Dual Retinitis with Cytomegalovirus and Herpes Simplex in a Paediatric Patient with Advanced Retinoblastoma: A Case Report

Retinite Dupla por Citomegalovírus e Herpes Simplex numa Criança com Retinoblastoma de Estadio Avançado: Um Estudo de Caso

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ABSTRACT

Herpesvirus retinitis is a serious infection of the retina typically found in immunosuppressed patients. We report the case of a 4-year-old boy with a history of enucleation of the left eye for intraocular advanced retinoblastoma, at time under systemic adjuvant chemotherapy, observed under anaesthesia for periodic disease follow-up. Right eye fundus evaluation showed multiple areas of focal haemorrhagic retinitis without retinal necrosis along the mid and far periphery. Aqueous and peripheral blood polymerase chain reaction revealed dual positivity for cytomegalovirus and herpes simplex virus type 1. The patient was managed with three intravitreal foscarnet injections, intravenous ganciclovir and foscarnet and the lesions gradually regressed. However, two months later, a reactivation of retinitis lesions occurred and four additional intravitreal foscarnet injections were needed. In cases of suboptimal therapeutic response or atypical retinitis presentations, we believe that prompt molecular analysis of ocular fluids for viral DNA detection is crucial to correctly identify the causative agent.

KEYWORDS: Child; Cytomegalovirus Retinitis; Eye Infections, Viral; Herpes Simplex; Molecular Biology; Retinoblastoma.

RESUMO

A retinite por herpes vírus é uma infeção retiniana grave encontrada frequentemente em pacientes imunodeprimidos. Neste estudo, reportamos o caso de um rapaz de 4 anos com história de enucleação do olho esquerdo por retinoblastoma invasivo intraocular e sob quimioterapia sistémica adjuvante, acompanhado periodicamente para monitorização da doença no olho direito. A fundoscopia revelou múltiplas áreas de retinite hemorrágica focal, sem necrose retiniana, localizadas na média e extrema periferia. A reação de polimerase em cadeia do humor aquoso e sangue periférico mostraram dupla positividade para citomegalovírus e herpes *simplex* tipo 1. O tratamento incluiu três injeções intravítreas de foscarnet, ganciclovir e foscarnet endovenosos. As

lesões regrediram gradualmente, no entanto, após dois meses, houve uma reativação das lesões de retinite, tendo sido necessárias quatro injeções intravítreas de foscarnet adicionais. As técnicas de biologia molecular, em casos de respostas sub-ótimas ao tratamento ou retinites atípicas, tornam-se cruciais na identificação do agente etiológico.

PALAVRAS-CHAVE: Biologia Molecular; Criança; Herpes Simplex; Infecções Oculares Virais; Retinite por Citomegalovirus; Retinoblastoma.

INTRODUCTION

Viral retinitis is one of the most common eye-related complications in patients with a supressed immune system. The main causative agents of viral retinitis are human herpesviruses, and it may have different clinical manifestations depending on the host´s immune status, ranging from acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), cytomegalovirus (CMV) retinitis, and non-necrotizing herpetic retinopathy (NNHR).[1] In this case report, we are focusing on CMV retinitis and NNHR.

CMV retinitis is an opportunistic infection usually found in individuals with severe systemic immunosuppression. It usually occurs in the context of a systemic CMV infection, which is reportedly underrecognized in children with retinoblastoma.[2] A 2019 study by Han and colleagues evaluated a group of 164 children with retinoblastoma for CMV infection, and found that approximately 27% of them were diagnosed with CMV infection during chemotherapy.[2] Among these, those who had started chemotherapy before 12 months of age had significantly greater risk, which is likely due to the downregulation of T cells that is present during early infancy.[2] There are two clinical variants described: 1) haemorrhagic CMV retinitis, which curses with extensive areas of retinal oedema and necrosis often involving the posterior pole with a "cottage cheese" appearance, and 2) granular CMV retinitis, with a more "gritty" appearance and more often involving the peripheral retina.[3] CMV retinitis typically progresses to full-thickness retinal necrosis, resulting in areas of atrophic and gliotic scarring.[3]

NNHR was described for the first time in 2003 by Bodaghi and colleagues through the advances in virological diagnostic techniques.[1,4] They demonstrated that DNA amplification from aqueous humour samples was highly sensitive in identifying the causative agents of atypical forms of unilateral or bilateral corticosteroid-resistant posterior uveitis, such as varicella-zoster virus (VZV) and herpes simplex virus type 1 (HSV-1), and thus described this new clinical entity.[1,4]

In the past, the diagnosis of herpetic retinitis was based on clinical evaluation and was subsequently confirmed by a favourable response to antiviral therapy.[1] In 1991, CMV genome was detected for the first time by polymerase chain reaction (PCR) of intraocular fluids, such as aqueous humour and vitreous, of patients with clinical features of CMV retinitis.[5] This discovery has completely revolutionised the approach to making the definitive diagnosis of intraocular infectious diseases.[1] Even though the diagnosis of retinitis is predominantly clinical, there is increasing evidence supporting the use of molecular biology techniques in aiding the detection of the causative agent, allowing an optimisation of the therapeutic strategy.[1,6]

The simultaneous identification of two distinct herpes virus causing retinitis in a non-human immunodeficiency virus (HIV) carrier has very rarely been reported in literature.[6] In this study, we present a rare case of dual retinitis caused by CMV and HSV1 confirmed with molecular biology techniques in a paediatric patient under systemic chemotherapy for locally invasive unilateral retinoblastoma.

CASE REPORT

We performed a retrospective case report with a review of medical records, RetCam photographs and images from optical coherence tomography (OCT) and magnetic resonance imaging (MRI) scans of the orbit.

A statement of informed consent was obtained from the patient's legal representative for the publication of the case report and corresponding images.

A 4-year-old African male was referred to the Portuguese National Referral Centre (Centro Hospital e Universitário de Coimbra, University of Coimbra) for the clinical suspicion of retinoblastoma in the left eye. The left eye examination revealed significant anterior chamber invasion by a voluminous tumoral mass, preventing a detailed fundus examination. The right eye examination was unremarkable. MRI showed an irregular, voluminous heterogenic tumour with diffuse calcifications and predominantly dark on T2-weighted imagens, with subretinal fluid and secondary serous retinal detachment in the outer inferior quadrant (Fig. 1). It was associated with proptosis, orbital wall and anterior chamber invasion and without apparent

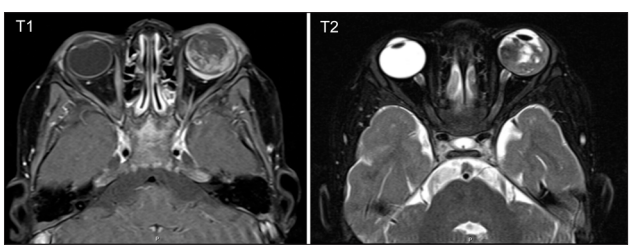

Figure 1. T1 and T2 weighted MRI images of left eye retinoblastoma.

optic nerve involvement. Retinoblastoma diagnosis was therefore assumed. The tumour was classified as group E by the International Classification for Intraocular Retinoblastoma (ICRB) and cT4b by the American Joint Commission on Cancer (AJCC) staging system (8th edition).[7] The patient was subsequently enrolled in ARET0321 Phase III clinical trial, which involved two sequential phases of systemic intravenous chemotherapy: induction phase and consolidation phase.

The induction phase consisted of four cycles of vincristine, cisplatin, cyclophosphamide and etoposide, followed by peripheral stem cell harvest. Following this phase, the tumour partially regressed with a significant reduction of tumour volume, but still with persistent total serous retinal detachment and anterior segment infiltration.

Two months after referral, the left eye was enucleated, and high-dose consolidation chemotherapy was immediately started, consisting of a combination therapy of carboplatin, thiotepa and etoposide. External beam radiation (45 Gy in 25 fractions) was followed. Chemotherapy-induced and radiotherapy-induced systemic toxicities, including oral mucositis, severe esophagitis, and severe bone marrow aplasia, complicated the post-operative period, so the patient was admitted to the Paediatric Oncology Unit.

Examination Under Anaesthesia (EUA) was conducted every four weeks for detailed fundus evaluation of the right eye as part of periodic disease follow-up. Four months after referral and two months from the start of consolidation chemotherapy, following right eye fundoscopy (documented with RetCam) revealed multiple areas of focal haemorrhagic retinitis without retinal necrosis and multiple whitish lesions distributed along the mid and far periphery (Fig. 2). At this time, the patient had a leucocyte and neutrophile count of 0 per microliter (μL). These findings, along with the patient´s suppressed immune system, were suggestive of a viral retinitis diagnosis. Anterior chamber paracentesis was performed for aqueous humour sampling and PCR was immediately requested for viral DNA detection on peripheral blood samples and aqueous humour. An intravitreal injection of foscarnet (1.2 mg/0.05 mL) was subsequently administered, but intravenous antiviral therapy was delayed due to severe pre-existing cytopenias. Two days later, PCR revealed dual positivity for CMV and HSV-1 on both aqueous humour and peripheral blood (CMV viral load 2 959 000 copies/mL and HSV-1 viral load 40 838 copies/mL on peripheral blood). Intravenous loading-dose ganciclovir (10 mg/kg/day) and foscarnet (180 mg/kg/day) were immediately started.

The patient was managed with a total of three intravitreal foscarnet injections and a twenty-one-day course of intravenous ganciclovir (10 mg/kg/day) and foscarnet (180 mg/kg/day) and was subsequently switched to prophylactic-dose oral foscarnet (90 mg/kg/day). The retinitis lesions gradually regressed over time, resulting in areas of chorioretinal scarring. Serum quantitative CMV and HSV-1 DNA also had a progressive decline. Bone marrow aplasia was successfully resolved.

However, at six-month follow-up, the ophthalmological observation under anaesthesia revealed a new, haemorrhagic, retinitis lesion located at the papillomacular bundle, along with extensive segmental inferotemporal vascular sheathing (Fig. 3). Intraoperative OCT was performed showing full-thickness hyperreflectivity, associated intraretinal haemorrhages and severe disruption of the retinal layers in the nasal half of the macula up until the fovea (Fig. 3). At this time, the patient had a leucocyte count of 5800/μL with a neutrophile count of 3450/μL. No complications were observed that could have triggered the reactivation of the infection. Four additional intravitreal foscarnet injections were weekly performed, and a fourteen-day cycle of intravenous loading-dose ganciclovir (10 mg/kg/day) and

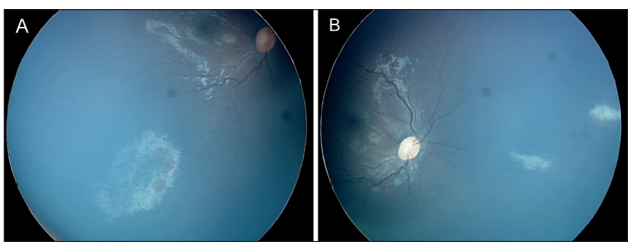

Figure 2. Right eye RetCam images at four-month follow-up showing one small macular lesion and two small lesions at the mid and far nasal periphery (A). A wider lesion was observed in the inferotemporal midperiphery, consisting of a confluent patch of haemorrhagic intraretinal whitening (B).

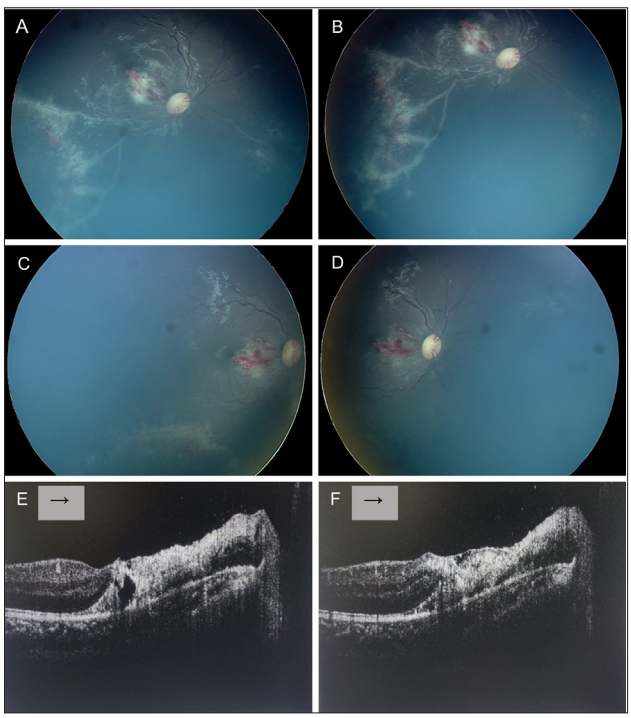

Figure 3. Right eye RetCam images at six-month follow-up showing a new active retinitis lesion located at the papillomacular bundle, segmental vascular sheathing and an area of chorioretinal scarring in the inferotemporal quadrant (A and B). One week after the first intravitreal foscarnet injection, the macular lesion appeared to have more haemorrhagic features (C and D), and intraoperative OCT images revealed a full thickness hyperreflectivity of the nasal aspect of the macula involving the fovea and associated intraretinal haemorrhages and severe disruption of the retinal layers (E and F).

loading-dose foscarnet (180 mg/kg/day) were completed. Currently, at eight-month follow-up the patient remains stable on prophylactic-dose oral foscarnet (90 mg/kg/day) and prophylactic-dose oral ganciclovir (5 mg/kg/day). Leucocyte count increased to 5600/μL with 2200 neutrophils/μL. However, visual acuity is not expected to recover due to the severe foveal impairment (Fig. 4).

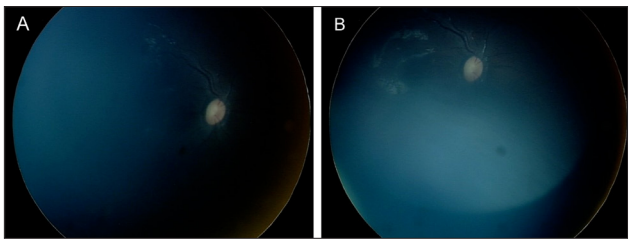

Figure 4. Right eye RetCam images at eight-month follow-up with complete resolution of foveal retinitis lesion, resulting in an area of macular scarring.

DISCUSSION

The clinical spectrum of herpetic eye disease is very wide, with its manifestations depending on the patient´s immunological status. Even though the diagnosis of retinitis is predominantly clinic, there is increasing evidence supporting the use of molecular diagnosis to aid the detection of the causative agent and enable the early and timely start of targeted therapy.[6]

Our patient´s past ocular history was relevant for advanced intraocular retinoblastoma in the fellow eye, for which he had completed several cycles of systemic neoadjuvant and adjuvant chemotherapy. Indeed, the most likely cause of CMV and HSV-1 reactivation in our patient seemed to be the severe immunosuppression following the intensive chemotherapy and cranial radiotherapy treatments. One of the chemotherapy agents used in the consolidation phase was thiotepa. Interestingly, in a 2023 case report, Bigagli *et al* described a case of CMV reactivation and secondary retinopathy associated with high dose thiotepa in a paediatric patient with history of high risk medulloblastoma.[8]

CMV retinitis is commonly observed in patients with deficient T cell response, such as acquired immunodeficiency syndrome, hematopoietic stem cell transplantation or solid organ transplantation and less frequently found in patients undergoing chemotherapy *per se*.[2,8] In the paediatric population under cancer treatment, the most common underlying neoplasm associated with CMV infection is retinoblastoma.[2] The study by Han *et al* found that approximately 50% of the children with retinoblastoma that were diagnosed with CMV infection further progressed to develop manifestations of CMV disease, such as pneumonia, hepatitis and retinitis.[2]

Current guidelines do not advocate routine monitoring for CMV infection and pre-emptive therapy in non-transplant patients with haematological malignancies.[9] Furthermore, there are no recommendations regarding CMV screening for other cancer patients, namely retinoblastoma.[2] Given the high CMV seroprevalence and significant morbidity from CMV infection during chemotherapy, Han *et al* proposed the establishment of active CMV screening and pre-emptive antiviral therapy in children with retinoblastoma, since the benefits of decreasing the incidence of CMV disease among patients at high risk for developing end-organ disease largely outweighs the risk of developing therapy side effects, such as neutropenia, which are usually transient.[2] Also, in the treatment of CMV retinitis, intravitreal therapy was found to offer a significant advantage over systemic therapy since it also substantially reduces the risk of CMV-related retinal detachment.[10]

NNHR is an atypical form of viral retinitis first described in 2003 by Bodaghi and colleagues, which described cases of posterior uveitis unresponsive to corticosteroids and positive PCR in aqueous humour for herpes virus, namely HSV and VZV.[4] Since then, very few cases have been described in literature, and these were mainly associated with retinal vasculitis on fundus examination.[1,11] This disease typically does not respond to conventional systemic steroid or immunomodulatory therapy, but shows a favourable response to systemic antiviral medication.[4]

Retinitis caused by multiple viruses has rarely been reported in patients other than human immunodeficiency virus (HIV)-carriers. Samanta *et al* recently reported a case of necrotizing viral retinitis with optic disc involvement and vasculitis attributed to CMV and HSV in a young girl with pemphigus vulgaris on systemic immunosuppressant therapy.[6] In 2020, another study reported a case of PORN in an HIV-positive man with dual infection due to CMV and VZV identified by PCR.[12] In both cases, aqueous humour PCR was the key to find the correct diagnosis.

There are two great challenges posed in the management of paediatric patients with retinitis. First, the child needs to be sedated under general anaesthesia in order to perform a thorough ophthalmological observation and to administrate intravitreal injections. Second, children may not always clearly express their complaints, and particularly in the case of our patient, caregivers did not perceive the impairment in visual acuity that occurred at the time of retinitis reactivation, which further delayed the diagnosis and treatment of the foveal retinitis lesion.

Even though this is a single, specific case study, we align with previous research.[6,12,13] in advocating molecular analysis of ocular fluids in cases of retinitis with atypical presentation or suboptimal response to antiviral therapy. In fact, aqueous humour PCR was found to have a clinical sensitivity of 82% and specificity of 100% in a retrospective case series of patients with infectious uveitis affecting the posterior segment, with a predictive value of positive and negative tests of 98.7% and 67.9%, respectively.[14] Also, an interventional study Khaler *et al* from found that PCR analysis of ocular fluid confirmed the initial diagnosis in 70.1% of patients with suspected infectious uveitis and altered the initial treatment in 17.7% of them.[15] This approach allows the early identification of the causative pathogen, thus enabling the prompt implementation of the appropriate treatment strategy and positively influencing the disease course and prognosis.

To our knowledge, this was the first case in literature to report non-necrotizing retinitis secondary to CMV and HSV-1 in a paediatric patient under immunosuppressive treatment for advanced retinoblastoma. Dual infection by CMV and HSV-1 was correctly identified by molecular biology techniques, which allowed the prompt initiation of the appropriate antiviral therapy.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

IF: Writing, literature research and editing of the manuscript.

JP, CF, AMM, GC: Review and supervision of the manuscript.

All authors approved the final version to be published.

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