• Letter to the Editor •

Bilateral cytomegalovirus retinitis in a patient with dyskeratosis congenita

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Dear Editor,

We are writing to present a case of bilateral sequential cytomegalovirus retinitis (CMVR) in a patient with dyskeratosis congenita (DC). DC is an inherited bone marrow failure syndrome characterized by a typical diagnostic triad of oral leukoplakia, nail dystrophy, and reticular hyperpigmentation[1]. DC can be inherited in one of the three forms, X-linked, autosomal dominant, and autosomal recessive. Mutations in 19 genes are associated with DC, and a fifth of the pathogenic mutations are found in *DKC1*, the gene coding for dyskerin[2]. Mutation of *DKC1* in X-linked DC severely impairs telomerase activity by blocking telomerase assembly and disrupts telomere elongation during reprogramming. DC affects all body systems, particularly the immune system[3]. Reported clinical ophthalmic features include alopecia areata of the eyelashes, pterygium, obliteration of the lacrimal puncta, telangiectasia, and optic atrophy[4-5]. However, only a few reports have shown retinal complications in patients with DC. In this report, we present a case of bilateral CMVR in a patient with DC.

Ethical Approval All procedures adhered to the tenets of Declaration of Helsinki. Written informed consent was obtained from the patients.

A 30-year-old man presented to our hospital with decreased vision in his right eye that started 7d previously. He was diagnosed with DC 20y prior based on the presence of the clinical triad: oral leukoplakia, nail dystrophy, and reticular hyperpigmentation (Figure 1A-1C). His uncle had DC and died because of malignancy. His nephew also has DC but without any complications. He had a genetic test and had been found to have c.109_111del mutation in the *DKC1* gene at Xq28. The patient was negative for human immunodeficiency virus infection. His CD4+ T-lymphocyte counts were 137 cells/μL (reference range of 500-1600 cells/μL). His best-corrected visual acuity (BCVA) was light perception in the right eye and 20/20 in the left eye. Examination of the right eye revealed a combined injection and clusters of keratic precipitates (Figure 1D). The patient had severe vitreous opacifications in the right eye. Therefore, the fundus could not be clearly visualized (Figure 1E). Examination of the left eye revealed no remarkable findings.

Endophthalmitis in the right eye was suspected and the patient underwent vitrectomy of the right eye. Well-circumscribed necrosis, hemorrhage, and vascular sheathing were observed during the surgery. Multiple small retinal tears similar to a fishing net pattern were observed in the necrotizing area. Silicone oil was then injected into the vitreous cavity to act as a tamponade to the retina. Vitreous microscopy and culture for bacteria and fungus were negative. Aqueous humor biopsies conducted for qualitative polymerase chain reaction (PCR) testing of the right eye revealed that it was positive for cytomegalovirus (CMV)-DNA. Thereafter, the patient's diagnosis was revised to CMVR in the right eye. The patient received intravitreal ganciclovir injections (3 mg/0.1 mL) in the right eye once per week and intravenous ganciclovir (250 mg *q.8h*) for two weeks, followed by oral ganciclovir (1000 mg *t.i.d*). At the 4wk follow-up visit, the necrotizing area had become restricted and the patient's BCVA was 20/333 in the right eye (Figure 2A). Although the BCVA of the left eye was 20/20, fundus examination revealed a granular and yellow-white region in the temporal periphery (Figure 2B). An aqueous tap of the left eye sent for PCR analysis was positive for CMV-DNA. The patient was therefore diagnosed with CMVR in the left eye. However, the patient showed pancytopenia at the same time, so the oral ganciclovir was discontinued. Intravitreal ganciclovir injection (3 mg/0.1 mL) was then administered

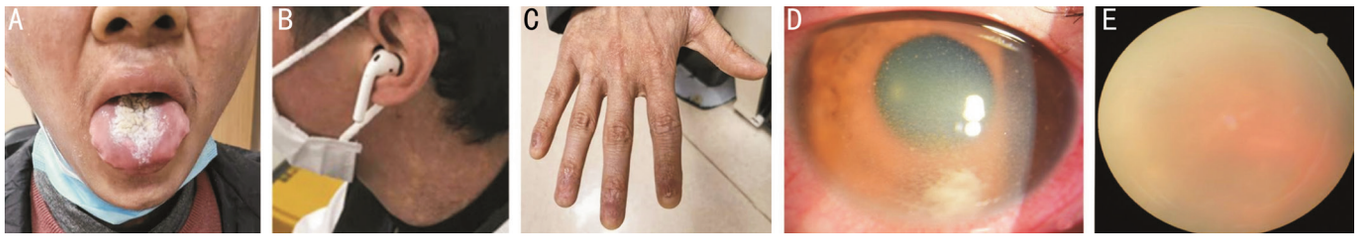

Figure 1 The clinical triad of oral leukoplakia (A), reticular hyperpigmentation (B), and nail dystrophy (C) in dyskeratosis congenita and the anterior (D) and posterior (E) segments of the right eye.

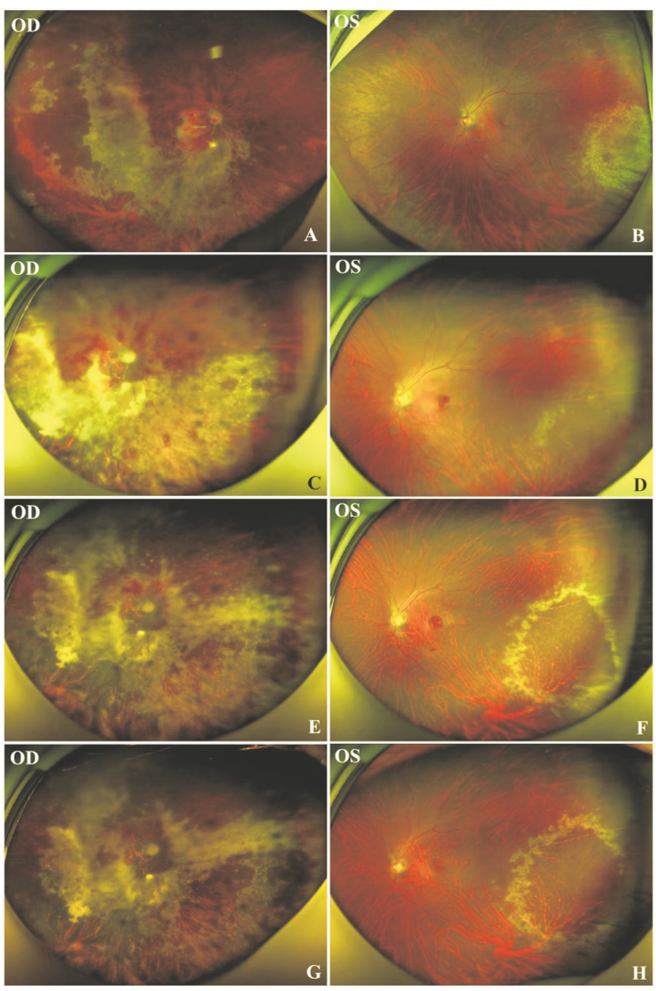

Figure 2 Follow-up findings of bilateral fundus examinations Examination of the right eye did not show any remarkable findings at the 4 (A), 8 (C), 12 (E), and 16wk (G) follow-up visits. A granular and yellow-white region was observed in the periphery of the fundus of the left eye at the 4wk follow-up visit (B). The yellow-white region regressed at the 8wk follow-up visit (D). The region reappeared as a circular spot at the 12wk follow-up visit (F) and remained until the 16wk follow-up visit (H). OS: Left eye; OD: Right eye.

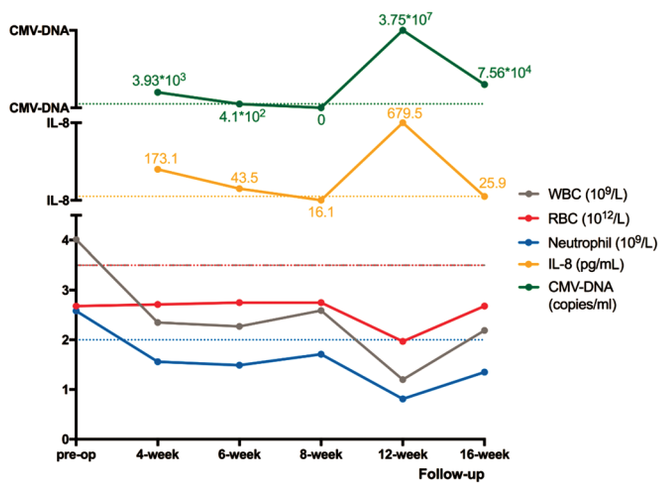

Figure 3 CMV-DNA load and IL-8 levels in the left eye and blood test result changes Green dotted line, maximum reference range of CMV-DNA load in the aqueous humor was 1×10^3 copies/mL. Yellow dotted line, maximum reference range of IL-8 level in the aqueous humor was 20 pg/mL. Blue dotted line, minimum reference range of neutrophil count was 2×10^9/L. Red and gray dotted line, minimum reference ranges of red (RBC) and white (WBC) blood cell counts were both 3.5×10^{12}/L. CMV: Cytomegalovirus.

to the left eye once per week. In addition, the patient began taking oral vitamin B4 and batilol to increase his white blood cell (WBC) count, as advised by a hematologist. Examination of the right eye at the 8wk follow-up visit did not reveal any remarkable findings (Figure 2C). Examination of the left eye showed regression of the yellow-white region in the temporal periphery of the fundus (Figure 2D). However, at the 12wk follow-up visit, the yellow-white region reappeared as a circular spot (Figure 2F) and remained until the 16wk follow-up visit (Figure 2H). The CMV-DNA load in the aqueous humor of the right eye at the 4, 6, 8, and 12wk follow-up visits are 1.92×10^4, 4.46×10^5, 4.32×10^6, and 2.89×10^5 copies/mL respectively. The CMV-DNA load in the aqueous humor of the left eye at the 4, 6, 8, and 12wk follow-up visits are 3.93×10^3, 4.1×10^2, 0, and 3.75×10^7 copies/mL respectively.

The changes in the CMV-DNA load and interleukin (IL)-8 levels in the aqueous humor of the left eye along with the changes in the blood test results are shown in Figure 3. The CMV-DNA load in the left eye decreased to zero at the 8wk follow-up visit but increased at the 12wk follow-up visit. Correspondingly, the WBC, red blood cell (RBC), and neutrophil counts decreased considerably at the 12wk follow-up visit. At the 16wk follow-up visit, the WBC, RBC, and neutrophil counts increased, whereas CMV-DNA load and IL-8 levels decreased.

In this report, we present a case of bilateral sequential CMVR in a patient with DC and analyze his clinical manifestations along with CMV-DNA and IL-8 levels in the aqueous humor.

To the best of our knowledge, this is the first report that analyzed CMV-DNA and IL-8 levels in a patient with DC. In the present case, the patient had bilateral sequential CMVR and developed pancytopenia after a 4wk antiviral treatment. CMV infection in the eye is a strong indicator of poor immune competence[6]. The clinical expression of CMVR is strongly associated with immune status. In immunosuppressed patients, a mixed clinical picture of intraocular inflammation with panretinal occlusive vasculopathy, more characteristic of retinal necrosis, and slowly progressive peripheral granular retinitis is observed[7]. CMVR in the contralateral eye occurs in up to 70% of patients and commonly in immunosuppressed patients[8]. The development of bilateral CMVR in this patient suggests severe immunodeficiency caused by DC. During treatment for such patients with immunodeficiency, special attention should be paid to the adverse reaction of the drug they use. We considered his pancytopenia as an adverse reaction to systemic antiviral treatment of ganciclovir. We then discontinued the systemic ganciclovir treatment and took intravitreal ganciclovir injections bilaterally.

As previously reported, IL-8 positively correlated with aqueous CMV-DNA load and declines after intravitreal administration of antiviral injections[9]. Aqueous humor IL-8 levels can be used as an indicator for treatment decisions[10]. However, no one reported the correlation of aqueous test and routine blood test in patients with DC. In this case, the yellow-white region in the left eye reappeared at the 12wk follow-up visit, indicating a relapse of retinitis. Simultaneously, the CMV-DNA load in the left eye increased from 0 to 3.75×10^7 copies/mL, in line with its clinical manifestation. The IL-8 level in the left eye also increased. Furthermore, the WBC, RBC, and neutrophil counts decreased significantly at the same time. This may be the reason for the relapsed retinitis in the left eye. Routine blood test is easier to do than aqueous test. The result of routine blood test could reflect the course of CMVR in some ways. Therefore, we believe that routine blood test could be a common monitoring practice during antiviral treatment for patients with immunodeficiency.

In conclusion, DC is a rare multisystem disorder commonly associated with immunodeficiency. Development of bilateral CMVR in the patient may suggest severe immunodeficiency caused by DC. During antiviral treatment for CMVR, special attention should be paid to patients with systemic disorders, especially those with immunodeficiency disorders, such as DC. Moreover, routine blood monitoring is necessary during antiviral treatment for these patients.

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