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Citation	Transplant Infectious Disease, 2015, v. 17 n. 3, p. 396-399
Issued Date	2015
URL	http://hdl.handle.net/10722/212549
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Progressive Outer Retinal Necrosis in a Renal Transplant Recipient: A Rare Treatment Success

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Author contributions: All authors were involved with the clinical management of the patient. Gary C.W. CHAN also wrote the manuscript.

Running head: VZV PORN in Renal Transplant Recipient

Key words: progressive outer retinal necrosis; renal transplantation; varicella zoster virus

Abbreviations: VZV, varicella zoster virus; PORN, progressive outer retinal necrosis; CMV, cytomegalovirus; HSV, herpes simplex virus; HIV, human immunodeficiency virus.

Word count: 1,205 (excluding abstract and references)

Origin of transplanted organ and mode of brain death: Unknown. Transplanted abroad.

Funding & conflict of interest: None

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Abstract

Kidney transplant recipients are subject to a variety of opportunistic infections. We present a rare case of varicella zoster virus (VZV) derived progressive outer retinal necrosis (PORN) in a renal transplant recipient, who presented with painless visual blurring. This clinical entity heralds an extremely poor visual prognosis and is an important condition to consider in any immunocompromised host. Early diagnosis by aqueous fluid sampling and immediate institution of combined systemic and intravitreal anti-viral therapy was successful in this individual.

Introduction

Infections are a common cause of morbidity and mortality in kidney transplant recipients. The traditional paradigm has recognized the emergence of opportunistic infections when patients are most heavily immunosuppressed, usually in the early period following engraftment. Isolated ocular manifestations of such infections are uncommon, with cytomegalovirus (CMV) retinitis being predominantly described in the literature.

Herein, we present a rare case of progressive outer retinal necrosis (PORN) due to varicella zoster virus (VZV) in a 53 year-old female who received a deceased donor kidney transplant more than 20 years ago. Treatment success was achieved with a prolonged course of combined intravitreal and systemic anti-viral therapy.

Case Report

A 53 year-old female with end-stage renal disease of unknown cause received a deceased donor renal transplant in 1993. Prior to transplantation, she had performed two years of continuous ambulatory peritoneal dialysis. No induction immunosuppression was utilized at the time of engraftment and she was maintained on steroid and cyclosporine

thereafter. Osteoporosis and diabetes mellitus were her only post-transplant complications, for which she is currently prescribed alendronic acid and gliclazide.

She presented with painless left sided visual blurring which progressively worsened over the course of two weeks. No prior trauma had taken place. Physical examination revealed blood pressure 117/82 mm Hg, heart rate 82 bpm in sinus rhythm and no relative afferent pupillary defect on neurological assessment. Preliminary laboratory findings include white blood cell count $8.8 \times 10^9/L$; hemoglobin 10.9 g/dL; platelet $303 \times 10^9/L$; C-reactive protein <0.35 mg/dl; creatinine 80 $\mu\text{mol/L}$; 12-hour cyclosporine level 59 $\mu\text{g/L}$ and no detectable CMV antigenemia. A recently measured glycated hemoglobin was 6.4%.

Indirect fundoscopy revealed peripherally situated multifocal retinal opacification with macular sparing and minimal vitritis in the absence of any vasculitis. These features are suggestive of PORN and differs from acute retinal necrosis where there is usually profound vitreal inflammation and arteritis. Intravitreal ganciclovir and intravenous acyclovir were empirically commenced. Subsequently, her left aqueous polymerase chain reaction for VZV returned positive, whilst that for CMV, herpes simplex virus (HSV) and mycobacterial tuberculosis were negative. Human immunodeficiency virus (HIV) and toxoplasma serology were non-reactive. VZV immunoglobulin G sero-positivity indicated the possibility of VZV PORN due to latent viral reactivation. Lymphocyte subset analysis revealed an isolated low CD4+ T lymphocyte count at 382 cells/uL (range 415-1418 cells/uL).

Intravitreal ganciclovir was administered at 2mg, twice per week, for five doses in total. With gradual resolution, intravenous acyclovir at 500 mg every eight hours was switched to oral valganciclovir after two weeks. Oral valganciclovir was continued at 900 mg twice daily for a total of thirteen weeks. Barrier laser therapy was performed thrice to prevent retinal detachment and her left eye visual acuity had gradually improved from 6/60 to 20/60 after twelve weeks. The pre- and post-treatment fundi photos are shown in Figures 1 and 2

respectively. Her contralateral eye remained unaffected throughout. At her last ophthalmological follow-up, eighteen months after her initial presentation, it was noted that her best-corrected visual acuity remained stable at 20/60. Furthermore, there had been no recurrences of the condition during this period and her kidney graft function remained normal throughout.

Discussion

PORN is a devastating retinal condition first described [1] and found almost exclusively in HIV infected individuals. It is characterized by multifocal retinitis that rapidly coalesce with the potential to produce total retinal necrosis within days to weeks. A high proportion of patients develop bilateral eye disease with subsequent retinal detachment, giving rise to extremely poor visual prognosis despite therapy [2]. The usual etiology is VZV but HSV [3] and CMV [4] have been implicated. Diagnosis in our patient was based on the clinical course and retinal appearance supported by aqueous fluid sampling, which has a high sensitivity and specificity [5]. Vitreal [6] or chorioretinal biopsy [7] may also be performed to identify the causative infectious agent. A handful of reports have described this entity after hematopoietic stem cell transplantation but it is extremely rare following renal transplantation.

Our patient underwent renal transplantation two decades ago and has been maintained only on steroid and cyclosporine throughout. She had no history of graft rejection necessitating steroid pulses or immunosuppressive intensification. Her cumulative immunosuppressive exposure is therefore relatively low, especially in the current era of triple agent immunosuppression for kidney allograft recipients. Moreover, her prevailing trough cyclosporine level had been kept to a minimum, measuring at 59 ug/L at the time of presentation, making it difficult to attribute PORN to a highly defective immune status.

At presentation, the CD4+ T lymphocyte count in our patient was only marginally reduced while most reported cases of PORN occurred in patients with a profoundly low CD4 count; a median count of 21/mm³ in one study [2] and 12/mm³ in another [8]. Herein, this represents the first reported case of PORN to occur in a patient with a CD4 count above 239 cells/uL [9]. However, this trivial reduction is likely significant in a patient taking cyclosporine, which induces immunosuppression by functionally inhibiting T cell activation.

Lymphoproliferative disorder is one of the most common malignancies complicating solid organ transplantation [10] and is also associated with CD4+ lymphocytopenia [11]. Our patient was found to have a monoclonal immunoglobulin A kappa paraprotein of 6.74 g/L and a bone marrow examination was performed, demonstrating mild plasmacytosis. She underwent a PET-CT, which demonstrated no evidence of lymphoproliferative disease or other obscure malignancy. Hematological follow up was consequently arranged to monitor the monoclonal gammopathy of undetermined significance.

The optimal treatment for VZV PORN is unknown and rapid retinal destruction necessitates aggressive therapy to preserve vision. Poor and inconsistent response to acyclovir alone has been noted for PORN, which may be due to inadequate local drug concentrations resulting from induced retinal ischemia. As such, the application of intravitreal anti-viral therapy appears to be a favorable option [12]. Our patient was treated with a prolonged course of intravitreal ganciclovir in combination with systemic acyclovir. With disease control, she was subsequently maintained on oral valganciclovir. Valganciclovir was favored as it overcomes the poor oral bioavailability of acyclovir, with the added advantage of being non-nephrotoxic in a kidney transplant recipient. Our patient had no prior history of prolonged acyclovir exposure that would lead to the development of a resistant VZV strain and disease control was attained rapidly. Her low prevailing level of

immunosuppression was therefore not further reduced to balance out the risk of transplant rejection.

Upon disease control, a repeat lymphocyte subset analysis was performed. It demonstrated immune reconstitution with the CD4 count measuring at 1202 cells/uL. No specific clinical events apart from PORN in this patient correlated temporally with the transient lymphocyte sub-population deviation.

This case highlights that VZV PORN should be considered in any renal transplant recipient presenting with visual blurring. In addition, the immune-dysregulation accompanying PORN demonstrates CD4+ lymphocytopenia, the relationship of which is incompletely understood. The lymphocytopenia appears to reconstitute upon clinical disease resolution, the clinical relevance of which is uncertain. When presenting in a solid organ transplant recipient, the possibility of a lymphoproliferative disease as a potential association should be borne in mind. Finally, it is illustrated that combination intravitreal and systemic anti-viral therapy can achieve a good outcome with preservation of vision in this devastating entity. However, early diagnosis is the key to success.

Figure Legends

Figure 1: Pre-treatment left eye fundus photo showing widespread multi-focal peripheral retinal opacification.

Figure 2: Post-treatment left eye fundus photo demonstrating resolution of retinal infiltrates. Discrete pigmented scars represent photocoagulation laser marks, performed to prevent retinal detachment.

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