Spectral-domain optical coherence tomography finding in cytomegalovirus retinitis in AIDS patients

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Abstract

● AIM: To observe the findings of spectral domain optical coherence tomography (SD-OCT) scan in cytomegalovirus retinitis (CMVR).

● METHODS: Forty-six eyes of 33 patients with acquired immunodeficiency syndrome and CMVR were enrolled in the study. Complete ophthalmologic examinations, color fundus photography, SD-OCT and fundus autofluorescence (FAF) were performed for all patients at the first visit and each follow-up visit. Retinal necrosis in CMVR was analyzed on SD-OCT and classified into two types, the typical type and the atypical type.

● RESULTS: Forty-one eyes of active CMVR and 4 eyes of recurrent CMVR were classified into typical type, and 4 eyes with graying retinal lesion without hemorrhage or only punctate hemorrhage were classified into atypical type. In active stage of CMVR, the retina in typical type was significant thickened with hyperreflective lesion and full-thickness disruption of retinal architecture with enlarged vessel; while in atypical type, the retina was also destroyed in all layers but without thickening or slightly thinned. The choroid, vitreous and retinal vessels were not significantly involved. In healed stage, the retina was thin with destroyed layers in both types. In typical type, FAF showed mottled hypofluorescence mixed with punctuate hyperfluorescence. In atypical type, the retina showed some “cavity” in outer nuclear layer, and FAF showed mild hyperfluorescence.

● CONCLUSION: SD-OCT show different changes in the retina in typical type and atypical type of CMVR, which should be useful in assisting diagnosis and follow-up management of the disease.

● KEYWORDS: cytomegalovirus retinitis; optical coherence tomography; fundus autofluorescence

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Cytomegalovirus retinitis (CMVR) is the most common severe ocular opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS). Although the incidence of CMVR decreased significantly in the era of highly active antiretroviral therapy, CMVR was still the leading cause of visual loss in AIDS patients¹². A study of AIDS patients in five countries in Africa and Asia found 37% of individual eyes with CMVR were blinded by the infection, which suggested that CMVR is a serious disease with a high rate of blindness in developing countries³. At present, the diagnosis and evaluation of CMVR is based on a combination of information gathered from medical history, clinical and laboratory findings, as well as imaging techniques. Among them, fundus examination is essential for the follow-up of CMVR patients, but it is difficult to evaluate some small or atypical lesions by fundus examination⁴. Spectral-domain optical coherence tomography (SD-OCT), as a non-contact, non-invasive and high-resolution imaging technique, is widely used to diagnose and follow-up of various retinal diseases. Understanding SD-OCT findings of different fundus changes in CMVR could be helpful in the diagnosis and follow-up of CMVR, especially for the atypical type of CMVR which is easily misdiagnosed or missed diagnosed in clinic.

In this report, we describe the clinical findings with SD-OCT imaging in 46 eyes of 33 patients with CMVR to observe the different changes of retina, retinal vessels, vitreous body and choroid on SD-OCT in patients with typical type and atypical type CMVR and in active and healed stages to explore the significance of SD-OCT in assisting the diagnosis and follow-up of this disease.
SUBJECTS AND METHODS

Ethical Approval This retrospective observational cohort study was conducted on AIDS patients with CMVR who presented to the First Affiliated Hospital of Zhejiang University from January 2015 to December 2018. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University and adhered to the tenets of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study. Diagnosis criteria for CMVR included:

1) patients with AIDS and CD4 T-lymphocyte cell (CD4+) counts <200 cells/μL; 2) the fundus showed typical signs such as fluffy, yellow-white retinal lesions, with or without retinal hemorrhage, with little inflammation of the vitreous. The necrotic lesions often spread out granularly. Blood vessels near the lesions may appear to be sheathed. Typical type was used to term such pizza-like CMVR in this study; 3) in rare cases with controversial findings, polymerase chain reaction (PCR) of aqueous or vitreous specimens for CMV was performed to confirm the diagnosis, which were referred to as atypical type in this study; 4) CMVR was divided into central type and peripheral type according to the location of the lesion. If the lesion was within 1500 microns of the fovea, it was defined as central type, otherwise, it was peripheral type.

The patients’ demographic data were recorded, including age, sex, CD4 count, and antiretroviral treatment. Best corrected Snellen visual acuity (VA), intraocular pressure (IOP) measurement, slit-lamp biomicroscope and indirect ophthalmoscope examination were performed initially and at every follow-up visit. Some patients were examined by fluorescein fundus angiography (FFA) and B-ultrasound.

All patients underwent SD-OCT scan (BluePeak-Spectralls, Heidelberg, Germany). The single-line scans and 20×30 dense volume scans passing through posterior pole were obtained in all the patients. The SD-OCT scan protocol of lesions varied according to the size and location of the CMVR lesions, with and without enhanced depth imaging (EDI) scan or fundus autofluorescence (FAF). In follow-up, the SD-OCT scans were performed in the same locations as baseline using the built-in eye-tracking function.

Anticytomegalovirus systemic therapy includes induction therapy and maintenance therapy. Patients received induction therapy in the hospital with ganciclovir 5 mg/kg intravenously (IV) q12h for 14-21d, except for patients with low white blood cell count or obvious bone marrow depression were given foscarnet 60mg/kg IV q8h or 90 mg/kg IV q12h for 14-21d. Combined vitreous injection of ganciclovir 2-4 mg/0.1 mL every week were performed for the central lesion to faster control of the infection until steady level of intraocular ganciclovir concentrations are achieved. After induction therapy, preferred maintenance therapy regimen is valganciclovir 900 mg once daily for at least 3-6mo which was stopped with inactive lesions and with CD4+ count >100 cells/μL for 3 to 6mo. However, due to the price of ganciclovir, most patients receive ganciclovir (1000 mg) three times a day in maintenance therapy. Recurrent cases will receive induction therapy again.

The patients were followed up once a week during induction therapy, once a month during maintenance therapy, and 1-3mo after withdrawal of medication.

RESULTS

Patient Characteristics Patients in this study were followed up from 3 to 39mo, mean length of follow-up was 9.6±7.8mo. Of the 33 patients (46 eyes) with AIDS (Table 1), there were 26 males and 7 females, ages ranged from 21 to 78y, with an average age of 39.7±13.9y. On the first diagnosis of CMVR, CD4+ count ≤50/μL was found in 26 patients (78.8%), CD4+ count 50-100/μL in 5 patients (15.1%) and CD4+ count >100/μL in 2 patients (6.1%). The average CD4+ count was 32.2±45.2/μL.

Fundus Finding At the first visit, of the 46 eyes with CMVR, 41 eyes were with active lesion and 5 eyes with scar lesions; 9 eyes (21.9%) were with frost-like dendritic vasculitis and 7 eyes (15.2 %) with optic neuritis. According to the location of lesion, 20 eyes (43.5%) were central type and 26 eyes (56.5%) peripheral type. During maintenance therapy (ganciclovir capsule 1000 mg oral three times a day) CMVR relapsed in 8 eyes (17.4%), secondary retinal detachment occurred in 9 eyes (19.5%), immune reconstituted uveitis in 5 eyes (10.9%). Five patients died during follow-up. At the last follow-up, the VA remained stable or improved in 35 eyes (71.7%) and decreased in 13 eyes (28.3%; Table 1).

SD-OCT Findings

Typical type According to the fundus examination, 41 eyes of active CMVR and 4 eyes of recurrent CMVR were classified into typical type. Some characteristic changes of retinal tissue, retinal vessels, vitreous body and choroid were documented on SD-OCT in typical type CMVR.

Retina In active stage, the retinal lesion showed significant thickening and hyperreflectivity in all the layers of retina with full-thickness disruption of retinal architecture on SD-OCT (Figure 1A, 1B). In healed stage, OCT showed thinned, hyperreflective tissue with destruction of all retinal layers (Figure 2A-2C) and FAF shows mottled hypofluorescence mixed with punctuate hyperfluorescence in retinal lesion (Figures 2B and 3A).

Choroid In active stage, due to the influence of significant thickening and hyperreflective signal of retina, the choroid layer cannot be clearly observed on SD-OCT (Figure 1A). In healed stage, compared with the healthy area, the choroid in all the lesion area was obviously thinned, especially in the choroidal capillary layer (Figure 2A, 2B). SD-OCT showed...
enhanced choroidal reflex below the healed lesions which correspond to the retina atrophy in the healed lesion areas (Figures 1C, 2A, 2B).

Vitreous Low level of inflammation was found in the vitreous of eyes with CMVR by fundus examination, however, vitreous cells were identified in 32 out of 41 eyes with active lesions.
Figure 1 Fundus photographs and OCT images in case 28 who affected with CMVR and cytomegalovirus papillitis  
A: First visit: fundus photography showed yellowish white retinal necrosis and retinal hemorrhage around the disc; OCT showed exudative retinal detachment in macular area and significant thickening and hyperreflective in temporal retina of optic disc with full-thickness disruption of retinal architecture (yellow arrow). 
B: Two weeks: after 2wk of anti-cytomegalovirus therapy, retinal necrotic lesion has disappeared on fundus photograph, OCT showed subretinal fluid absorption and the edema of the necrotic lesion relief (yellow arrow). 
C: Six weeks: fundus photography showed optic atrophy and the retinal necrosis and most of the retinal hemorrhage were absorbed; OCT showed complete absorption of subretinal fluid and retinal thinning in temporal retina of optic disc (yellow arrow).

Figure 2 Fundus photography and OCT images in healed stage  
A: Case 10; B: Case 31; C: Case 26. In the three healed lesions, compared with the healthy area, the choroid in the lesion area was obviously thinned, especially in the choroidal capillary layer. With the retina atrophy in the healed lesion areas, OCT showed enhanced choroidal reflex below the healed lesions.
which show hyperreflective deposits in vitreous on OCT imaging (Figures 1A, 4B). After anti-CMV treatment, the hyperreflective deposits in vitreous decreased significantly with the absorption of the lesion and the improvement of inflammation (Figures 1C, 4E). In healed stage, 17/25 eyes showed persistence posterior hyaloid thickening with traction on the retina (Figure 2B1, 2C1).

Retinal vessel  CMVR may accompany with frosted branch angiitis, retinal vessels near the lesions may appear to be sheathed like frosted branches of a tree. In all the 5 eyes of central type CMVR complicated with frost-like dendritic vasculitis, SD-OCT showed obvious dilation of the involved retinal vein with hyperreflex thickening of the vascular wall in the active stage (Figure 4B, 4C). However, there was no obvious change in the arterial wall in the lesion area. After anti-CMV treatment, vascular inflammation subsided, and dilatation and thickening of retinal vein was not observed by SD-OCT (Figure 4E, 4F).
Exudative retinal detachment

Central type CMVR, especially cytomegalovirus papillitis (CMVP), is often accompanied by exudative retinal detachment. In this study, exudative macular detachment occurred in 5 of 7 eyes with CMVP. Figures 1 and 4 documented two patients with CMVP.

Initial SD-OCT imaging showed neuroepithelial detachment in macular area, a patch of intraretinal and subretinal hyperreflective deposits (hemorrhage, exudation; Figures 1A, 4B). A few weeks after anti-CMV treatment, SD-OCT imaging demonstrated a complete absorption of subretinal fluid and a small amount of hyperreflective subretinal deposits (hard

Retinal Detachment

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exudation). After absorption of the subretinal fluid, disruption of the photoreceptor IS/OS junction was observed in the original detachment area (Figures 1C, 4E).

**Rhegmatogenous retinal detachment** Nine of the 46 eyes developed rhegmatogenous retinal detachment (RRD), 7 eyes occurred during follow-up and 2 eyes presented at first visit (both eyes were found in the case 27). All 9 cases of secondary RRD occurred in CMVR healed stage. The secondary RRD in CMVR often involve scar atrophy area. The retina in detachment area was thin and the surface can be accompanied by posterior vitreous cortex pull on SD-OCT (Figure 5B).

**Atypical Type** Four eyes show atypical manifestations, in which the fundus showed graying retinal lesion without hemorrhage or only punctate hemorrhage (Figures 3B, 5A). The final diagnosis of CMVR was confirmed by the results of CMV DNA testing of aqueous humor.

In active stage, the atypical type lesion on SD-OCT showed destruction of retinal structure in all layers, but the retina was not thickened or slightly thinned, and the choroid, vitreous and retinal vessels were not significantly involved (Figures 3B, 5B). In healed stage, the retinal lesion showed thinning and destroyed retina with some “cavity” in outer nuclear layer (Figures 3D, 5B), and showed mild hyperfluorescence on FAF (Figure 3D).

**DISCUSSION**

The typical type of CMVR is characterized by “pizza” fundus change. CMVR is usually diagnosed based on identification of characteristic retinal changes by fundus examination. In the present study, the fundus of 41 eyes of active CMVR and 4 eyes of recurrent CMVR showed typical type retinitis. The characteristic changes of this type on OCT are significant thickening and hyperreflectivity in all the layers of retina with full-thickness disruption of retinal architecture, which are consistent with previous studies.

The atypical type CMVR has rarely been reported previously. In the present study, 4 eyes showed graying retinal lesion without hemorrhage or only punctate hemorrhage during maintenance therapy period. PCR evaluation of aqueous humor from the four eyes confirmed high copy numbers of CMV DNA, supporting the diagnosis of CMVR. The lesion showed destruction of retinal structure in all layers of retina and retinal vessels were not significantly involved (Figures 3B, 5B). In healed stage, the retinal lesion showed thinning and destroyed retina with some “cavity” in outer nuclear layer (Figure 3D), and showed mild hyperfluorescence on FAF. The final diagnosis of CMVR was confirmed by the results of CMV DNA testing of aqueous humor (5.8×10^2 copies/mL) and the fundus changes which included the gradually enlarged lesion (Figure 3C), which was progressively absorbed after intravitreal injections of ganciclovir (2 mg; Figure 3D). This case suggests the value of OCT in the diagnosis of atypical CMVR in early stage.

In addition to retinal changes, there are different findings in retinal pigment epithelium (RPE) and choroid complex between typical type and atypical type CMVR in the healed stage. The characteristic type showed thinned, hyperreflective tissue with destruction of all retinal layers, and the choroidal capillary layer of the lesion was obviously thinned; FAF show hypofluorescence with mottled hyperautofluorescence in the healed lesion (Figure 3A) which were consistent with the report of Invernizzi et al.[5] and Yeh et al. In comparison, in atypical type, OCT showed some “cavity” in ONL and choroidal layer largely unaffected with hyperautofluorescence on FAF (Figure 3D). These differences suggested that the atypical type lesion has little effect on RPE and choroid. The above observations support the theory that CMV reaches the eye through retinal vessels, infects retinal vascular endothelial cell first, then spreads to the inner layer of the retina, and finally moves downward, potentially involves RPE and choroid. Frosted branch vasculitis (FBA) is one of the common signs of CMVR. FFA shows no occlusion or stasis but late leakage from the sheathed vessels. With characteristic of tomography, OCT could observe the vascular cross-section.
SD-OCT showed thickened vessel wall without occlusion, the veins are mainly involved and the arteries are not involved. Venous involvement may be associated with its slower blood flow, CMV virus in the blood is more likely to infect vascular endothelial cells, and stimulate the infected vein dilatation and vascular wall inflammatory substances deposition. The perivenous exudation usually clears and the vascular diameter returned to normal within several weeks after anti-CMV treatment without combined corticosteroid therapy. Since the exact pathogenesis mechanism of FBA is not clear, the characteristic changes of OCT can help us to better understand the essence of FBA. Compare with other ophthalmic examination, OCT also has some advantages in assisting diagnosis and treatment in AIDS patients with CMVR. First of all, compared with FFA, OCT is a simple and non-invasive technique, which can reduce the exposure risk of medical staff and is more easily to be accepted by patients and doctors. Secondly, AIDS combined with CMVR is a disease requiring long-term follow-up by repeated clinical examinations. The follow-up pattern of OCT could accurately monitor and compare the changes of the lesions in the course of treatment. In addition, it could provide FAF images while completing the OCT scan which supplied more information and data to analyze CMVR. Lastly, some changes, which are difficult to detected by indirect ophthalmoscopy, could clearly observed by SD-OCT, such as subtretinal fluid, retinal thickness changes or minor changes in the range of lesions.

This study has certain limitations. First, the retrospective observational nature and small numbers of patients included. However, to our knowledges, this study is the largest to date to report the findings of SD-OCT for CMVR in patients with AIDS. Second, peripheral lesions could not be entirely scanned because of limitation of OCT machine. Third, the OCT characteristic changes in atypical type CMVR we found from small sample, the clinical characteristics and histological changes of this atypical CMVR need further investigation. In conclusion, typical type and atypical type CMVR showed different changes in retina, vitreous and choroid in SD-OCT. The SD-OCT observation in CMVR could be helpful to understand the pathological mechanism and prognosis of CMVR. OCT should be considered a useful tool in diagnosis and follow-up of CMVR.

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