Clinical characteristics in the misdiagnosis of cytomegalovirus retinitis: A retrospective analysis of eight patients

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Purpose: To highlight characteristics in the misdiagnosis of cytomegalovirus retinitis (CMVR). **Methods:** Misdiagnosed cases related to CMVR were analyzed retrospectively at the Department of Ophthalmology, Beijing Youan Hospital, from July 2017 to October 2019. The medical records were reviewed by two independent senior ophthalmologists and the patients' clinical characteristics were analyzed. **Results:** Eight patients (16 eyes) were identified with misdiagnoses related to CMVR. Six of the patients with CMVR were previously unaware of their human immunodeficiency virus (HIV) infection; one patient with CMVR concealed their history of HIV infection. The cases were initially misdiagnosed as diabetic retinopathy (1/7, 14.3%), branch retinal vein occlusion (1/7, 14.3%), ischemic optic neuropathy (1/7, 14.3%), Behçet's disease (1/7, 14.3%), iridocyclitis (2/7, 28.6%), and progressive outer retinal necrosis (1/7, 14.3%). One patient with binocular renal retinopathy and chronic renal insufficiency was misdiagnosed with CMVR. Four eyes (4/16, 25%) presented with pan-retinal involvement. Fourteen eyes (14/16, 87.5%) had optic disc or macular area involvement. At the final diagnosis, one patient was blind, and two patients had low vision. Seven AIDS patients showed an extremely low level of $CD4^+$ T lymphocytes (median of 5 cells/μl; range 1–9 cells/μl). **Conclusion:** CMVR may be misdiagnosed in the absence of known immune suppression. CMVR and HIV screening cannot be overlooked if a young male patient presents with yellowish-white retinal lesions. These misdiagnosed patients had severe retinitis associated with poor vision.

Key words: AIDS, cytomegalovirus retinitis, HIV, misdiagnosis

Cytomegalovirus retinitis (CMVR), as an opportunistic infectious retinal disease, is most commonly seen in acquired immune deficiency syndrome (AIDS) patients and is the most common cause of AIDS-related blindness.[1] Its diagnosis is important because CMVR both predicts and contributes to the mortality of HIV patients.[2,3] It can also occur in other patients with immunosuppression after organ or stem cell transplantation, individuals with potential immune dysfunction, such as advanced age, diabetes, hypertension, or renal insufficiency[4,5] and after intravitreal injection (hormonal or non-hormonal).[6–8]

For AIDS-related CMVR, previous research has shown that earlier CMVR diagnosis was associated with better visual outcomes and was helpful for preventing vision loss.[9] In this study, the medical records of patients with misdiagnosed CMVR, or other diseases misdiagnosed as CMVR, were retrospectively reviewed to highlight the clinical characteristics of misdiagnosis and to raise awareness of the need for an accurate diagnosis of this disease.

Methods

Study design and patients

This was a retrospective study conducted in the Department of Ophthalmology, Beijing Youan Hospital, from July 2017 to October 2019. CMVR in this study was diagnosed according to the gold standard: dilated examination of the entire retina with an indirect ophthalmoscope by a trained clinician.[10] Signs may appear as wedge-shaped areas of retinal whitening with associated hemorrhages, granular, opaque, white lesions, or frosted branch angiitis.[11] Misdiagnosis of CMVR refers to CMVR misdiagnosed as another disease, or another disease misdiagnosed as CMVR. The retrospective analysis identified patients who experienced misdiagnosis and irrelevant management by different ophthalmologists at different centers. This study was approved by the Beijing Youan Hospital, Capital Medical University Institutional Review Board (LL2018150K) and adhered to the tenets of the Declaration of Helsinki. All patients provided written, informed consent.

Data collection

Clinical data were reviewed by two independent senior ophthalmologists, including initial symptoms (chief complaint),

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duration, ophthalmologic examination, laboratory examination, previous diagnosis, previous treatment, and outcomes. CMVR lesions were documented through ultrawide-field (UWF) fundus imaging systems (Optos Daytona®; Optos PLC, Dunfermline, United Kingdom). Baseline data including sex, age, and comorbidities were recorded. Laboratory examinations included polymerase chain reaction (PCR) for HIV viral load, and flow cytometry for CD4$^+$ T lymphocytes. HIV infection was diagnosed using Western Blot analysis.

To obtain etiological evidence and exclude dual infection, we conducted standard aqueous tap in the operating room. PCR tests were conducted on the aqueous humor specimen for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV).

Statistical analysis

All data were analyzed using descriptive statistics in SPSS 25.0 software.

Results

Eight patients were misdiagnosed at their initial presentation. Seven patients with CMVR were misdiagnosed with other ocular diseases, and one patient with renal retinopathy was misdiagnosed with CMVR. The median age of the eight patients was 37.5 years (range: 20–46 years). All (8/8, 100%) patients were male. Six CMVR patients were previously unaware of their infection with HIV and were finally diagnosed with AIDS. One CMVR patient concealed their history of HIV infection. All AIDS patients showed other opportunistic infections or comorbidities with an extremely low level of CD4$^+$ T lymphocytes (5 cells/ul; range 1–9 cells/ul). All patients presented with binocular involvement (16 eyes). Six of the misdiagnosed CMVR patients received inappropriate treatment before their final diagnosis. Six patients finally revealed that they had been underreporting systemic symptoms, including abdominal pain, diarrhea, oral leukoplakia, rash, itchy skin, nausea, and vomiting [Table 1].

CMVR was initially misdiagnosed as diabetic retinopathy (1/7, 14.3%), branch retinal vein occlusion (1/7, 14.3%), ischemic optic neuropathy (1/7, 14.3%), Behçet's disease (1/7, 14.3%), iridocyclitis (2/7, 28.6%), and progressive

outer retinal necrosis (1/7, 14.3%). Fourteen eyes with CMVR varied in location and pattern of retinal signs: 4 eyes presented with pan-retinal involvement and all 14 eyes showed optic disc or macular area involvement; five eyes presented with typical signs including yellowish-white retinal lesions and retinal hemorrhage; four eyes with optic neuropathy; four eyes with opaque, white, granular retinal lesions and no hemorrhages; one eye presented with both optic neuropathy and frosted branch angiitis. Aqueous specimen tested for herpes virus etiologies were proved to be negative for HSV, VZV, and EBV, but positive for CMV for patients with clinically diagnosed CMVR. At the point of the final correct diagnosis, one patient (case 1) was blind, and two patients (cases 3 and 7) had low vision. One patient with renal retinopathy and chronic renal insufficiency presented with yellowish-white retinal lesions and retinal hemorrhage around the optic disc, which was misdiagnosed as CMVR. The characteristic ophthalmologic findings of these patients are presented in Table 2.

Case 1

A 38-year-old male patient with a history of blurred vision in both eyes and diabetes mellitus, both of two months duration, was diagnosed with diabetic retinopathy (oculus uterque, OU) and macular edema (OU) at a local hospital and received a binocular intravitreal injection of glucocorticoid. Following progressive deterioration of vision, he was to receive an intravitreal injection of anti-vascular endothelial growth factor (VEGF). The preoperative HIV antibody screening test was positive and he was referred to an infectious disease hospital. Fundus examination revealed pan-retinal yellowish-white necrotizing retinitis associated with multiple scattered granular lesions and retinal hemorrhages in both eyes, with involvement of the optic disc and macular area [Fig. 1]. Aqueous CMV viral load was 279,000 copies/ml in the right eye and 20,600 copies/ml in the left eye. A diagnosis of bilateral CMVR was established. He was admitted to the hospital and treated with intravenous and binocular intravitreal ganciclovir.

Case 2

A 39-year-old male patient had a history of blurred vision in the left eye of one month duration. He was initially diagnosed at a local hospital with branch retinal vein occlusion (oculus

Table 1: Clinical features of the initially misdiagnosed patients

Case	Initial diagnosis	Initial treatment	Confirmed diagnosis	Systemic disease	CD4$^+$T cell (/µl)
C1	Diabetic retinopathy	Intravitreal injection of glucocorticoid	CMVR	AIDS; Pulmonary infection; Oral fungal infection	5
C2	Branch retinal vein occlusion	Intravitreal injection of anti-VEGF	CMVR	AIDS; EBV infection; Severe anemia	2
C3	Behçet's disease	Topical and systemic glucocorticoid	CMVR	AIDS; Pulmonary infection; Oral fungal infection	5
C4	Iridocyclitis	Topical glucocorticoid	CMVR	AIDS; Syphilis; Dyslipidemia	9
C5	Ischemic optic neuropathy	Systemic glucocorticoid	CMVR	AIDS; Oral fungal infection; Chronic itching	3
C6	Iridocyclitis	Topical glucocorticoid	CMVR	AIDS; Pulmonary infection; Leukopenia	9
C7	Progressive outer retinal necrosis	Intravitreal injection of ganciclovir and foscarnet	CMVR	AIDS; Pulmonary infection; Oral fungal infection	1
C8	CMVR	None	Renal retinopathy	Renal failure; Renal anemia	192

M=Male; CMVR=Cytomegalovirus retinitis

Table 2: Ocular presentations of the initially misdiagnosed patients

Case/ Eye	Confirmed diagnosis	Fundus manifestations	Optic disc/macular area involved	BCVA at baseline
C1				
OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	LP
OS	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	LP
C2				
OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	60/200
OS	CMVR	Optic neuropathy: yellowish-white necrotizing lesions involving the optic disc and retina, vitreous opacity	Yes	LP
C3				
OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	30/200
OS	CMVR	Optic neuropathy: yellowish-white necrotizing lesions involving the optic disc and retina	Yes	30/200
C4				
OD	CMVR	Opaque white granular lesions	No	80/200
OS	CMVR	Opaque white granular lesions and vitreous opacity	Yes	60/200
C5				
OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	No	12/20
OS	CMVR	Optic neuropathy: yellowish-white necrotizing lesions involving the optic disc and retina and vascular sheathing	Yes	80/200
C6				
OD	CMVR	Optic neuropathy: yellowish-white necrotizing lesions involving the optic disc and retina	Yes	80/200
OS	CMVR	Optic neuropathy: yellowish-white necrotizing lesions involving the optic disc and retina	Yes	20/200
C7				
OD	CMVR	Opaque white granular lesions	Yes	40/200
OS	CMVR	Opaque white granular lesions	Yes	30/200
C8				
OD	Renal retinopathy	Soft and hard exudates, linear retinal hemorrhages around the optic disc	Yes	80/200
OS	Renal retinopathy	Soft and hard exudates, linear retinal hemorrhages around the optic disc	Yes	12/20

BCVA=Best corrected visual acuity; C=Case; M=Male; LP=Light perception; OD=Oculus dexter; OS=Oculus sinister

dexter, OD), and vitreous hemorrhage (oculus sinister, OS). He received an intravitreal injection of anti-VEGF treatment for the left eye and oral Chinese patent medicine. With the progressive deterioration of vision in the left eye and blurring of vision in the right eye, optical coherence tomography revealed macular edema (OD). The preoperative HIV antibody screening test at another hospital was positive and he was referred to an infectious disease hospital. Fundus examination revealed local retinal hemorrhage ("brush-fire") at the superior-nasal macular area, with retinal whitening and exudative retinal detachment around the lesion in the right eye [Fig. 1], severe vitreous opacity and yellowish-white necrotizing lesion around the optic disc in the left eye. Aqueous CMV viral load was 4557 copies/ml in the right eye. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and treated with intravenous and binocular intravitreal ganciclovir.

Case 3

A 27-year-old male patient gave a history of blurred vision, loss of central vision, and scotoma in both eyes of three weeks' duration. He was initially diagnosed with Behçet's disease (OU) and received treatment with topical and systemic glucocorticoids. However, the blurred vision deteriorated and blood tests were administered at another hospital. The HIV

antibody screening test was positive. Fundus examination revealed focal yellowish-white necrotizing retinitis associated with superficial retinal hemorrhage in the inferior quadrant of the optic disc in the right eye and around the optic disc, along with marginal yellowish-white lesions and central retinal atrophy in the left eye [Fig. 1]. Aqueous CMV viral load was 3859 copies/ml in the right eye and 4572 copies/ml in the left eye. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and was given intravenous and binocular intravitreal ganciclovir.

Case 4

A 46-year-old male patient gave a history of blurred vision and floaters in both eyes of three months' duration. He was initially diagnosed with iridocyclitis (OU) at the local hospital. He received treatment with periocular glucocorticoid injection (triamcinolone acetonide and dexamethasone). He received blood tests at another hospital and the HIV antibody screening test was positive. Fundus examination revealed superior, opaque, white, granular lesions in the right eye; nasal, opaque, white, granular lesions, a swollen optic disc; and vitreous opacities in the left eye [Fig. 1]. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and was given intravenous ganciclovir.
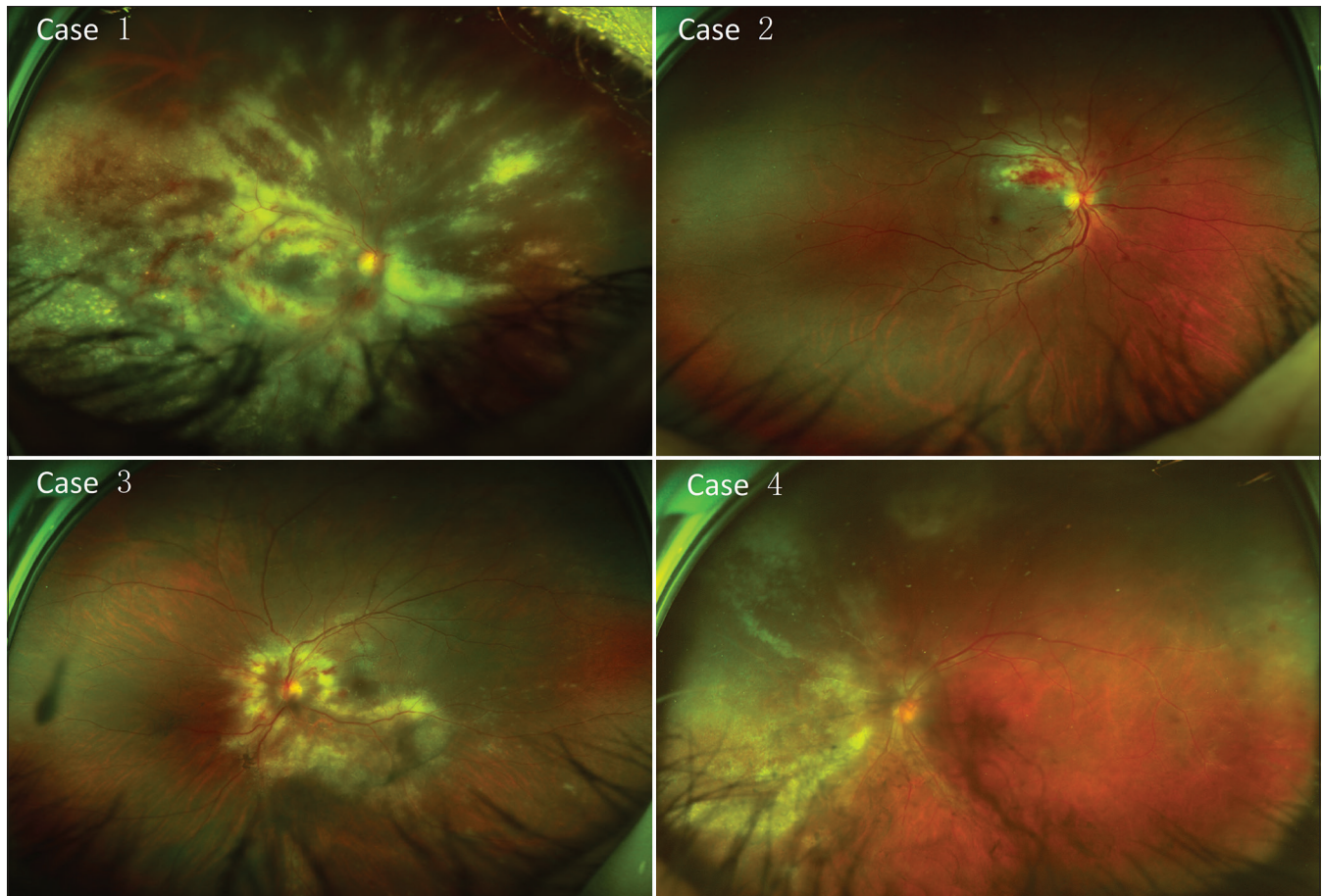
Figure 1: Ultrawide-field (UWF) fundus images of case 1–4 at final diagnosis

Case 5

A 37-year-old male patient gave a history of blurred vision in both eyes of one month duration and deteriorating vision of one week duration. He was initially diagnosed with ischemic optic neuropathy (OU), treated with intravenous pulse injections of methylprednisolone (40 mg, QD) for four days, and was maintained on oral steroids. With the progressive deterioration of vision, he received blood tests at another hospital and the HIV antibody screening was positive. Fundus examination revealed focal yellowish-white necrotizing retinitis associated with superficial retinal hemorrhage in the inferior quadrant of the optic disc in the right eye, around the optic disc in the left eye, and optic disc swelling and retinal vasculitis with perivascular sheathing (frosted-branch angiitis) in the left eye [Fig. 2]. A diagnosis of CMVR (OU) was established. Aqueous CMV viral load was 13,640 copies/ml in the left eye. He was admitted to the hospital and wasgiven intravenous ganciclovir and foscarnet. The left eye received intravitreal ganciclovir injection.

Case 6

A 44-year-old male patient gave a history of blurred vision and floaters in both eyes of four months' duration. He did not report his history of HIV infection, because he did not realize that this could be related to his ocular complaint. He was initially diagnosed with iridocyclitis (OU) at the local hospital and treated with glucocorticoid eye drops. With the progressive deterioration of vision, he told his doctor

about his six-year history of untreated HIV infection. Fundus examination revealed binocular pan-retinal superficial retinal hemorrhage associated with yellowish-white necrotizing retinitis, involving both optic discs and macular areas [Fig. 2]. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and received intravenous ganciclovir. He declined any ophthalmic therapy.

Case 7

A 28-year-old male patient gave a history of blurred vision in both eyes of ten days' duration. He was initially diagnosed with progressive outer retinal necrosis (OU) and treated with intravitreal injection of ganciclovir and foscarnet. His HIV antibody screening test was positive. The fundus examination revealed quadrantally distributed opaque white granular lesions without retinal hemorrhage in both eyes [Fig. 2]. Optical coherence tomography (OCT) showed a full-thickness disorganized retina. Aqueous CMV viral load was 328,000 copies/ml in the right eye. PCR analysis of aqueous VZV, HSV, and EBV were both negative. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and received intravenous and binocular intravitreal ganciclovir.

Case 8

A 20-year-old male patient gave a history of blurred vision in both eyes of two weeks' duration and a positive HIV antibody screening test of one week duration. He had a seven-year history of nephrotic syndrome. He was initially diagnosed with
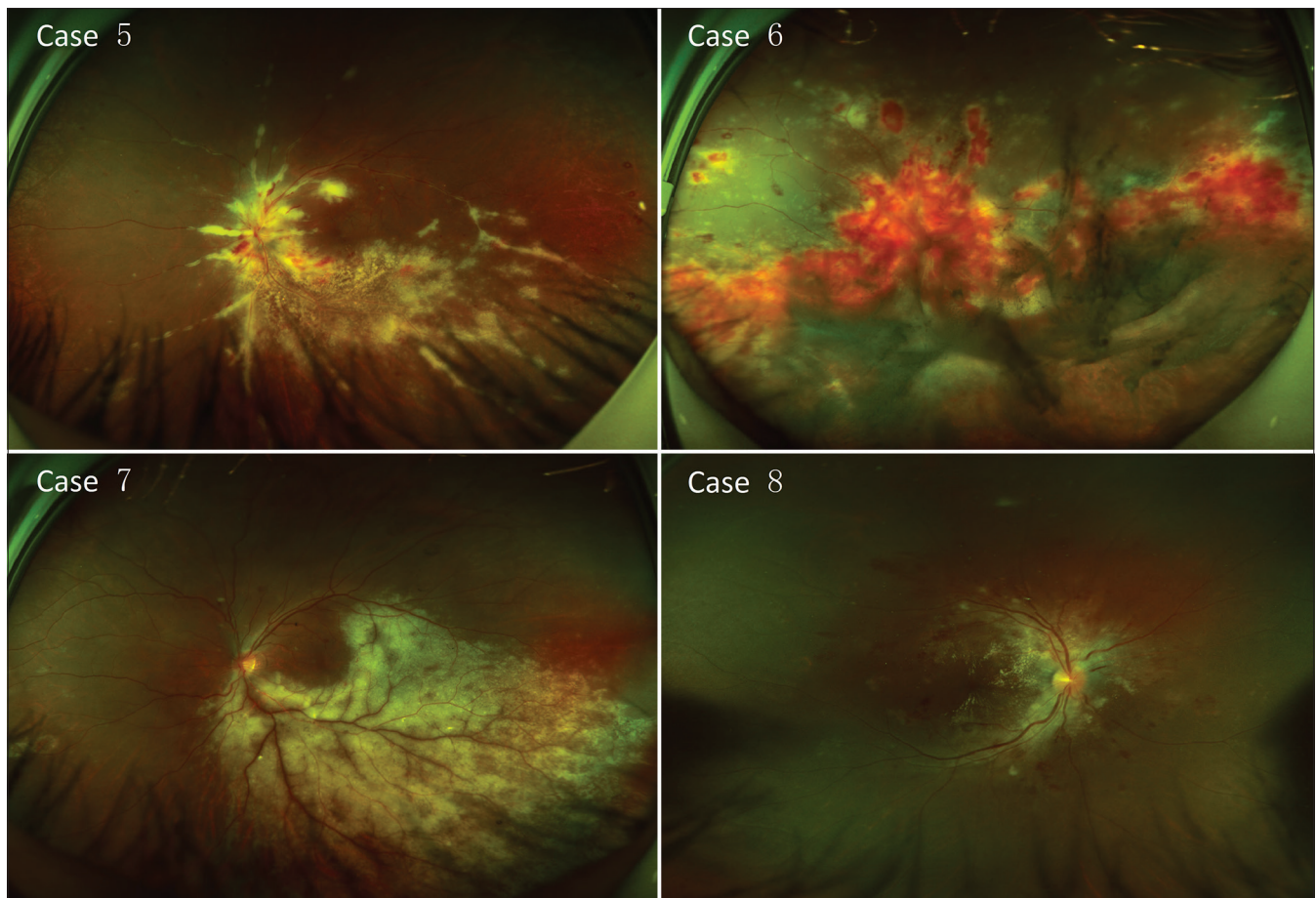
Figure 2: Ultrawide-field (UWF) fundus images of case 5–8 at final diagnosis

CMVR (OU) and was to receive treatment with intravenous ganciclovir. However, the HIV confirmatory test was negative, blood HIV-RNA was not detected, the ratio of CD4+/CD8 + T lymphocytes was within normal limits, and CD4+ T lymphocytes was 192/μl. Fundus examination revealed indistinct optic disc margins in each eye, a yellowish-white lesion around the optic disc associated with linear retinal hemorrhage, and retinal hard exudates in the macular area [Fig. 2]. He denied drug abuse, blood transfusion, sexual transmission, and other risk factors, so the doctor ruled out HIV infection. He was finally diagnosed with renal retinopathy (OU), chronic renal insufficiency, and uremia.

Discussion

The diagnosis of CMVR based on the clinical appearance of the fundus and documentation of an immunodeficient status can be achieved without ophthalmological expertise via retinal images[12] or binocular indirect ophthalmoscopy in patients with AIDS.[13] However, as a treatable disease, delays in the diagnosis and treatment of CMVR may lead to irreversible loss of vision and systemic deterioration.

Six young patients consulted the ophthalmology department due to their ocular symptoms before a diagnosis of AIDS, and one patient concealed their history of HIV infection. When their diagnosis of AIDS was clear, the blood CD4+ T lymphocyte was extremity low, indicating a very poor immune state.

Seven patients in this study diagnosed with AIDS showed an extremely low level of CD4+ T lymphocytes, ranging from 1 cell/μl to 9 cells/μl. The delay of HIV diagnosis may have serious consequences, compromising management and enhancing risk of disease propagation.[14]

The CMVR lesions had also deteriorated when the final diagnosis was clear. Involvement was binocular in all eyes, one patient was blind, and two patients had low vision on final diagnosis. Involvement was pan-retinal in four of the sixteen eyes. Fourteen eyes had optic disc or macular area involvement, which is associated with poor visual prognosis.[15]

It is a known fact that patients with retinitis, mimicking CMVR need to be tested for immunosuppressed state, mainly HIV, among others. Lessons from these misdiagnoses were that CMVR was easily overlooked at the first visit with general ophthalmologists, and tests for HIV were ignored subsequently. Firstly, some misdiagnoses might be partly attributed to underreporting of systemic symptoms at the ophthalmology department since four patients developed variable non-ocular manifestations before or during the disease, including abdominal pain, diarrhea, oral leukoplakia, rash, itchy skin, nausea, and vomiting, which indicated systemic disease. Secondly, not every general ophthalmologist had a well-rounded understanding of CMVR.

Histologically, CMVR appears as areas of full-thickness retinal necrosis and edema or exudative detachment.[16]

Clinically, it has a young male predominance,[17] as found in this study. Retinal features of CMVR were conspicuous and varied. A range of clinical classifications exist based on retinal manifestations,[18] uveitis activity,[19] or the involvement of immune reconstitution inflammatory syndrome (IRIS).[20] There are four recognized clinical retinal manifestations: typical edematous, atypical indolent, perivascular, and optic neuropathy.[17] In this study, the range of findings in eyes with CMVR included pan-retinal yellowish-white lesions, local retinal hemorrhage, exudative retinal detachment, retinal atrophy and white granular lesions without hemorrhages. In contrast to the lesions in CMVR, the yellowish-white lesions from renal retinopathy coincided with retinal hard exudate near the macular area, which is rarely seen in CMVR. These clinical findings were in line with previous reports that retinal features of CMVR were truly conspicuous and diverse: hemorrhagic necrotizing lesion, granular lesion, frosted branch angiitis, and optic neuropathy lesion.[21] A clear understanding about retinal features of CMVR can help to ensure that CMVR and HIV screening are considered for young retinitis sufferers.

The yellowish-white lesions and retinal hemorrhages are characteristic manifestations in CMVR, but could be easily confused with diabetic retinopathy, retinal vein occlusion, renal retinopathy, intraocular lymphoma,[22] Coats' disease,[23] ocular toxoplasmosis,[24,25] or progressive outer retinal necrosis. CMVR and progressive outer retinal necrosis might present similar fundus changes, which could be difficult for inexperienced doctors, but they differ in terms of etiology, treatment, and prognosis.[26,27] Confusing features were the signs of inflammatory reaction in the anterior segment or vitreous body, which could present challenges for retinal observation and lead to a misdiagnosis of iritis, or Behçet's disease. For ambiguous cases, PCR analysis of aqueous or vitreous specimens may be helpful to differentiate infected and noninfected diseases, obtain etiological evidence and exclude dual infection.[28] Most initial diagnoses mentioned in this series are described in the literature as differentials of retinitis. However, timely consideration of CMVR and HIV screening test will benefit patients.

This study is limited by its retrospective nature, without long-term follow-up. Because these patients were from other provinces far from Beijing, their periodic follow-ups at this center were difficult. The long-term effects on mortality and vision loss were not mentioned in this study.

Conclusion

This study highlights the clinical characteristics of seven misdiagnosed CMVR cases and one renal retinopathy case misdiagnosed as CMVR. CMVR and HIV screening cannot be overlooked if a young male patient presents with yellowish-white retinal lesions. These misdiagnosed cases were severe and were associated with poor vision. Ophthalmologists should be aware of the signs of CMVR and its differential diagnosis, as well as related systemic symptoms.

Conflicts of interest
There are no conflicts of interest.

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