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CASE REPORT

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Frosted branch angiitis as an immune recovery response in newly diagnosed acquired immunodeficiency syndrome and systemic cytomegalovirus infection

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Abstract

Frosted branch angiitis (FBA) is an uncommon form of severe retinal perivasculitis associated with systemic inflammatory/infectious diseases. In this report, we describe a case of FBA and macular edema as a result of immune recovery response in a patient newly diagnosed with HIV infection and cytomegalovirus viremia.

KEYWORDS

cytomegalovirus retinitis, frosted branch angiitis, HIV, HIV-retinitis, inflammatory cells in the vitreous, macular edema, retinal vasculitis

1 | INTRODUCTION

In this report, we describe a case of a frosted branch angiitis and macular edema which may have developed as a result of immune recovery uveitis under HAART in an HIV patient also with systemic cytomegalovirus infection.

Frosted branch angiitis (FBA) is a relatively rare form of panretinal perivasculitis, characterized by widespread, severe sheathing of the retinal vessels and mild to moderate anterior uveitis. Although initially described as affecting both arteries and veins, particularly in younger patients, it predominantly involves the veins.[1,2] Initially reported in pediatric patients, it is now known to be associated with systemic inflammatory/infectious diseases in young adults. So far, FBA has been reported in association with Epstein–Barr virus, Herpes simplex virus, streptococcus, toxoplasmosis, human immunodeficiency virus (HIV), cytomegalovirus (CMV) and systemic conditions such as *Adamantiades-Behçet* disease, systemic lupus erythematosus, Crohn's disease, glomerulonephritis, leukemia, and lymphoma. Its association with such a wide spectrum of diseases suggests that FBA may be more a clinical sign rather than a distinct syndrome.[3,4]

In patients infected with HIV, CMV retinitis was a common finding before the introduction of highly active antiretroviral therapy (HAART), characterized by low CD4+ T-cell count and only mild anterior uveitis and low grade retinal perivasculitis. HAART has led to a dramatic decrease in HIV mRNA and a restoration of CD4+ T-cell counts, often with a rebound improved immune reaction

associated with substantial intraocular inflammation, termed immune recovery uveitis (IRU).[5]

2 | CASE REPORT

A 37-year-old man presented to our internal medicine department after being referred from a community hospital with newly diagnosed HIV-infection. He suffered from HIV-related meningoencephalitis in the frontobasal lobe (Figure 1A) and highly active cytomegalovirus (CMV) viremia. The patient had a severe immunodeficiency with CD4 lymphocyte cell depletion down to 19/µl and a HIV virus load of 1,288,314 copies/ml. The initial CMV virus load measured up to 2,800,000 copies/ml. An extensive serology for simultaneous viral and opportunistic infections such as Borrelia, Treponema pallidum, Epstein–Barr virus (EBV), spring–summer encephalitis virus, herpes simplex virus (HSV), Mumps, Coxackie, ECHO, Rubella, Varicella zoster virus (VZV) was negative. A lumbar puncture was performed but was negative for CMV, EBV, HSV-1 and HSV-2, and VZV. An ophthalmological screening was requested to rule out CMV retinitis. The slit lamp examination showed unremarkable anterior segments and biomicroscopy with a 90D lens demonstrated normal retina in both eyes. Best corrected visual acuity (BCVA) was right eye (RE) 1,0 and left eye (LE) 0,8. The patient was put on HAART with Zidovudin, Dolutegravir, and Nevirapin as well as intravenous ganciclovir (5 mg/Kg bodyweight twice a day). After 5 weeks of intravenous ganciclovir, the CMV virus load had reached undetectable levels, the CD4+ T-cell count was increasing at 148/µl while the HIV replication rate decreased to 545 copies/ml. The patient was discharged.

A couple of days after discharge (1.5 months after the initial admission), the patient presented again to our emergency department with decreased vision LE, headache, and photophobia. Best corrected visual acuity was 0,7 RE and 0,08 LE and the eye pressure 15 mmHg in both eyes. Slit lamp examination demonstrated a clear cornea with endothelial dusting and mild anterior uveitis (1+ SUN Grading Scheme),[6] and extensive perivascular retinal sheathing along major retinal veins and their branches with disseminated retinal hemorrhages particularly from the posterior pole to the middle periphery in both eyes, LE more than RE (Figure 2A,B). Fluorescence angiography demonstrated blocking of signal at areas of vascular sheathing and hemorrhage but good retinal perfusion. Additionally, the LE demonstrated edema of the optic disc as well as leakage on fluorescein angiography (Figure 2C,D). Optical coherence tomography (OCT) of the RE demonstrated a subclinical macular edema with central retinal thickness of 316 µm, the LE demonstrated significant macular edema with CRT 1016 µm explaining the massive drop in vision (Figure 2E,F). Serologic examination demonstrated a reactivation of CMV viremia with up to 296,000 viral copies/ml and a drop in the CD3+ and CD4+ T-helper lymphocyte count down to 120/µl, the cytotoxic CD3+ and CD8+ T-helper lymphocyte count down to 196/µl (CD4+/CD8+ ratio 0.60). There was also a low-grade HIV replication up to 361 copies/ml. We diagnosed frosted branch angiitis due to immune recovery status in the setting of systemic CMV infection complicated by CMV retinitis. The patient was admitted and was put again on intravenous ganciclovir. Because of the extensive retinal inflammation in both eyes with macular edema and profound vision loss of the LE, following consultation with his treating physician, the patient was also put on 100 mg Decortin (prednisone) for 3 days with weight adapted doses thereafter and slow tapering over the next 2 weeks. The patient showed gradual resolution of the perivascular infiltrations over the next 2 weeks with resolved intraocular inflammation (0, SUN Grading Scheme),[6] resolving perivasculitis as well as hemorrhages, improved macular edema (LE

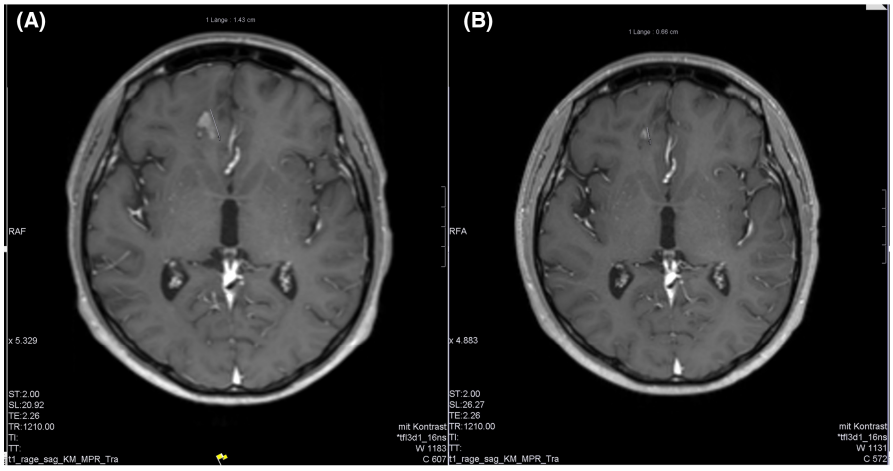

FIGURE 1 Cranial MRI demonstrating the frontobasal lesion (white arrow) on the left panel (A), subsequently significantly smaller on the right panel (8 weeks post-discharge) (B). (MRI: magnet resonance imaging).

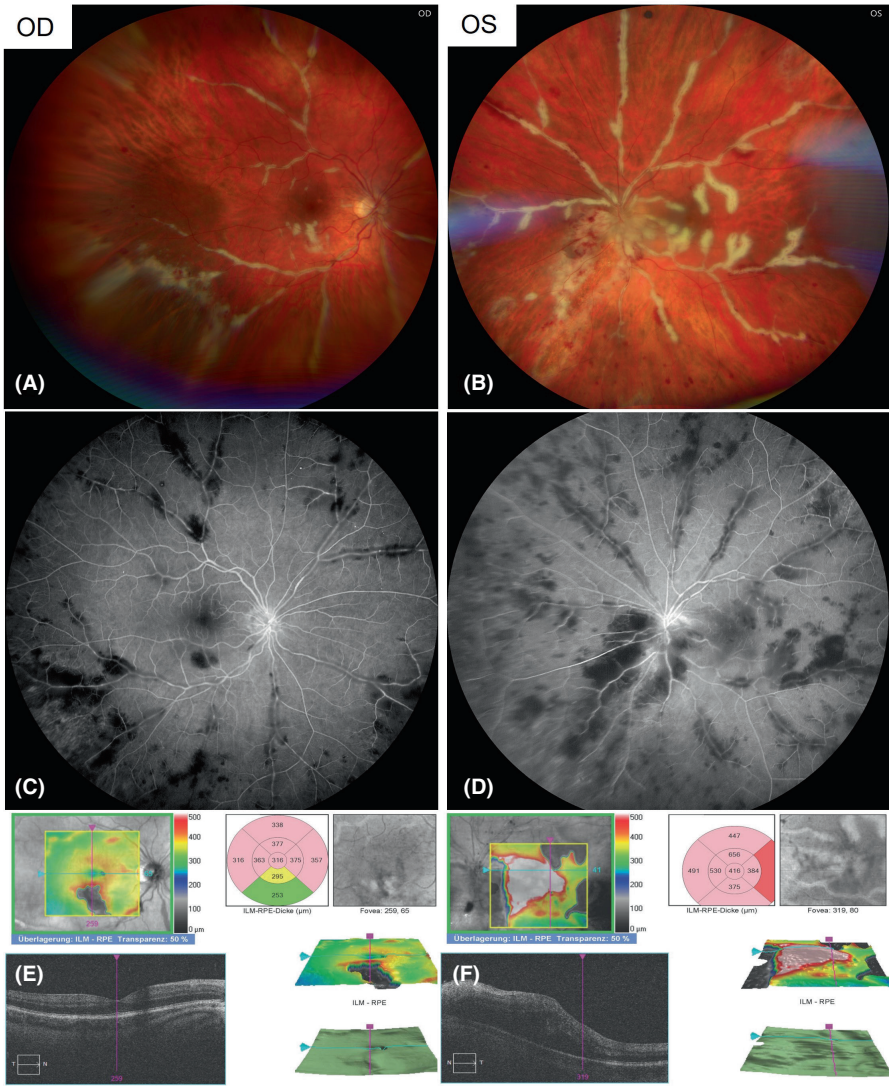

FIGURE 2 Fundus photos and fluorescence angiography with the corresponding OCTs. Please note the normal appearance of the right macula with CRT 316 µm and extensive macular edema of the left eye with CRT of 1016 µm. The left eye also demonstrates optic disc edema with leakage on angiography and blurred macular appearance due to edema. There is extensive signal blockage along the infiltrates which, extend centrally with pronounced macular edema explaining the massive drop in vision. (OCT: optical coherence tomography, CMV: cytomegalovirus).

CRT 526 µm), and partial vision recovery (BCVA 0.32 LE) and was discharged. The patient was kept on treatment utilizing an intravenous port for ganciclovir therapy at home for a year. The CMV virus load decreased further to 28,375 copies/ml. Six weeks after discharge, the retina improved further with macular edema reduction and resolution of vascular sheathing. The CMV levels were non-detectable. The CD3+ and CD4+ T-helper lymphocyte count had risen to 458/µl and there was stable low-grade HIV replication at 249 copies/ml. On the last follow-up 8 weeks post-discharge, both eyes had a quiet anterior chamber with resolution of endothelial dusting, normal pressure (12 and 15 mmHg), vitreous with haze, and the macular edema completely resolved (338 µm RE, 279 µm LE), with only traces of perivascular sheathing and resolving hemorrhages. BCVA improved to 0.7 LE (Figure 3A–D) and the meningoencephalitis regressed considerably (Figure 1B, 8 weeks post-discharge). Thereafter the patient was followed by his local ophthalmologist.

3 | DISCUSSION

We describe a case of a bilateral FBA in an HIV-patient in the context of HAART and recovering immune system with systemic CMV infection complicated by bilateral CMV retinitis, macular edema, and mild anterior uveitis.

In the setting of HIV infection, FBA is uncommon with the majority of the few reported cases associated with CMV retinitis.[7] CMV retinitis is the most frequent form of infectious retinitis in patients diagnosed with HIV.[8] A diagnosis of CMV retinitis is usually made clinically based on fundus appearance.[8,28] Before the introduction of HAART, CMV retinitis with mild retinal perivasculitis and anterior uveitis affected up to 40% of HIV patients with CD4+ T-cell count below 50 cell/mm.[5] There are two forms of CMV retinitis, one fulminant and one indolent. In the fulminant form, lesions demonstrate the classic features of disease with hemorrhagic necrotizing retinitis extending along the major vascular arcades of the posterior

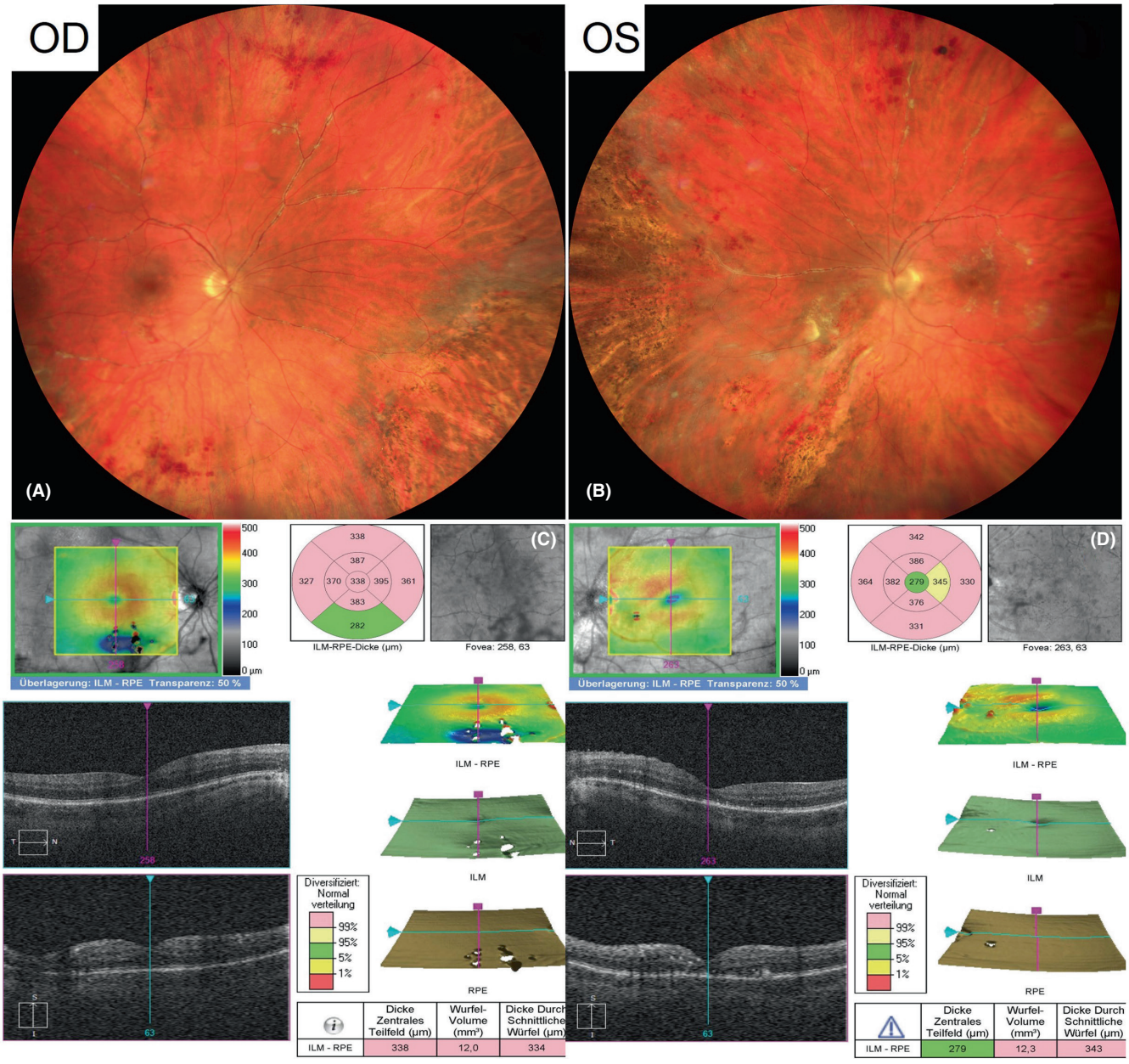

FIGURE 3 Fundus photos with the corresponding OCTs almost two months after admission show both eyes improved. Please note the OCT of both eyes; the right macula has still a normal appearance with CRT 330 µm; the left macula edema has improved with CRT 279. (OCT: optical coherence tomography, CMV: cytomegalovirus, FBA: frosted branch angiitis).

retina, probably reflecting the hematogenous spread of the virus.[10,11] In the indolent form, the peripheral retina is usually involved demonstrating white granular lesions associated with minimal or no hemorrhage at the active borders and retinal atrophy at the seemingly inactive central areas.

Our case has similarities with previous reports of FBA in patients infected with HIV particularly in the context of a recovering immune system.[7,12] Karavelas et al. hypothesized that HAART-related immune recovery plays a role in this disorder.[5] The exact cause of FBA however remains unknown. Although most investigators hypothesized inactivity of CMV retinitis, patients with active CMV retinitis can develop FBA with antigen antibody complex deposition and direct CMV infection of the vessel wall as pathogenetic processes.[13-15] Moreover, low level of viral replication or protein expression (HIV) despite the absence of clinically active CMV retinitis might also play a role in the pathogenesis of FBA.[16] Our case adds to the few cases reported in the literature with FBA associated with HIV, and a recovering immune system. The necessity of prolonged antiviral treatment against CMV is emphasized in order to avoid relapses in the sensitive period of remission. Although the use of systemic corticosteroids

has been questioned in the past, we demonstrate good tolerance and effectiveness both in the treatment of FBA and the macular edema.

For FBA, no standard treatment is known. Most primary cases (idiopathic), have been systemically supported with corticosteroids with good anatomical and functional response.[17] In cases where systemic corticosteroids were contraindicated due to side effects, targeted modulation of immune response with monoclonal anti-TNF-a antibodies (infliximab or adalimumab) has also shown good results with prompt remission.[18,19] In secondary cases as in this one, treatment requires close collaboration between the eye care specialist and the treating physician for an individualized plan depending on the immune status, concomitant medications, and individual tolerance. The availability of HAART has allowed clinicians to reconsider treatment of CMV retinitis in those patients for whom immune reconstitution and thus complete inactivity of CMV retinitis without concurrent specific anti-CMV is anticipated.[20-22] However, it is difficult to predict whether or when the immune system will establish control of CMV without additional anti-CMV treatment. Thus, the delay in immune reconstitution after initiation of HAART should still prompt anti-CMV treatment in every case of newly diagnosed CMV retinitis such as intravenous or intravitreal ganciclovir, foscarnet in resistant cases or even oral valganciclovir.[2,23] Anti-CMV drugs however are, in general, virostatic and cannot completely eliminate the viral DNA from the retinal cells. Therefore, if immunosuppression persists and anti-CMV treatment is stopped, progression of the disease is inevitable in the longer term. Without therapy, progression of CMV occurs within 2–3 weeks.[24] Even under maintenance therapy, relapses occur, probably because resistant strains of the virus evolve or the immune function of the patient declines. With the introduction of HAART however this concept of life-long maintenance therapy has been challenged. In our case, the discontinuation of ganciclovir treatment after the first presentation could have possibly triggered the reactivation of CMV viremia and consequent retinal reaction in a recovering immune system.

While the use of systemic corticosteroids is the treatment of choice in primary cases, in secondary cases, particularly in immunocompromised patients, it is controversial due to the additional suppression of the immune system without any antiviral effect.[13,14,25] The use of corticosteroids has been further contraindicated as antiviral-CMV treatment alone was beneficial in HAART-naïve HIV-infected patients.[13,14,25] However, as FBA is mainly a clinical sign, some individuals responded also well to steroid treatment after antiviral treatment induction, especially in the presence of CMV-associated immune recovery uveitis.[12,26,27] Given the extensive retinal findings in both eyes particularly with macular edema and visual loss, we felt that the patient could benefit from systemic corticosteroid treatment which was supported by the treating infectiologist.[18,19] However with active CMV-retinitis, continuous antiviral treatment to reduce future morbidity, as mentioned above, is mandatory with intravenous ganciclovir administration or intravitreal ganciclovir, foscarnet in resistant cases or even valganciclovir.[2,23,28] With intravitreal ganciclovir, one can achieve therapeutic levels by circumventing the inefficiency of gancyclovir crossing the blood–retina barrier. In HIV patients on Zidovudine, intravitreal ganciclovir is particularly helpful as Zidovudine may preclude the use of systemic gancyclovir because of added myelosuppressive effect.

In conclusion, FBA could be a sign of CMV-associated immune recovery response. In patients with active HIV infection, CMV retinitis can be prevented by taking early HAART and maintaining a CD4+ T cell count >100 cells/mm^3. Recognizing the early manifestations of the CMV and initiating and sustaining proper therapy are crucial to avoid further ocular morbidity.

AUTHOR CONTRIBUTIONS

Elisa Huynh: Conceptualization; writing – original draft; writing – review and editing. **Argyrios Chronopoulos:** Conceptualization; writing – original draft; writing – review and editing. **James Scott Schutz:** Conceptualization; writing – original draft; writing – review and editing. **Bernd Claus:** Formal analysis; investigation. **Marwa Erwemi:** Data curation; resources; supervision; writing – review and editing. **Hermann Krastel:** Data curation; project administration; supervision; validation. **Lars-Olof Hattenbach:** Data curation; project administration; supervision; validation.

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None.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

PATIENT CONSENT STATEMENT

Written patient consent has been signed and collected in accordance with the journal's patient consent policy.

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