Retrospective analysis of misdiagnosis of cytomegalovirus retinitis

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Abstract

Background

Initial misdiagnosis of cytomegalovirus retinitis (CMVR) may lead to irreversible loss of vision and systemic deterioration. We retrospectively reported some misdiagnosis related to CMVR.

Methods

The medical records of 92 consecutive patients diagnosed or misdiagnosed as CMVR were reviewed retrospectively at the ophthalmology department of Beijing youan hospital from July 2017 to October 2019. The primary outcome measure was to evaluate cases with CMVR who were initially misdiagnosed or who were misdiagnosed as CMVR.

Results

In 8 (8.7%) out of the 92 patients, the initial diagnosis was incorrect. The median age of the eight patients was 37.5 years (range 20-46 yeas). All (7/7, 100%) patients were male. Patients with CMVR were initially misdiagnosed as diabetic retinopathy (1/92,1.1%), branch retinal vein occlusion (1/92,1.1%), ischemic optic neuropathy (1/92,1.1%), Behcet's disease (1/92,1.1%), iridocyclitis (2/92, 2.3%), and progressive outer retinal necrosis (1/92,1.1%). One patient with binocular renal retinopathy and chronic renal insufficiency was misdiagnosed as CMVR (1/92,1.1%). All patients presented binocular involvement (sixteen eyes), and two patients (four eyes) presented pan-retinal involvement. Fourteen eyes (14/16, 87.5%) had optic disc or macular area involved. One patient is blind, and two patients had a low vision when the diagnosis is finally clear. Five patients had systemic symptoms. Seven patients were finally diagnosed with AIDS showing an extremely low level of CD4 + T lymphocyte: median of 5 cells/ul (range 1-9 cells/ul).

Conclusion

The misdiagnosis of CMVR can occur in young male patients. The ophthalmologist should pay more attention to CMVR and systemic symptoms insulting to avoid deterioration of vision and delaying in the management of systemic conditions.

Background

Cytomegalovirus retinitis (CMVR) is an opportunistic infectious retinal disease. CMVR is most commonly seen in AIDS (Acquired Immune Deficiency Syndrome) patients and is the most common cause of vision loss in these patients[1]. It can also occur in other patients receiving immunosuppression after solid organ or stem cell transplantation, individuals with potential immune dysfunction, such as advanced age, diabetes, hypertension, or renal insufficiency [2]and patients after intravitreal injection (hormonal or non-hormonal)[3–5]. For patients with definite AIDS, CMVR can be confirmed by a fundus examination. It is easy to disregard CMVR for non-HIV patients or patients who are not clear about their human

immunodeficiency virus (HIV) infection, so leading to unnecessary examinations, incorrect treatment, deterioration of vision and systemic condition. In this study, we retrospectively reviewed the medical records of seven patients with CMVR and one patient misdiagnosed as CMVR. We aim to appeal to the ophthalmologists to attach more attention to CMVR.

Methods

The medical records of 92 consecutive patients diagnosed/misdiagnosed with CMVR were reviewed retrospectively at Beijing infectious ophthalmopathy center, Beijing Youan Hospital, Capital Medical University, from July 2017 to October 2019. Patient clinical history and demographic data were recorded. Each patient underwent a complete medical evaluation for systemic illness, and laboratory investigations where indicated. The clinical diagnosis of CMVR primarily based on the presence of characteristic fundus findings in susceptible individuals [6]. We retrospectively analyzed eight cases that were initially misdiagnosed, seven were initially misdiagnosed as other diseases elsewhere and presented to our center at later stages of the disease, one patient presented to our center initially and misdiagnosed AS CMVR. Six patients consulted the ophthalmology department first for the ocular symptom before the diagnosis of AIDS. Six patients had received inappropriate treatments before the confirmed diagnosis. 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.

Results

Eight (8.7%) out of the 92 patients were incorrectly diagnosed at the initial presentation. The median age of the eight patients was 37.5 years (range 20–46 years). All (8/8, 100%) patients were male. Patients were initially misdiagnosed as diabetic retinopathy (1/92, 1.1%), branch retinal vein occlusion (1/92, 1.1%), ischemic optic neuropathy (1/92, 1.1%), Behcet's disease (1/92, 1.1%), iridocyclitis (2/92, 2.3%), and progressive outer retinal necrosis (1/92, 1.1%). One patient with binocular renal retinopathy and chronic renal insufficiency was misdiagnosed as CMVR (1/92, 1.1%). Five patients had systemic symptoms. Seven patients were diagnosed with AIDS and other opportunistic infections with an extremely low level of CD4⁺T lymphocyte: 5 cells/ul (range 1–9 cells/ul). All patients presented binocular involvement (sixteen eyes), and two patients (four eyes) presented pan-retinal involvement. Optic disc or macular area was involved in fourteen eyes. One patient (case 1) is blind, and two patients (cases 3 and 7) had a low vision when the diagnosis is clear. Six patients misdiagnosed as CMVR were received incorrect treatment before the final diagnosis. Among seven patients (fourteen eyes) with CMVR in this study: five eyes presented typical form with yellowish-white retinal lesions and retinal hemorrhages; four eyes presented optic neuropathy; four eyes presented opaque white granular retinal lesions with no hemorrhages; one eye presented both optic neuropathy and perivascular form. The characteristic ophthalmologic findings of these patients were presented in Table 2.

Table 1
INITIAL MISDIAGNOSIS OF PATIENTS WITH CMVR

No	Age	Gender	Initial diagnosis	Initial treatment	CONFIRMED DIAGNOSIS	SYSTEMIC SYMPTOMS	SYSTEMIC disease	CD4 ⁺ T (/ul)
1	38	M	Diabetic retinopathy	Intravitreal injection of glucocorticoid	CMVR	None	AIDS; Pulmonary infection; Oral fungal infection	5
2	39	M	Branch retinal vein occlusion	Intravitreal injection of anti-VEGF	CMVR	None	AIDS; EBV infection; Severe anemia	2
3	27	M	Behcet's disease	Topical and systemic glucocorticoid	CMVR	Abdominal pain; Diarrhea; Oral leukoplakia	AIDS; Pulmonary infection; Oral fungal infection	5
4	46	M	Iridocyclitis	Topical glucocorticoid	CMVR	None	AIDS; Syphilis; Dyslipidemia	9
5	37	M	Ischemic optic neuropathy	Systemic glucocorticoid	CMVR	Rash; Itchy skin	AIDS; Oral fungal infection Chronic itching	3
6	44	M	Iridocyclitis	Topical glucocorticoid	CMVR	Recurrent fever and cough	AIDS; Pulmonary infection; Leukopenia	9
7	28	M	Progressive outer retinal necrosis	Intravitreal injection of ganciclovir and foscarnet	CMVR	Intermittent diarrhea	AIDS; Pulmonary infection; Oral fungal infection	1
8	20	M	CMVR	None	Renal retinopathy	Nausea; Vomiting	Renal failure; Renal anemia	192
M = male; VEGF = vascular endothelial growth factor								

Table 2

PRE- AND POST-TREATMENT VISUAL ACUITIES IN THE INITIALLY MISDIAGNOSED PATIENTS

No	EYE	CONFIRMED DIAGNOSIS	Fundus manifestations	Optic disc /macular area involved	Extent	Corrected visual acuity
1	OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	Panretinal	LP
	OS	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	Panretinal	LP
2	OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	Focal lesions at the posterior pole	60/200
	OS	CMVR	Yellowish-white necrotizing lesions, superficial retinal hemorrhages around the optic disc and vitreous opacity	Yes	Focal lesions at the posterior pole	LP
3	OD	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages	Yes	Focal lesions at the posterior pole	30/200
	OS	CMVR	Yellowish-white necrotizing lesions and superficial retinal hemorrhages around the optic disc	Yes	One quadrant	30/200
4	OD	CMVR	Opaque white granular lesions	No	One quadrant	80/200
	OS	CMVR	Opaque white granular lesions and vitreous opacity	Yes	Two quadrants	60/200
5	OD	CMVR	Superficial hemorrhages and yellowish-white necrotizing lesion	No	Focal lesions at the posterior pole	12/20
	OS	CMVR	Superficial hemorrhages, yellowish-white necrotizing lesion around the optic disc and vascular sheathing	Yes	One quadrant	80/200
6	OD	CMVR	Superficial hemorrhages and yellowish-white necrotizing lesion around the optic disc	Yes	Panretinal	80/200
	OS	CMVR	Superficial hemorrhages and yellowish-white necrotizing lesion around the optic disc	Yes	Panretinal	20/200
7	OD	CMVR	Opaque white granular lesions	Yes	Two quadrants	40/200
	OS	CMVR	Opaque white granular lesions	Yes	Two quadrants	30/200
8	OD	Renal retinopathy	Soft and hard exudates, linear retinal hemorrhages around the optic disc	Yes	Focal lesions at the posterior pole	80/200
	OS	Renal retinopathy	Soft and hard exudates, linear retinal hemorrhages around the optic disc	Yes	Focal lesions at the posterior pole	12/20

M = male; LP = light perception; OD = oculus dexter; OS = oculus sinister;

Case 1

A 38-year-old male patient gave a history of blurring of vision in both eyes of 2 months duration and diabetes mellitus for two months. He was erroneously diagnosed as diabetic retinopathy (oculus uterque, OU) and macular edema (OU) at the local hospital and received a binocular intravitreal injection of glucocorticoid. With the progressive deterioration of vision, he planned to receive the intravitreal injection of anti-VEGF treatment. The preoperative HIV antibody screening test turned out to be positive. He was recommended to infectious disease hospital. Fundus examination revealed pan-retinal yellowish-white

necrotizing retinitis associated with a wide range of retinal hemorrhages in both eyes, with optic disc and macular area involved. Aqueous CMV viral load was 279000 copies/ml in the right eye and 20600 copies/ml in the left eye. A diagnosis of bilateral CMVR was established. He was admitted to the hospital and accepted intravenous ganciclovir and intravitreal injection of ganciclovir.

Case 2

A 39-year-old male patient gave a history of blurring of vision in the left eye of a 1-month duration. He was initially diagnosed with branch retinal vein occlusion (oculus dexter, OD), vitreous hemorrhage (oculus sinister, OS) at the local hospital. He received the 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 turned out to be positive in another hospital. He was recommended to infectious disease hospital. Fundus examination revealed local retinal hemorrhages (brush-fire) on the superior nasal of macular area, with retinal whitening and exudative retinal detachment around the lesion in the right eye, severe vitreous opacity and yellowish-white necrotizing lesion around the optic disc in the left eye (Fig. 1). 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 accepted intravenous ganciclovir and intravitreal injection of ganciclovir.

Case 3

A 27-year-old male patient gave a history of blurring of vision in both eyes of 3 weeks duration. He was initially diagnosed as Behcet's disease (OU). He received treatment with topical and systemic glucocorticoids. However, the blurred vision deteriorated. He got blood tests in another hospital. The HIV antibody screening test turned out to be positive. Fundus examination revealed focal yellowish-white necrotizing retinitis associated with superficial retinal hemorrhages in the inferior quadrant of optic disk in the right eye, and around the optic disc in the left eye. 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 ganciclovir and intravitreal injection of ganciclovir.

Case 4

A 46-year-old male patient gave a history of blurring of vision and floaters in both eyes of 3 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 in another hospital. The HIV antibody screening test turned out to be positive. Fundus examination revealed superior opaque white granular lesions in the right eye, nasal opaque white granular lesions swollen optic disc, and vitreous opacity in the left eye. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and was given intravenous ganciclovir and intravitreal injection of ganciclovir.

Case 5

A 37-year-old male patient gave a history of blurring of vision in both eyes of 1-month duration and deterioration of 1-week duration. He was initially diagnosed as ischemic optic neuropathy (OU), treated with intravenous pulse injections of methylprednisolone (40 mg, QD) for four days, and later on, maintained on oral steroids. With the progressive deterioration of vision, he received blood tests in

another hospital. The HIV antibody screening test turned out to be positive. Fundus examination revealed focal yellowish-white necrotizing retinitis associated with superficial retinal hemorrhages in the inferior quadrant of optic disk in the right eye, around the optic discs in the left eye, and optic disc swelling and retinal vasculitis with perivascular sheathing (similar to frosted-branch angiitis) in the left eye. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and was given intravenous ganciclovir and intravitreal injection of ganciclovir.

Case 6

A 44-year-old male patient gave a history of blurring of vision and floaters in both eyes of 4 months duration. He was initially diagnosed as iridocyclitis (OU) at the local hospital and treated with glucocorticoid eye drops. With the progressive deterioration of vision, he told his doctor his history of HIV infection for six years without any treatment. Fundus examination revealed binocular pan-retinal superficial retinal hemorrhages associated with yellowish-white necrotizing retinitis, involving both optic disc and macular area. A diagnosis of CMVR (OU) was established. He was admitted to the hospital and received intravenous ganciclovir. He refused any ophthalmic therapy.

Case 7

A 28-year-old male patient gave a history of blurring of vision in both eyes of 10 days duration. He was initially diagnosed as progressive outer retinal necrosis (PORN) (OU) and treated with intravitreal injection of ganciclovir and foscarnet. Whereafter, the HIV antibody screening test was positive. The fundus examination revealed quadrantally distributed opaque white granular lesions without retinal hemorrhages in both eyes (Fig. 2). Optical coherence tomography showed a full-thickness disorganized retina. Aqueous CMV viral load was 328000 copies/ml in the right eye. PCR analysis of aqueous varicella-zoster virus (VZV) and herpes simplex virus (HSV) are both negative. A diagnosis of CMVR (OU) was established. He was admitted to our hospital and received intravenous ganciclovir and intravitreal injection of ganciclovir.

Case 8

A 20-year-old male patient gave a history of blurring of vision in both eyes of 2 weeks duration and positive HIV antibody screening test of 1-week duration. He had a nephrotic syndrome for over seven years. He was initially diagnosed as CMVR (OU) and planned to receive treatment with intravenous ganciclovir. The HIV confirmatory test turned out to be negative, blood HIV-RNA was not detected, the ratio of CD4⁺/CD8⁺T lymphocyte was reasonable, and CD4⁺T lymphocyte was 192 /ul. Fundus examination revealed binocular blurring edge of the optic disc, yellowish-white lesion around the optic disc associated with linear retinal hemorrhages, and retinal hard exudates in the macular area (Fig. 3). 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 is not tricky basing on the clinical appearance of the fundus and documentation of an immunodeficient status. Even nonophthalmologists can achieve it through retinal images[7] or binocular indirect ophthalmoscopy for patients with AIDS[8]. However, as a treatable disease, delay in the diagnosis and treatment of CMVR may lead to irreversible loss of vision and systemic deterioration. In

our study, 8 (8.7%) out of 92 patients were misdiagnosed. Six patients consulted the ophthalmology department first for the ocular symptom before the diagnosis of AIDS, and one patient concealed the history of HIV infection. When their diagnosis of AIDS was clear, the blood CD4 + T lymphocyte was extremely low, which means the body's immune state is very poor and progressed to an advanced stage. Seven patients in this study diagnosed with AIDS showed an extremely low level of CD4 + T lymphocyte, ranging from 1 cells/ul to 9 cells/ul. The delay of HIV infection may lead to serious consequences: compromising timely management and enhancing propagation of the epidemic in the country[9].

Besides, the CMVR lesions in this study had deteriorated when final diagnosis was clear. All eyes presented binocular involvement. One patient is blind, and two patients had a low vision when the diagnosis is precise. Four eyes presented pan-retinal involvement. Fourteen eyes had optic disc or macular area involved, which is associated with poor visual prognosis[10].

Some misdiagnoses were partly attributed to the underrated systemic symptoms insulting at the ophthalmology department because four patients developed variable extraocular manifestations before or in the course of the disease: abdominal pain, diarrhea, oral leukoplakia, rash, itchy skin, nausea, and vomiting, which prompted systemic diseases. However, since the visual dysfunctions are the main problem and, therefore, qualified patients for permanent disability, they had concealed these extraocular symptoms from those involved in their care.

CMV infection reaches the eye through hematogenous spread. Histologically, CMVR appears as areas of full-thickness retinal necrosis and edema or exudative detachment[11]. Clinically, it has a young male predominance[12], as showing in this study. There are various findings of the fundus in CMVR, not just "cheese and ketchup" changes. It has various clinical classification according to the clinical fundus forms[13], Standardization of Uveitis Nomenclature working group descriptors[14], or the involvement of immune reconstitution inflammatory syndrome (IRIS)[15]. There are four recognized clinical forms, including typical form, edematous; atypical form, indolent; perivascular form; and optic neuropathy[12]. Among six patients (12 eyes) with CMVR in this study: 5 eyes presented typical form with yellowish-white retinal lesions and retinal hemorrhages; 4 eyes presented optic neuropathy; 4 eyes presented opaque white granular retinal lesions with no hemorrhages, which could be easily misdiagnosed by inexperienced doctors; 1 eye presented both optic neuropathy and perivascular form.

These yellowish-white lesion and retinal hemorrhages were characteristic manifestations but could be easily confused with diabetic retinopathy, retinal vein occlusion, renal retinopathy, intraocular lymphoma[16], Coats' disease[17] or ocular toxoplasmosis[18]. The seventh patient showed quadrantally distributed white granular lesions without retinal hemorrhages and was misdiagnosed as PORN, which is also a kind of necrotizing herpetic retinopathies detected in immune-compromised patients[19]. CMVR and PORN might present confusing fundus changes, which could be difficult for inexperienced doctors, but they are different in the aetiological agent, treatment, and prognosis[20].

The eighth patient was initially misdiagnosed as CMVR, because of the yellowish-white lesion and retinal hemorrhages around the optic disc. With HIV-infection finally excluded, chronic renal insufficiency

confirmed, and retinal hard exudates near the macular area, the patient was finally diagnosed with renal retinopathy. The critical distinguishing signs of CMVR and renal retinopathy is retinal hard exudates near the macular area, which is rarely seen in CMVR. Other confusing features were the signs of inflammatory reaction in the anterior segment or vitreous body, which may be misleading to the diagnosis of iritis, or Behcet's disease. For ambiguous cases, PCR analysis from aqueous or vitreous specimens can be helpful to different infected and non-infected diseases, and find the pathogen[21].

HIV infection might be firstly diagnosed in the ophthalmology department because of CMVR. An ophthalmologist should pay more attention to the diagnosis of CMVR to avoid delayed ocular or systemic treatment. In our study, the rate of misdiagnosis was 8.7%. However, this retrospective study suffers from certain limitations without long-term effective follow-up.

Conclusion

An ophthalmologist should be wary of CMVR in the young man with yellowish-white retinal lesion with associated hemorrhages, or opaque white granular lesions, which may be an initial manifestation of HIV infection. Careful fundus examination and systemic symptoms insulting may help in arriving at a correct diagnosis and avoiding unnecessary tests or wrong management.

Abbreviations

HIV:Human immunodeficiency virus; AIDS:Acquired Immune Deficiency Syndrome;
CMVR:Cytomegalovirus retinitis; PORN:Progressive outer retinal necrosis; OD:Oculus dexter; OS:Oculus sinister; OU:Oculus uterque; VEGF:Vascular endothelial growth factor; IRIS:Immune reconstitution inflammatory syndrome.

Declarations

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Ethics approval and consent to participate

This study was approved by the Beijing Youan Hospital, Capital Medical University Institutional Review Board (LL-2018-150-K), and adhered to the tenets of the Declaration of Helsinki.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors contributed equally in this work. All authors read and approved the final manuscript.

Consent for publication

All authors consent for publication. All individual persons in this study consent for publication.

Competing interests

There are no competing interests.

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Figures

Figure 1

Case 2: CMVR misdiagnosed as branch retinal vein occlusion. Local retinal hemorrhages (brush-fire) on the superiornasal of macular area, with white “exudative” lesion and exudative retinal detachment around the lesion

Figure 2

Case 7: CMVR misdiagnosed as progressive outer retinal necrosis. Quadrantly distributed opaque white granular lesions without retinal hemorrhages

Figure 3

Case 8: Renal retinopathy misdiagnosed as CMVR. Blurring edge of the optic disc, yellowish-white lesion around the optic disc associated with linear retinal hemorrhages, and retinal hard exudates in the macular area.