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Case Report

Cytomegalovirus Retinitis in Immunosuppressed Patients: Case Studies

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Keywords

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Abstract

Introduction: CMVR is the most common opportunistic ocular infection in severely immunocompromised individuals. Herein, we report three immune deficient patients with CMVR.

First case: A 15-year old girl with the diagnosis of HIV infection and diffuse large B-cell lymphomaadmittedto hospital with the complaint of blurred vision on her left eye. She was then diagnosed as CMVR. She was started on chemotherapy together with antiretroviral treatment. CMVR fully resolved after 6 months of parenteral and intravitreal ganciclovir therapy.

Second case: A 17-year old boy with the diagnosis of PID (IL-21 receptor deficiency) admitted with the complaint of diminished visual acuity. Absolute CD4 count was 50 cells/mm^3 and fundoscopic examination revealed CMVR. Although several antiviral agents were administered, progression of the disease could not be prevented.

Third case: A4-month old girl with the diagnosis of SCID was diagnosed as bilateral CMVR after fundoscopic examination which had been performed during CMV viremia. She was given systemic ganciclovir and foscarnet treatment. Unfortunately she passed away because of disseminated CMV infection.

Conclusion: Routine ophthalmologic examinations for CMVR should be performed in immunocompromised patients.

ABBREVIATIONS

CMV: Cytomegalovirus; CMVR: CMV retinitis; HIV: Human Immunodeficiency Virus; IL-21: Interleukin 21; CD4: Cluster of Differentiation 4; PID: Primary Immune Deficiency; SCID: Severe Combined Immune Deficiency

INTRODUCTION

Cytomegalovirus (CMV) is an important cause of morbidity and mortality in immunocompromised individuals. Depression of cellular immunity because of primary immunodeficiency syndromes (PID) or secondary to immunosuppressive therapies increases the likelihood of symptomatic CMV infection. CMV may disseminate throughout the body, and the eyesmay be particularly affected [1].

CMV retinitis (CMVR) is the most common opportunistic ocular infection. Before the introduction of highly active antiretroviral therapy, approximately 5% of the pediatric HIV caseshad been suffering from CMV induced ocular disorders [2]. CMVR is also frequentlyobserved in children withPIDs, who are under immunosuppressive therapy for either malignant disorders, solid organ orhematopoietic stem cell transplantation(HSCT) [3].

Herein we report three immunocompromised patients with variable etiologiesin whom CMVR had occurred in their courses of illnesses.

CASE PRESENTATION

Case 1

A previously healthy, 15-year old girl was referred to our

clinic after she had been diagnosed as HIV infection during her evaluation for cervical lymphadenopathy. It is later ascertained that her mother hadalsobeen positive for HIV and she was out of treatment. Thus, she was accepted to haveperinatally acquired HIV infection. On admission, HIV viral load was 758.000 copies/ml and absolute CD4 count was 200 cells /mm [3]. Histopathological examination of cervical lymph node excisional biopsy revealed diffuse large B cell lymphoma. She was started on antiretroviral therapy together with chemotherapy. After six months, she was admitted to hospital with the complaint of suddenly onset blurred vision on her left eye. Fundoscopic examination revealed yellow-white retinal lesions with arterial sheathing in the superotemporalmidperipheral area (Figure 1). CMV DNA was detected in the examination of aqueous humor confirming the diagnosis of CMVR. At the same time, CMV viral load was negative in peripheral blood. HIV viral load and absolute CD4 count were found as 105.000 copies/ml and 50 cells /mm^3, respectively. Her ocular complaints and fundoscopic findings fully resolved after 6 months of treatment with parenteral and intravitreal ganciclovir therapy.

Case 2

A 17-year old boy who had been followed upwith the unidentified PID in our clinical immunology department for thirteen years, was presented with diminished visual acuity on his left eye. He had had recurrent lower respiratory tract infections, hepatosplenomegaly, recurrent skin rashessince early childhood. Laboratory examination had revealed CD4 lymphopenia, low serum IgG3 and near normal IgG levels.He had been given regular intravenous immunoglobulin replacement therapy together with antiasthmatic medication due to unremitting wheezy episodes.

At about 17 years of age, he was admitted to our clinic with newly onset diminished visual acuity on his left eye. Fundos copic examination revealed CMVR in the inferotemporalmidperipheral area (Figure 2). Serum CMV DNA level and absolute CD4 count were 10.520 copies/mL and 50 cells/mm^3, respectively. He was started on parenteral and intravitreal ganciclovir therapy. In the course of the treatment, emerging active lesions on left eye were detected and he had total vision loss. Several treatment modalities including parenteral and/or intravitreal ganciclovir, valganciclovir, foscarnet and cidofovirwere applied since he was unresponsive to treatment. Nevertheless, invasion of the other eye could not be prevented. Meanwhile, the patient was diagnosed as IL-21 receptor deficiency and was undergone HSCT. But unfortunately, he passed away immediately after the transplantation due to acute onset of massive pulmonary hemorrhage.

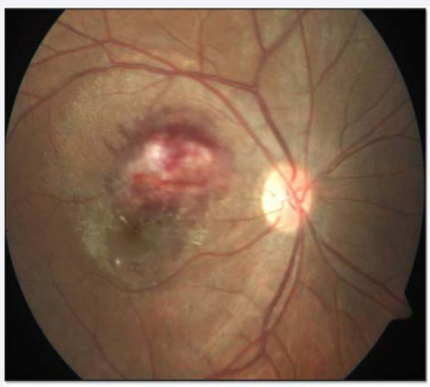

Figure 1 Case 1, fundoscopic examination.

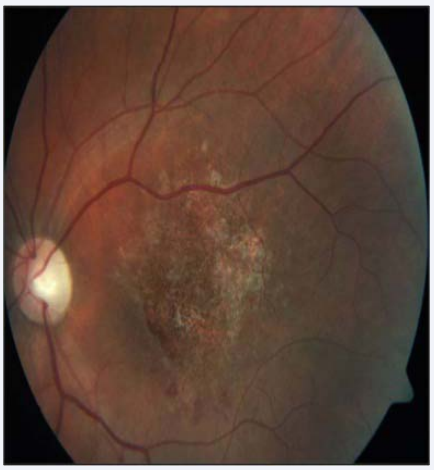

Figure 2 Case 2, fundoscopic examination.

Case 3

Our third case was a 4-month old girl with the diagnosis of T (-), B (-), NK (+) severe combined immunodeficiency who had been a candidate for HSCT. Since she had diffuse pulmonary infiltrates on her chest X-ray, she was tested for CMV infection which revealed serum CMV DNA level as 5.000.000 copies/ml. Fundoscopic examination for possible CMV involvement showed granular appearance and yellow-white retinal lesions with bilateral arterial sheathing at the posterior pole. These findings were compatible with CMVR. She was first given parenteral ganciclovir treatment and then altered to foscarnet because of clinical and microbiological treatment failure in the third month of therapy. Unfortunately, the patient passed away due to multi-organ failure related to systemic CMV infection.

Clinical findings, ophthalmologic features and treatment modalities of the cases were detailed in (Table 1) and (Table 2).

DISCUSSION

CMVRis mainly observed in immunocompromised patients either with PIDs or secondary immune deficient disorders. It is more obviouswhen the cellular immunity is altered. It can cause subtle visual disturbances or even be asymptomatic. Therefore, it can be undetected in patients who are under risk of CMVR unless it is particularly searched for. Delay in treatment can result in retinal scars and vision loss [4]. Herein, we reported three cases of CMVR with underlying variable immune deficient disorders. Among those, two patients suffered from PIDs. In that case, the only chance of immune reconstitution is HSCT. The other patient was diagnosed with acquired immune deficiency syndrome (AIDS) and lymphoma, in whom antiretroviral treatment could aid in improvement of the immunity. Treatment of CMVRcould only be achieved in that patient after the reconstitution of the immunity.

Table 1: Clinical features of patients with CMVR.

No, Gender	Primary diagnosis	Age at diagnosis (years)	Systemic-treatment	Lymphocytesubgroupanalysis (cells/mm^3)	Extraocularinvolvement	Follow-up time (months)	Immunereconstitution	Outcome
1, F	HIV infection, Blymphoma	17	AZT, 3TC, LPV/r, CHOP	CD4:200 CD8:1250	No	6	Yes	Survival
2, M	IL-21 receptordeficiency	17	IVIG, TMP-SMX	CD4:50 CD8:635	No	24	No	Exitus
3, F	SCIDs	0,3	IVIG, TMP-SMX	CD4:160 CD8:650	Pneumonia, hepatitis, encephalitis	3	No	Exitus

AZT: Zidovudine; CMV: Cytomegalovirus; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisolone; HIV: Human Immunodeficiency Virus; IVIG: Intravenous Immunoglobulin; LPV/r: lopinavir/ritonavir; SCIDs; Severe Combined Immunodeficiency Syndrome; TMP-SMX; Trimethoprim/sulfamethoxazole: 3TC; lamivudine.

Table 2: Ophthalmologic features and treatment course of patients with CMVR.

No	Laterality at presentation	Visual acuity	Location of active	Initial Induction Therapy (weeks)	Maintenance Therapy	Reactivation (Episodes)	Ocular Outcome
1	LE	Blurred	ST-MPA	IV andintravitrealganciclovir (4)	PO ganciclovir	No	20/20
2	BE	LE: 20/50 RE: 20/20	LE: IT-MPA RE: PP	IV andintravitreal ganciclovir (8)	IV foscarnet IV cidofovir	Yes (3)	LE: 0/20 RE: 8/20
3	BE	BE: CSM	BE: PP	IV ganciclovir (12)	IV ganciclovir	No	BE: CSM

CMV: Cytomegalovirus; LE: Left Eye, RE: Right Eye; BE: Bilateral Eye; CSM: Central, Steady, Maintained with 14–prism diopter base-down test; IT: Inferotemporal; IV: Intravenous; MPA: Midperipheral area; PO: oral; PP: Posterior pole; ST: Superotemporal

The prevalence of CMVR in HIV infected children is estimated as 5%, and it commonly affects thosewith low CD4 count and active HIV replication. Before the introduction of antiretroviral therapy, patients with CMVRespecially had CD4 counts <50 cells/mm^3 with minimal ocular inflammation [5]. Although there is limited data, unlike HIV infection, CMVR can be observed even in the presence ofhigh CD4 counts in patients who are on immune suppressive therapy for malignancy [6]. Our first case was diagnosed with AIDS and lymphoma concomitantly. She had very low CD4 cell counts at the time of CMVR. It is reasonable to think that AIDS was the main predisposing factor for the development of CMVR in this patient.

IL-21 has been shown to regulate cytotoxic activity of natural killer cells, proliferation of lymphocytes and differentiation of B lymphocytes and Th17 cells. IL-21 effects on both innate and adaptive immune responses and plays crucial roles in the processes of autoimmune diseases, inflammatory disorders and malignancy. Up to date, only four cases, two kindred,have been identified with the loss-of-function mutations in IL-21 receptor. Early diagnosis of IL-21R deficiency and allogeneic HSCT may avoid fatal complications [7,8]. In light of our knowledge, our patient is the first reported case of CMVR related to IL-21 receptor deficiency. This patient had severe lymphopenia at the time of infection with very low CD4 counts.

The optimal treatment of CMVR in children has not been established. Present therapeutic regimens with ganciclovir and foscarnet are identical to those which have been used in adult patients with drug doses adjusted for body weight [9,10]. The most important factor in determining the response to therapy is reconstitution of host immunity, particularly the cellular one. For our two patients with PIDs, in whom CD4 lymphopenia could not be reversed, no improvement in CMVR could be obtained by different modalities of medical therapy. However, the patient with AIDS and lymphoma recovered from CMVR with immune reconstitution gained after antiretroviral treatment.

In conclusion, routine ophthalmologic examinations should be performed in patients with primary and secondary immune deficiencies in terms of CMVR. Immune reconstitution may allow discontinuation of anti CMV therapy and may improve systemic prognosis. Early diagnosis and proper treatment of CMVR may avoid irreversiblevisual loss.

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