Case Report

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Bilateral cytomegalovirus retinitis comorbid with diabetic macular edema

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Abstract:

Cytomegalovirus (CMV) retinitis comorbid with diabetic retinopathy is uncommon. We report a case of bilateral CMV retinitis and diabetic retinopathy in a patient who underwent pancreas transplantation and share the experience of the treatment outcome. An 18-year-old male diagnosed with type-1 diabetes mellitus received pancreas transplantation and immunosuppressive therapy suffered from progressively blurred vision in both eyes for several days. His visual acuity was 20/100 in the right eye and 20/50 in the left eye. Ophthalmic examination revealed bilateral diabetic macular edema (DME) without intraocular inflammatory signs in either eye. The DME subsided after 2 monthly intravitreal injections of aflibercept. However, bilateral panuveitis with CMV retinitis was observed after antivascular endothelial growth factor therapy. The retinitis subsided gradually but completely after systemic and intravitreal antiviral therapy. However, bilateral DME recurred and persisted despite repeated injections of aflibercept during the resting follow-up period. Our case suggests that CMV retinitis can coexist with other retinal diseases, including diabetic retinopathy. Treatment is difficult in such cases.

Keywords:

Cytomegalovirus, cytomegalovirus retinitis, diabetic macular edema, diabetic retinopathy, pancreas transplantation

Introduction

Cytomegalovirus (CMV) infection is a common opportunistic infection in patients receiving immunosuppressive therapy after organ transplantation. CMV retinitis is a key manifestation of CMV infection with adverse outcomes for the visual system and high mortality rate if left untreated.[1-3] Clinical presentations of CMV retinitis include full-thickness yellow-white retinal necrosis and retinal hemorrhage. Retinal vasculitis with vessel sheathing, vitritis, and papilledema may be observed. Complications include epiretinal membrane, cystoid macular edema (CME), neovascularization, cataract, and severe proliferative vitreoretinopathy.[4-6]

Blood sugar in young patients with type-1 diabetes mellitus (DM) is usually difficult to control, and pancreas transplantation is a final treatment. Although blood sugar could more easily be controlled after pancreas transplantation, aggressive immunosuppressive therapy should be used in these cases, and elevated risk of systemic infections, including CMV retinitis, could happen. Furthermore, patients with type-1 DM were reported to suffer from a higher incidence of diabetic retinopathy.[7] Occasionally, images of CMV retinitis appear similar to those of diabetic retinopathy. Mixture of clinical presentations and mechanisms and of these two diseases makes the diagnosis and treatment being more complicated.

Herein, we report a case of a patient with CMV retinitis comorbid with diabetic macular edema (DME) and share the experience of the treatment outcome.

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Case Report

An 18-year-old man presented with progressively blurred vision in both eyes for 3 days. The patient had been diagnosed with DM at the age of 8 years and had received a pancreas transplant 6 months before this episode because of frequent episodes of life-threatening hypoglycemia. His glycated hemoglobin (HbA1c) level before receiving the transplant was 8.3%. After transplantation, systemic immunosuppressive agents, including mycophenolate, tacrolimus, everolimus, and corticosteroid, were prescribed. Prophylactic valganciclovir was prescribed for several months and then gradually tapered. His blood sugar stabilized after transplantation, and his HbA1c level was approximately 7.7% at his initial visit to the ophthalmic clinic.

At the first presentation, his best-corrected visual acuity was 20/100 in the right eye and 20/50 in the left eye. No corneal keratic precipitates, anterior chamber cells, or vitreous haze were observed, but diffuse retinal hemorrhage and several small perivascular exudations were noticed in both eyes. Fluorescein angiography (FA) revealed bilateral diffuse microaneurysms, retinal ischemic areas, and DME [Figures 1a and 1b]. Optical coherence tomography (OCT) confirmed bilateral macular edema with intraretinal and subretinal fluids in both eyes [Figure 1c and 1d]. The patient initially received a diagnosis of nonproliferative diabetic retinopathy with DME and received 2 monthly intravitreal injections of 2 mg of aflibercept. During these 2 months, an episode of graft failure with acute T-cell-mediated rejection followed by diabetic ketoacidosis with a blood sugar level of up to 852 mg/dL occurred. After shifting the patient's systemic immunosuppressant therapy to mycophenolate and tacrolimus, his blood sugar stabilized, and his HbA1c level returned to 6.3% after 1 month.

However, the patient complained of subjective progression of blurring 1 month after the second anti-vascular endothelial growth factor (anti-VEGF) injection. Bilateral multiple keratic precipitates, three plus of anterior chamber cells, one plus of anterior chamber flare, and one plus of anterior vitreous cells were noticed. Fundus examination revealed 0.5 plus of vitreous haze, bilateral optic papillitis, diffuse perivasculitis, and yellowish retinitis lesions at the peripheral retina [Figure 2a]. OCT revealed bilateral disc swelling with improvement of macular edema [Figure 2b and 2c]. Serological examination and polymerase chain reaction (PCR) of CMV DNA in the serum confirmed the diagnosis of systemic CMV infection. Anterior chamber paracentesis revealed CMV DNA levels of 19,784,976 copies/mL and 6,848,642 copies/mL in the right and left aqueous humors, respectively. Bilateral CMV retinitis was diagnosed.

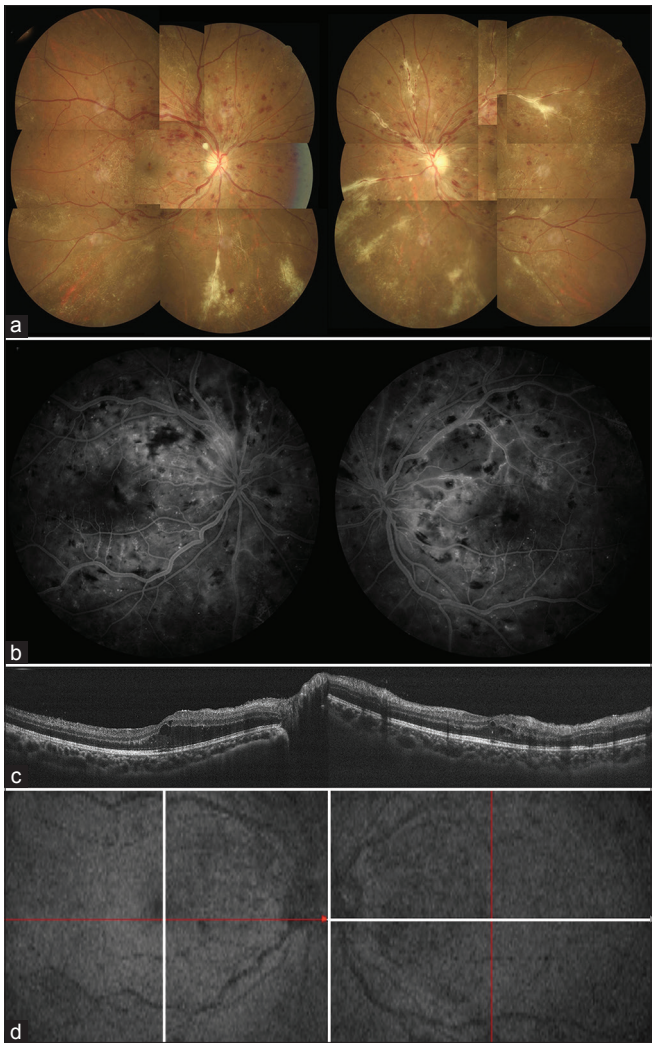

Figure 1: (a) Fundus examination showing bilateral diffuse retinal hemorrhage and few small perivascular exudations. (b) Fluorescein angiography showing bilateral diffuse microaneurysms, retinal ischemic areas, and diabetic macular edema. (c) Optical coherence tomography showing bilateral macular edema with intraretinal and subretinal fluids. (d) Infrared image showing the location of the optical coherence tomography section

The patient was subsequently treated with intravenous ganciclovir combined with low-dose oral corticosteroids. Intravitreal injections of 2 mg of ganciclovir were performed twice weekly in both eyes for 9 weeks. After remission of the inflammation in the anterior chamber and disappearance of all vasculitis and retinitis lesions at the peripheral retina, weekly injections of 3 mg of ganciclovir were maintained for 6 weeks until the CMV DNA was undetectable in both eyes [Figure 3]. The patient's blood sugar remained stable throughout the antiviral therapy course.

Unfortunately, although the uveitis and retinitis substantially improved, recurrence of the bilateral macular edema was noted 2.5 months after the final injection of aflibercept [Figure 4a and 4c]. Repeated FA revealed large nonperfusion areas in the posterior

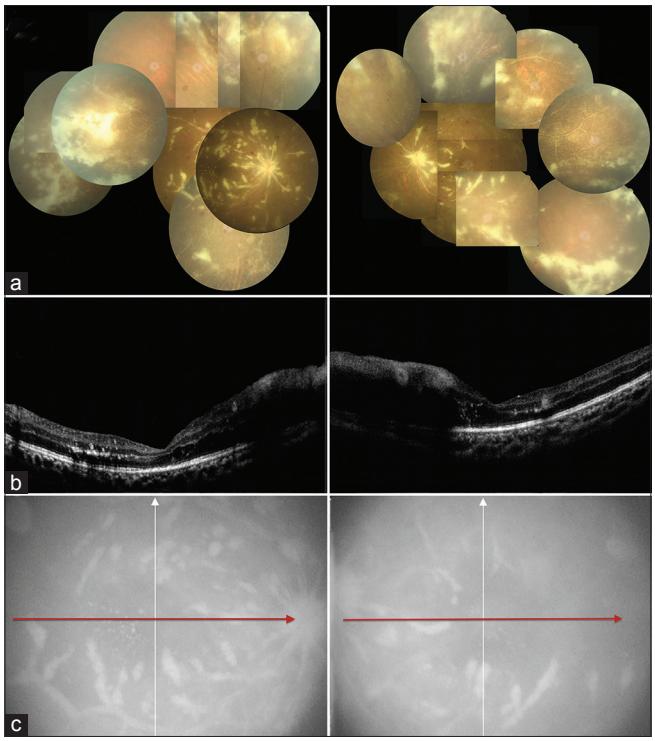

Figure 2: (a) Fundus examination showing bilateral optic papillitis, diffuse perivasculitis, and yellowish retinitis lesions at peripheral retinal lesions. (b) Optical coherence tomography showing bilateral significant disc swelling but improvement of macular edema. (c) Infrared image showing the location of the optical coherence tomography section

pole without vasculitis [Figure 4b]. Three additional injections of aflibercept were performed in combination with antiviral therapy. However, the macular edema persisted and responded unfavorably even when the therapy was combined with the subtenon injection of triamcinolone. At the end of follow-up (8 months after the first presentation), the patient's visual acuity was 20/100 in both eyes.

Discussion

We report a case in which a patient with type-1 DM received immunosuppressive therapy suffered from diabetic retinopathy comorbid with CMV retinitis. The lifetime risk for CMV retinitis was estimated as 30% among patients with acquired immune deficiency syndrome,[8] and the incidence of CMV retinitis varies in bone marrow and solid organ transplant recipients who are treated with systemic immunosuppressive drugs. Clinically, comorbidity of CMV retinitis and diabetic retinopathy is rare. Although the two diseases share some similar clinical presentations in the retina, several indications suggested that our patient had both diseases simultaneously.[6] First, the initial FA exhibited diffuse microaneurysms and capillary dye leakage, which indicated diabetic retinopathy and has rarely been documented in early CMV retinitis. The second

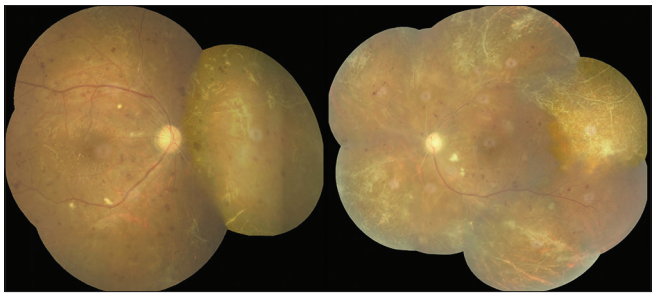

Figure 3: After anti-viral treatment, fundus examination showing disappear of all vasculitis and retinitis lesions at peripheral

indication was that the CME in both eyes resolved completely with only anti-VEGF therapy and without systemic or intraocular antiviral treatment despite his peripheral retinitis lesions progressing significantly during that period.

Intravitreal injection of anti-VEGF or corticosteroid is a common and an effective treatment for DME. Studies have suggested that CMV retinitis occurs after local immunosuppression through intravitreal triamcinolone acetonide for DME in immunocompetent patients.[9,10] Nevertheless, only one case report documented CMV retinitis occurrence after the intravitreal injection of bevacizumab, and it identified no evidence of systemic or local immunosuppression. Disruption of the blood–retinal barrier due to diabetic retinopathy was suggested as playing a role in CMV retinitis development in that case.[11] Animal studies have indicated that an increase in leukocyte entrapment could be observed in rats with DM because of alterations in leukocyte properties and microvasculature changes in diabetic retinopathy, and leukocytes latently infected with CMV may become entrapped in the retina.[12] In addition, mycophenolate use has been identified as a significant risk factor for CMV infection in solid organ transplant patients.[13-17] Our patient not only had advanced diabetic retinopathy but also was treated with mycophenolate after transplantation; we believe that the weak blood–retinal barrier and systemic immunocompromised status simultaneously contributed to the high risk of CMV infection in his retina.

Studies have demonstrated the relationship between the number of cells and CMV DNA level in the aqueous humor of patients,[18] which is in agreement with the findings in our patient. PCR revealed high viral loads of 1.9×10^7 and 6×10^6 copies/mL in the patient's right and left aqueous humors, respectively. In addition, a prominent anterior chamber reaction was identified, which contrasted with the minimal anterior chamber inflammation observed in typical CMV retinitis.[19,20] The diagnosis and treatment of CMV retinitis is mainly based on clinical presentation.[2] Ando *et al*. demonstrated that the CMV genome could remain detectable in the

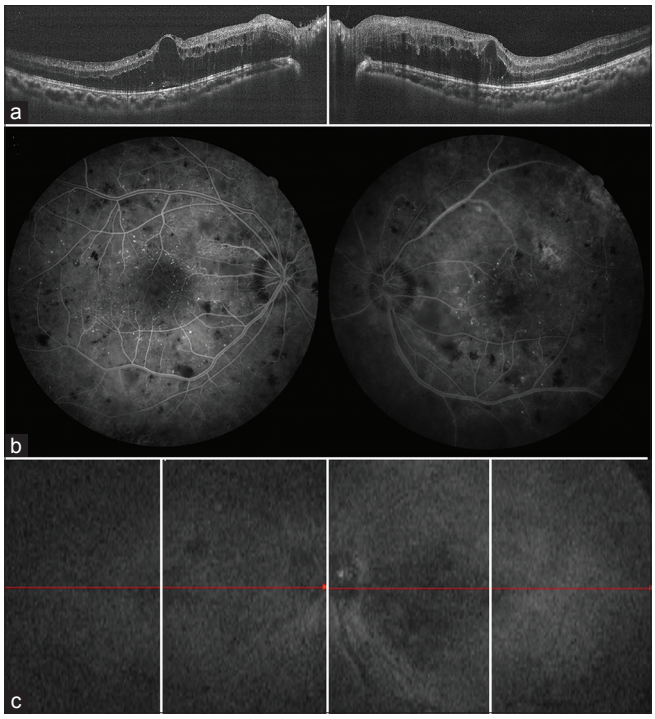

Figure 4: (a) Optical coherence tomography showing recurrence of bilateral macular edema noted at 2.5th month after the second injection of aflibercept. (b) Fluorescein angiography showing large non-perfusion areas in posterior pole without vasculitis. (c) Infrared image showing the location of the optical coherence tomography section

aqueous humor for as long as 8 weeks after antiviral administration, particularly in patients who originally had a high concentration of the viral genome.[18] Our patient initially had a high CMV viral load in his aqueous humor. The clinical retinitis images exhibited a marked improvement several weeks after the antiviral therapy; however, the viral load did not become undetectable until 15 weeks after therapy. Whether the DNA load or clinical images should be the key indicator of antiviral therapy intensity remains unclear.

After several months of antiviral therapy, the macular edema in both eyes recurred despite satisfactory control of retinitis. Repeated FA revealed many large nonperfusion areas and microaneurysms in the posterior pole without vasculitis or papillitis. Although the patient's systemic immune status and sugar level did not alter substantially during that period, inflammation caused by immune recovery cannot be ruled out. The intraocular inflammatory signs, including the cells in anterior chamber or vitreous, remained minimal. The macular edema responded insufficiently to 3 months of intravitreal injections of aflibercept, one of which was combined with subtenon triamcinolone. Inflammation caused by CMV retinitis may lead to occlusive vasculitis, not only on the affected side but also in distant areas of the retina.[21] We believe that the patient's wide-ranging retinitis and severe parapapillary vasculitis at initial presentation may have contributed to the progression of retinal ischemia in the macular bundle, followed by intractable macular edema.

In conclusion, we report a case of diabetic retinopathy comorbid with CMV retinitis. The combination of clinical presentations and mechanisms of these two diseases rendered the diagnosis and treatment more challenging. Clinicians should exercise caution when treating this condition, particularly in patients with DM who have undergone immunosuppressive therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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