent damage. This syndrome is generally reversible with appropriate patient care. Monitoring of renal function, cyclosporinemia, magnesemia, and arterial blood pressure are of utmost importance. Given that allograft patients are susceptible to infectious and vascular complications, PRES remains a diagnosis of exclusion.

REFERENCES