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NEOVASCULAR COMPLICATIONS FROM CYTOMEGALOVIRUS NECROTIZING RETINOPATHY IN PATIENTS AFTER HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Purpose: To report the incidence and clinical features of neovascular complications from cytomegalovirus (CMV) necrotizing retinopathy in patients after haploidentical hematopoietic stem cell transplantation.

Methods: Thirty-nine patients (58 eyes) of CMV necrotizing retinopathy after haploidentical hematopoietic stem cell transplantation in our institute between January 2018 and June 2020 were retrospectively reviewed, and cases that developed neovascular complications during follow-up were identified and described.

Results: Two (2 eyes) cases that developed neovascular glaucoma from CMV necrotizing retinopathy were identified. Both of them manifested as granular peripheral retinitis, panretinal occlusive vasculitis, and some degree of intraocular inflammation, which were consistent with chronic retinal necrosis. Insidious progression of isolated immune-mediated occlusive vasculitis that could only be observed on fundus fluorescein angiography without active retinitis or intraocular inflammation was recognized to be the cause in one of two cases.

Conclusion: Neovascular glaucoma developed in 5.1%/cases and 3.4%/eyes complicated by CMV chronic retinal necrosis and vasculitis in patients after haploidentical hematopoietic stem cell transplantation, which warrants the needs for long-term follow-up. Immune-mediated CMV vasculitis could be an isolated manifestation in patients with a minimal immune deviation and may only be found on fundus fluorescein angiography, which emphasizes the importance of fundus fluorescein angiography on a regular basis during follow-up.

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Haploidentical hematopoietic stem cell transplantation (HHSCT) expanded the selection range of donors and makes it easier to obtain donor lymphocytes in subsequent adoptive immunotherapy.[1,2] But a T-cell repletion and depletion approach around HHSCT and subsequent immunomodulatory therapy increases the risk of cytomegalovirus (CMV) disease after HHSCT.[3] With a growing number of patients receiving HHSCT worldwide,[2] CMV necrotizing retinopathy is becoming more and more common in ophthalmic clinic.

Chronic retinal necrosis (CRN), which was first reported by Schneider et al in 2013,[4] is caused by CMV infection and mainly affects patients with limited immune dysfunction, such as aging and diabetes. Its clinical characteristics include slowly progressive granular retinitis, occlusive panretinal vasculitis, and varying degrees of intraocular inflammation, which resemble those of acute retinal necrosis except for the slow progression and a more limited extent of the retinitis.[5] Several cases with neovascular complications secondary to CRN had been reported.[4,6,7] Occlusive vasculitis and large area of nonperfusion on the retina that already existed at initial presentation was the main cause. There were only two CRN cases reported after Schneider et al, and both of them developed neovascular glaucoma (NVG) during follow-up.[6,7] To the best of our knowledge, no cases of neovascular complications/NVG have been reported in patients with CMV CRN after HHSCT. Besides, there has been no detailed report on CRN and its neovascular complication in China.

Our study was to report the incidence and clinical features of cases developing neovascular complications/NVG from CMV CRN after HHSCT. Particularly, we noted that isolated insidious immune-mediated CMV retinal vasculitis without the progression of retinitis or evidence of intraocular inflammation could result in enlarging the nonperfusion area and finally causes NVG.

Patients and Methods

We performed a retrospective study of all CMV necrotizing retinopathy after HHSCT in the Peking University People's Hospital between January 2018 and June 2020. Cytomegalovirus necrotizing retinopathy diagnosis was established by a recent history of HHSCT, presence of suggestive clinical and fundus imaging features, positive CMV-DNA load but no other human herpes virus DNA in aqueous, and exclusion of other possible etiologies that are clinically similar to CMV necrotizing retinopathy, such as syphilis, tuberculosis, and toxoplasmosis. Neovascular complications were defined by the following criteria: 1) neovascularization of iris and/or angle with/without anterior synechiae; 2) neovascularization of retina on fundus examination or fundus fluorescein angiography (FFA); 3) large nonperfusion area shown by FFA that corresponded to neovascularization; and 4) no other causes could be attributed to, such as retinal vein occlusion and diabetic retinopathy. Increased intraocular pressure (IOP) together with neovascular complications is defined as NVG. We collected information on clinical features, multimodal fundus images, treatments, and outcomes.

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Peking University People's hospital under grant No. 2018PHB196-01. Written informed consent was obtained from each patient before enrollment.

Results

A total of 39 cases (58 eyes) of CMV necrotizing retinopathy after HHSCT were identified, and all of them were HIV-seronegative. Among, two cases (2/39, 5.1% cases; 2/58, 3.4% eyes) fulfilled the criteria for neovascular complications and both of them developed NVG during follow-up. Both patients manifested as peripheral granular retinitis, occlusive panretinal vasculitis, and certain degrees of intraocular inflammation, which were consistent with CRN described by Schneider et al.[4] Aqueous cells were found in one patient, and vitritis existed in both patients. Both patients showed negative whole blood CMV-DNA ($< 1 \times 10^3$ IU/mL)[8] when CMV necrotizing retinopathy was diagnosed.

Considering the potential effect of myelosuppression[9] and delaying recovery of CMV-specific T-cell responses of ganciclovir,[10,11] borderline and progressively subtherapeutic vitreous concentrations,[12] and suboptimal effect for macula and/or optic disk–threatening disease when ganciclovir was given intravenously,[13] together with negative results of whole blood CMV-DNA, after discussion with hematologists and the two patients, intravitreal ganciclovir injection combined with a dose reduction of immunomodulatory drugs for chronic graft-versus-host disease without systemic ganciclovir were prescribed for both of them.[14,15] Intravitreal injections were given as loading doses twice per week, followed by maintenance dosing once a week. Aqueous CMV-DNA was monitored by quantitative nucleic acid amplification testing.[16] Retinitis regressed, lesions healed, and aqueous CMV-DNA decreased to negative ($<1 \times 10^3$ IU/mL)[8] after series of injections in both cases.

Neovascular glaucoma developed within weeks in one patient and 9 months later in the other. Although antivascular endothelial growth factor drug intravitreous injection, panretinal photocoagulation, and antiglaucoma surgery when necessary were able to control IOP, the outcome of visual acuity was poor.

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Insidious progression of isolated occlusive vasculitis that could only be observed on FFA without active retinitis or intraocular inflammation was observed in the second patient, which was rather different from the first.

Case Presentations

Case 1

A 29-year-old man was referred for evaluation of progressive vision loss in the left eye over the past 20 days. He was in this status after HHSCT + 165 days because of acute lymphocytic leukemia. On presentation, his immunosuppressive medications included prednisone 5 mg daily and cyclosporine 50 mg twice daily for chronic graft-versus-host disease. The engraftment status was well, with neutrophil count 2.83×10^9/L and platelet 88×10^9/L. The total T-lymphocyte count was 1.850×10^9/L. The patient was treated with a 2-week course of oral ganciclovir after a single-positive whole blood CMV titer (1.32×10^3 IU/mL) 1 month ago. No further evidence of CMV-DNAemia was noted despite regular surveillance.

The visual acuity was 20/20 in the right eye and 20/50 in the left eye. Intraocular pressure was 14 mmHg and 28 mmHg, respectively. Biomicroscopy revealed 1+ aqueous and 2+ vitreous cell in the left eye. Fundus ophthalmoscopy revealed a 2-o'clock hour patch of granular retinitis in the temporal periphery and a linear lesion with one end pointing to the optic disk lying in the nasal equator, as well as a few retinal hemorrhages along retinal vessels (Figure 1, A and B). Cytomegalovirus necrotizing retinopathy was suspected and aqueous sample from the left eye was obtained. Quantitative nucleic acid amplification testing for CMV in aqueous was 3.99×10^5 IU/mL, whereas whole blood CMV-DNA was negative ($<1 \times 10^3$ IU/mL). Additional workup including fluorescent treponemal antibody absorption, HIV serologies, serum toxoplasma IgG and IgM, T-SPOT.TB, and chest X-ray were all negative.

Ganciclovir intravitreal injection was administered as well as reducing the dose of cyclosporine to 50 mg daily. Quantitative nucleic acid amplification testing for CMV in the aqueous was performed during each time of injection. After 6 times of injections, aqueous CMV-DNA decreased to negative, but the visual acuity dropped to hand motion and IOP increased to 45 mmHg. Although intraocular inflammation and granular lesion seemed regressed, superficial hemorrhage along retinal vessels exaggerated (Figure 1, C and D). Neovascularization was observed in the iris and an angle with 360° anterior synechia. Fluorescein angiography confirmed the presence of 360° retinal nonperfusion (Figure 1, E and F), proposing the diagnosis of NVG. Antivascular endothelial growth factor drug intravitreal injection, Ahmed valve implantation, and panretinal photocoagulation were given. Final visual acuity, 13 months after presentation, was light perception in the left eye. There was no involvement of the right eye and no recurrent retinitis in the left eye during the follow-up period.

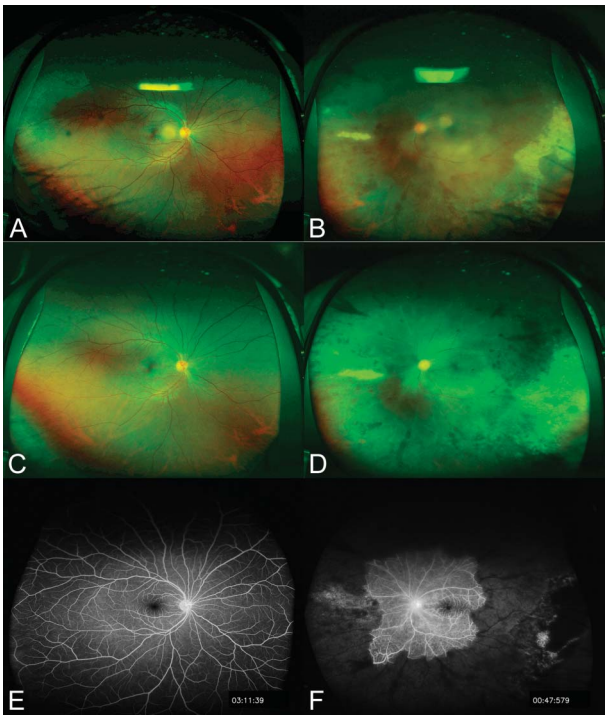

Fig. 1. Patient 1. **A** and **B.** Fundus photograph at presentation. A 2-o'clock hour patch of granular retinitis in the temporal periphery and a fusiform lesion with one end pointing to the optic disk lying in the equator, as well as a few retinal hemorrhages along retinal vessels in the left eye. The right eye was unremarkable. **C** and **D.** Fundus photograph after 6 times of intravitreous injection of ganciclovir and aqueous cytomegalovirus DNA was negative by then. Intraocular inflammation and granular lesion seemed regressed but superficial hemorrhage along retinal vessel exaggerated in the left eye. The right eye was unremarkable. **E** and **F.** Corresponding fundus fluorescein angiography of (**C**) and (**D**) confirmed the presence of 360° retinal nonperfusion. The right eye was unremarkable.

Case 2

A 34-year-old woman reported a 2-week history of progressive vision loss in both eyes. The medical history was notable for HHSCT status + 145 days because of acute lymphocytic leukemia. She was taking prednisone 10 mg daily and cyclosporine 50 mg twice daily for chronic graft-versus-host disease. The patient was treated with oral ganciclovir for 3 weeks because of a 2-week course CMV-DNAemia with peak whole blood CMV-DNA 2.33×10^4 IU/mL 2

months ago. No further evidence of CMV-DNAemia was noted despite regular surveillance. The neutrophil count was 1.91×10^9/L, platelet 76×10^9/L, and total T-lymphocyte count was 1.630×10^9/L the day before she presented.

At initial evaluation, the visual acuity was 20/30 and 20/50 in the right and left eye, respectively, and IOP was 16 mmHg and 15 mmHg in the right and left eye, respectively. There was minimal anterior chamber inflammation but 2+ vitreous cells in both eyes. Fundus ophthalmoscopy showed fan-shaped granular retinitis that started from the right fovea and extended to the inferotemporal in the right eye, and a 2-o'clock hour patch of granular retinitis in the temporal periphery of the left eye. Bilateral CMV necrotizing retinopathy was suspected, and aqueous CMV-DNA was 4.56×10^5 IU/mL and 3.43×10^5 IU/mL for the right and left eye, respectively. Whole blood CMV-DNA was negative ($<1 \times 10^3$ IU/mL). Additional workup including fluorescent treponemal antibody absorption, HIV serologies, serum toxoplasma IgG and IgM, T-SPOT.TB, and chest X-ray were all negative.

Intravitreal injection of ganciclovir was prescribed for both eyes, combined with reducing the dose of prednisolone to 5 mg daily and cyclosporine to 50 mg daily. Quantitative nucleic acid amplification testing for CMV in the aqueous was performed during each time of injection. After five injections, aqueous CMV-DNA was negative ($<1 \times 10^3$ IU/mL) and granular retinitis regressed in both eyes (Figure 2, A and C). Fluorescence fundus angiography revealed a small patch of nonperfusion area in the temporal periphery in both eyes (Figure 2, B and D). The patient was discharged and followed regularly. Two months later, the patient reported another course of vision decreasing in both eyes. The visual acuity was 20/30 and 20/60 for the right and left eye, respectively. Fundus examination indicated recurrence of CMV necrotizing retinopathy from the border of the former scar, and aqueous CMV-DNA was 1.32×10^4 IU/mL and 2.14×10^4 IU/mL for the right and left eye, respectively. Whole blood CMV-DNA was still negative. After another four times of ganciclovir intravitreal injection, aqueous CMV-DNA turned negative again. Fundus examination indicated an enlarged scar (Figure 2, E and G) as well as a nonperfusion area in the temporal periphery on FFA (Figure 2, F and H) in both eyes. Over the next 8 months, the patient was followed up using fundus ophthalmoscopy and fundus photographs. No signs of recurrence were observed in either eye except growing vascular sheathing in the left side, and IOP was always within the normal range. But when she showed up again 9 months later, the visual acuity of the left eye dropped to 20/200 with IOP increased to 35 mmHg. The visual acuity and IOP in the right eye were 20/25 and 18 mmHg, respectively. Neovascularization was observed in the left angle without anterior synechiae. No cells were found in the anterior chamber or the vitreous. Fundus ophthalmoscopy revealed vessel sheathing all around the left fundus. No additional findings could be found in the right eye compared with 9 months ago. Fundus fluorescence angiography indicated a small patch of nonperfusion area in the temporal periphery that did not

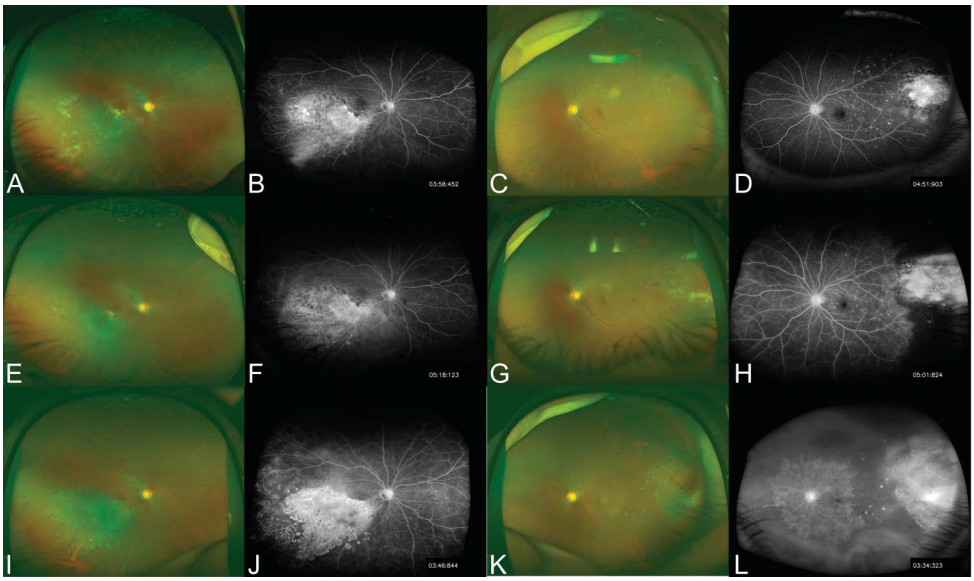

Fig. 2. Patient 2. **A–D.** Fundus photograph and corresponding FFA after the first episode of CMV necrotizing retinopathy. Granular lesions on both sides regressed leaving a small patch of nonperfusion area in the temporal periphery in the left eye. **E–H.** Fundus photograph and corresponding FFA after the secondary episode of CMV chronic necrotizing retinopathy. Bilateral scar enlarged as well as the nonperfusion area in the temporal periphery on FFA. **I–L.** Nine months later without intraocular CMV reactivation, wide-spread vessel sheathing was found all around the left fundus besides the scar in the temporal periphery. No additional findings could be found in the right eye compared with 9 months ago. Fundus fluorescein angiography indicated a small patch of nonperfusion area in the temporal periphery that did not connected to the retinal scar in the right eye and 360° retinal nonperfusion in the left eye, including the nasal retina.

connect to the retinal scar in the right eye and 360° retinal nonperfusion in the left eye, including the nasal retina. Neovascular glaucoma was diagnosed, and anti-vascular endothelial growth factor and panretinal photocoagulation was given. One week later, IOP decreased to 19 mmHg and angle neovascularization regressed, but the visual acuity remained at 20/200. The patient was followed for another 6 months, and no disease progression was further observed.

Discussion

It is estimated that approximately 5,000 allo-HSCT procedures are performed in China annually,[17] and the proportion of HHSCT was 30.8%.[1] The cumulative incidence of CMV necrotizing retinopathy was reported to be 2.3% 1 year after HHSCT.[18] In this study, intraocular neovascular complications further developed in 5.1%/cases and 3.4%/eyes in these patients. Thus, the incidence of intraocular neovascular complications was about 1.81/person-year within the first year after HHSCT in China. Although rare, considering the growing number of patients receiving HHSCT in China[1] and the poor visual outcome for patients who developed such complications during follow-up, attentions should be drawn and early detection and intervention are important.

Ever since the first case of neovascular event complicating CMV necrotizing retinopathy reported by Saran et al in 1996,[19] a dozen of similar cases could be found in the literature at present.[6,7,20–22] Neovascular complications of HIV-related CMV retinitis are rare, but the incidence was recognized to be higher in non-HIV patients.[21,22] All the cases reported share similar clinical manifestation including granular peripheral retinitis, panretinal occlusive vasculitis, and some degree of intraocular inflammation, which fit the criteria of acute retinal necrosis defined by the American Uveitis Society.[5] Schneider et al[4] proposed that CRN caused by CMV is related to the immune status of the host. In limited immuno-compromised patients, the manifestation of CMV retinitis may be a spectrum of mixture of acute retinal necrosis and CMV retinitis, from acute retinal necrosis-like end in patients with lesser degrees of immune dysfunction to classic CMV retinitis-like end in whom more serious immune compromise exists. In their case series, patients with CRN were reported to have symptoms for weeks to months and were observed to have little progression even without antiviral management.

In Schneider's report, granular retinitis, occlusive panretinal vasculitis, and intraocular inflammation occurred at the same time. No progression or reactivation of retinitis was noted after antiviral treatment, but no further FFA findings were described during follow-up. Four of the five patients developed neovascular complications, and vessel occlusion and extensive retinal nonperfusion seem to have already existed at the initial presentation in all four cases.[4] A similar clinical picture was seen in our first case and in cases reported by Matsuoka et al in 2017[7] and Cho et al in 2018.[6] Our second case was different in that, at the first episode, the appearance and enlargement of nonperfusion area was accompanied by active retinitis and was relatively small. After the second episode of CMV reactivation, intraocular inflammation and retinitis seemed calm all the time on fundus biomicroscopy and fundus photographs, but actually, the nonperfusion area continued growing during the 8 months' follow-up and could only be observed on FFA, which emphasizes the importance of FFA on a regular basis to monitor patients with CMV necrotizing retinopathy. Limited immune dysfunction, the continuous replication of CMV in vascular endothelial cells and CMV-specific T-cell-mediated endothelial cell damage may be the possible mechanism for this phenomenon.[4,6,20,22] In addition to the spectrum proposed by Schneider et al,[4] insidious immune-mediated CMV vasculitis may be an isolated manifestation for CMV necrotizing retinopathy when immune deviation was even lesser than patients with CRN.

The discrepancy of incidence of neovascular complications between Schneider's report and ours (80% vs. 5.1%) was most probably because of patient selection, as we included all patients with CMV necrotizing retinopathy irrespective of their clinical appearance, but Schneider et al only included patients manifested as CRN. Patients with CRN had minimal symptoms in the early stage of the disease and showed up only when the retinal nonperfusion area grew large enough to cause significant visual impairment. But for patients with classic CMV retinitis (fulminant/edema type), floaters and vision loss caused by vitritis and macular involvement prompted them to see doctors immediately when disease occurred and then retinal vessel occlusion could be stopped with proper management. Neovascular complications were more common in patients with CRN when cases of CMV necrotizing retinopathy were retrospectively reviewed.

It is interesting that both patients developed unilateral neovascular complications, especially the enlargement of nonperfusion area only happened to the left eye but not the right eye of the second patient. The exact reason for this was unknown. Ocular immune-privilege effect and local CMV-specific T-cell immune deviation may be a feasible explanation[22–25] but further investigations were needed.

Intravenous ganciclovir is considered the first-line treatment for CMV disease after HSCT[26] and solid organ transplantation[27] and was recommended for CMV retinitis in the 2017 European Conference on Infections in Leukemia guideline.[26] We had concerns about using it in our patients due to its potential effect of myelosuppression[9] and delaying the recovery of CMV-specific T-cell responses,[10,11] combined with its relatively low permeability into the vitreous[12] and the negative results of whole blood CMV-DNA testing at presentation. After discussion with hematologists and the two patients, local ganciclovir injection combined with dose reduction of immunomodulatory drugs without systemic ganciclovir were prescribed. Retinitis was sufficiently controlled, which was confirmed by negative aqueous CMV-DNA in the end in both cases. Considering the possible mechanism of isolated CMV vasculitis, systemic ganciclovir may produce a better outcome and reduce the incidence of neovascular complications, but more observations and evidences are needed. And its benefits must be balanced with its potential side effects. Besides, considering the high risk of NVG and its poor visual outcome, prophylactic panretinal photocoagulation should be performed right at once when extensive retinal nonperfusion was found on FFA.

In conclusion, although rare, NVG developed in 5.1%/cases and 3.4%/eyes of patients with CMV necrotizing retinopathy after HHSCT. Immune-mediated CMV vasculitis could be an isolated manifestation in patients with minimal immune deviation and could only be found on FFA, which warrants the needs for long-term follow-up and FFA on a regular basis.

Key words: cytomegalovirus, chronic retinal necrosis, haploidentical stem cell transplantation, neovascular glaucoma, retinal vasculitis.

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