



Maculopathy and Posterior Reversible Encephalopathy Syndrome Presumably Associated with Tacrolimus

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Abstract

Tacrolimus is an immunosuppressant drug used in solid organ transplantation to reduce rejection rates and to prevent graft versus host disease (GVHD) in haematopoietic stem cell transplantation (HSCT). Tacrolimus is a fungal metabolite produced by *Streptomyces tsukubaensis*. It works as a calcineurin inhibitor reducing interleukine-2 (IL-2) production and activation of T cells [1]. Along with cyclosporine and other calcineurin inhibitors, tacrolimus is associated with posterior reversible encephalopathy syndrome (PRES) [2], optic neuropathy and only a few cases reported in the literature of maculopathy. About one-third of patients who develop PRES can present visual impairment, most of them fully recover after drug suspension, although there have been partial recovery cases reported [3].

Keywords: Tacrolimus; Maculopathy; Posterior Reversible Encephalopathy Syndrome (PRES)

Case Presentation

We present a 28-year-old female diagnosed with severe aplastic anaemia for which she underwent an allogeneic HSCT. Her conditioning preparation was cyclophosphamide plus fludarabine, and the GVHD prophylaxis was cyclosporine (CsA blood level: 271 ng/ml). Her post-transplant course was complicated for seizures. A brain MRI was performed which showed increased FLAIR and T2 signal in the occipital lobe compatible with PRES attributed to cyclosporine. Due to this, she was switched to tacrolimus. Twelve weeks following initiation of tacrolimus therapy (6 mg/day) she developed a progressive reduction in visual acuity (VA) over three days. At that moment, she was normotensive, and her renal function was normal.

Initial assessment revealed VA of 0.05 in both eyes and normal pupillary reflexes. The visual field demonstrated bilateral central

scotomas. The anterior segment examination was normal as well as the intraocular pressure. Retinal examination revealed bilateral faint concentric circles in the posterior pole, roughly larger in her left eye accompanied by multiple small white dots. The left eye also displayed two subretinal haemorrhages interpreted as Roth's spots. The optic nerves had an unremarkable appearance (Figure 1).

Macular OCT and fluorescein angiography were performed, the latter shows perifoveal bilateral filtering in greater quantity in the left eye, which is accentuated at exam late times (Figure 1). However, macular OCT fails to identify intraretinal or subretinal fluid.

After 48 hours from the first assessment, the patient's AV decreased to no light perception (NPL) in both eyes. The rest of the ophthalmological exam showed no change.

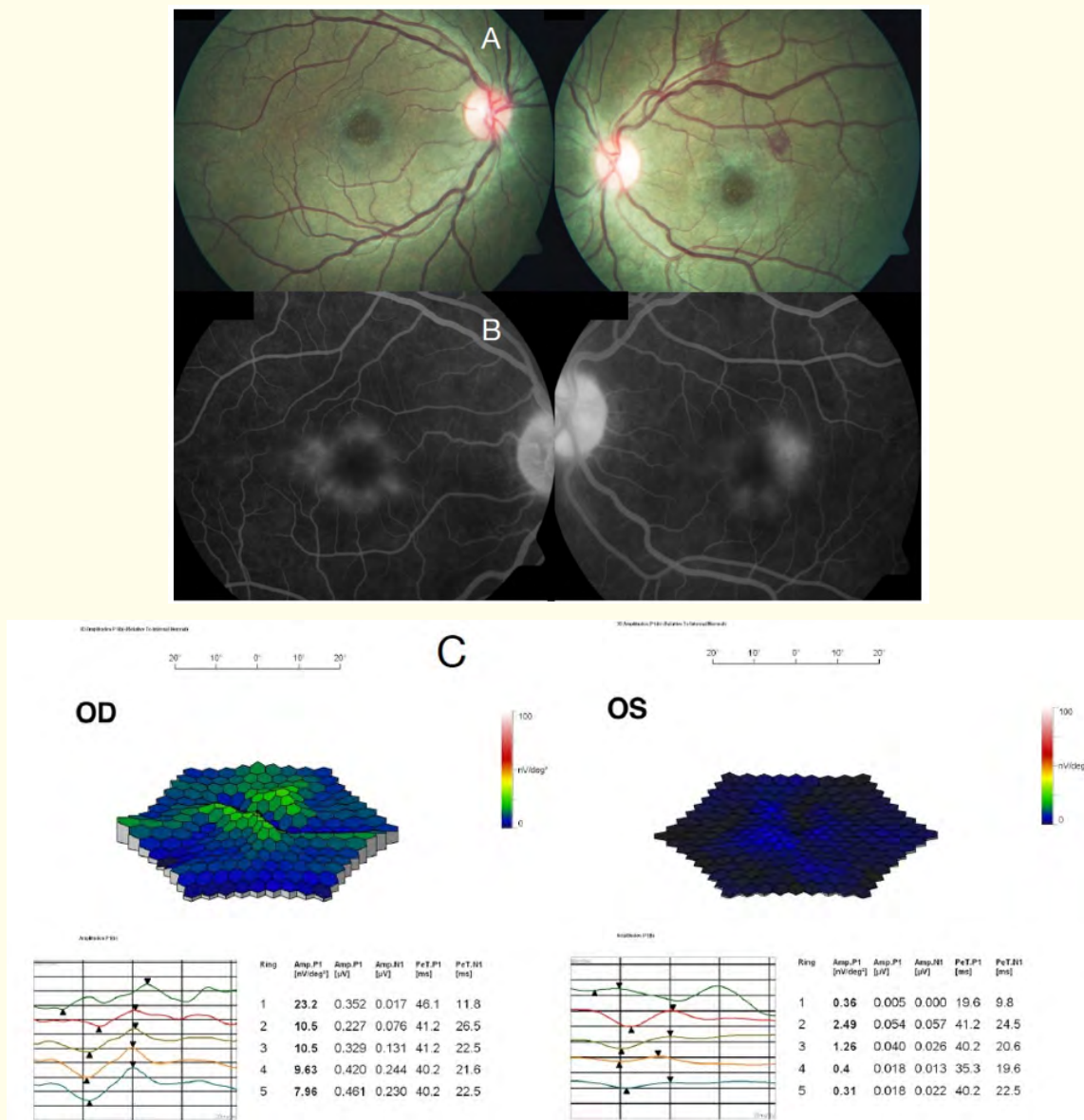


Figure 1: A: Fundus Photographs. B: Fluorescein angiography, both eyes showed the presence of filtration staining in perifoveolar region in both eyes. C: Multifocal electroretinogram in both eyes.

Considering the examination did not explain the patient’s VA, a brain and optic pathway MRI was carried out which revealed a recurrence of leukoencephalopathy in the occipital region, interpreted as a tacrolimus-induced PRES (Figure 2). Tacrolimus was replaced by Mycophenolate mofetil 1,5g twice a day. Multifocal ERG was carried out following discharge showing a severe decrease in the amplitude of the waves within five central rings (Figure 1).

At 1 year follow-up, without receiving tacrolimus, the VA had improved to 0.25 in the Right eye, and 0.13 in the Left eye and fundus examination revealed mild bilateral alteration in the retinal pigmented epithelial cells.

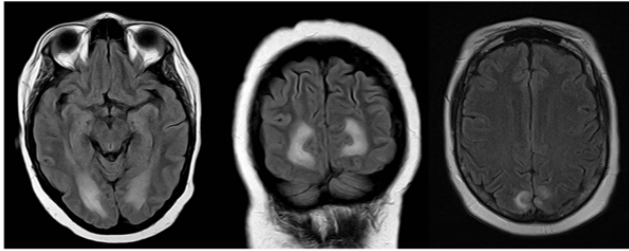


Figure 2: Hyperintensity of the periventricular and subcortical white matter of the occipital regions of both hemispheres, representing vasogenic edema in a typical pattern of PRES.

Discussion

Aplastic Anaemia (AA) is a life-threatening form of bone marrow failure which, if untreated, is associated with high rate mortality. Most cases are due to immune injury to multipotent hematopoietic stem cells. AA is a rare disorder with an incidence of approximately two cases per million per year in western countries and two to three times higher in Asia [4].

In severe aplastic anemia, HSCT is generally performed from marrow harvest rather than peripheral blood collection, and the best donor is a full match related. Because severe AA is not a neoplastic disease, the preparation is generally with a reduced intensity conditioning. The most utilized regimen is Cyclophosphamide plus Anti-thymocyte globulin with or without Fludarabine, and most of the regimens use Cyclosporine or Tacrolimus for GVHD prophylaxis [5].

The toxicity of calcineurin inhibitors is well described in the literature, being neurotoxicity the most frequent of them. This is how in 1996 the Posterior Reversible Leukoencephalopathy Syndrome was initially described, characterized by white and gray matter abnormalities secondary to vasogenic edema [3]. These immunosuppressive drugs would cause up to 44% of PRES reported in an extensive multicenter study with 70 confirmed patients [4]. In this syndrome, the parieto-occipital region is predominantly affected in 98% of cases. Still, it could affect other areas of the central nervous system such as frontal lobe (68%), temporal lobe 40%, and cerebellar hemispheres 30% [6].

Clinical presentation of this disease is varied, however visual symptoms have been reported in up to 36% of patients [4]. These

range from diplopia, visual field deficits, color vision disturbances, and decreased VA to total bilateral blindness, as in the case of our patient. Cortical blindness [7], internuclear ophthalmoplegia, optic neuropathies associated or not with PRES [8], and maculopathies secondary to the use of tacrolimus [9] have been reported as etiology. Nevertheless, according to our best understanding, this is the first case where both complications are evident simultaneously.

The pathophysiology proposed for PRES would be activation and damage of the vascular endothelium, activation of the immune system, and the release of proinflammatory cytokines [10]. This is how the development of hypertension in an accelerated way, as in cases of preeclampsia, lead to the breakdown of the self-regulation systems of the blood-brain barrier and consequently to secondary vasogenic edema. The relative lack of sympathetic innervation in the posterior circulation would explain the preference for compromising the posterior part of the brain. However, there are multiple reported cases of normotensive or hypotensive patients who develop PRES [11]. Hence the endothelial dysfunction would be explained by direct cytotoxicity of the immunosuppressive drugs.

On the other hand, retinal damage has not been extensively studied. However, the fluorescein retinal angiography of this patient reveals endothelial damage at the macular area, since the contrast filters throughout the procedure. It is important to note that the blood-brain barrier presents a broad similarity to the blood-retinal barrier both in its structure and functionality. Moreover, in vitro cytotoxicity has been reported in cultures of retinal pigmented epithelium cells exposed to tacrolimus in doses of 1000 ng/ml and 2500 ng/ml, showed a decrease in cell viability in relation to those cells exposed to concentrations less than 10 ng/ml for 24 hrs [12]. This is a possible explanation regarding retinal pigmented epithelium damage seen in this patient as well as in the case reported by Taehyuk Koh., *et al.* which persists over time [9], even after the resolution of PRES. This evident toxicity would explain in part why some patients have a partial recovery of vision even years after the acute encephalopathy event.

Conclusion

Calcineurin inhibitors have become an excellent therapeutic tool for multiple pathologies, including some ophthalmological diseases. The therapeutic range of Tacrolimus has not been clearly

defined and is guided by blood levels. Most individuals display optimal response to tacrolimus with trough whole blood levels of 5.0 to 15.0 ug/L. However, its adverse effects such as PRES and its possible retinal toxicity are known, being able to be permanent even once the dose is reduced or suspended, suggesting the possibility of idiosyncrasy. Retinal pigmented epithelium damage has been poorly described and studied but it would explain the permanent impairment in visual acuity and visual field even once the leukoencephalopathy has resolved.

There are 3 calcineurin inhibitors available for medical use. Cyclosporine, Tacrolimus and Pimecrolimus, the latter only for topical treatment. Cyclosporine has long been used for what its side effects are better known for, such as gum enlargement and bleeding, facial hair growth, tenderness and pain around the eyes and cheeks, stomach discomfort, runny nose and pimples whereas that seizures and visual impairment are less frequent.

Pimecrolimus for its part has been used topically for the treatment of atopic dermatitis and psoriasis. Its most frequent side effects are burning, itching, and pain in hairy areas while systemic symptoms as stomach pain and flu-like symptoms are less frequent. From my point of view, these drugs are extremely safe and special attention should be given to labile patients, for example patients with kidney or liver failure and users of multiple drugs. (Polypharmacy). For example, recently transplanted patients where the most serious complications have been seen due to this type of drug.

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