Frosted branch angiitis due to cytomegalovirus-associated unmasking immune reconstitution inflammatory syndrome: a case report and literature review

Shi Tang†, Ning Zhao‡, Li Yang Wang§ and Ying Wen*†

Abstract
Background: Cytomegalovirus (CMV) retinitis is a common opportunistic infection in patients with acquired immunodeficiency syndrome. The common funduscopic manifestations are haemorrhagic necrotising variety and granular variety. Frosted branch angiitis (FBA), as a special form, when it occurred after antiretroviral therapy (ART), could possibly be associated with immune reconstitution. We report a case of FBA secondary to CMV infection-associated unmasking immune reconstitution inflammatory syndrome (IRIS).

Case presentation: A 27-year-old man with human immunodeficiency virus infection developed FBA after 35 days of ART. The left Aqueous humour (AqH) tested positive for CMV DNA, and the patient was diagnosed with CMV retinitis. The degree of intraocular inflammation was reflected by increased levels of interleukin (IL)-6 and IL-8 in AqH. After anti-CMV treatment and continuous ART for several months, his FBA and vision significantly improved. CMV DNA became undetectable in the left AqH, and the IL-6 and IL-8 levels in AqH decreased.

Conclusion: FBA could be a sign of CMV-associated unmasking IRIS. Anti-CMV treatment alone or combination with steroid treatment may be administered, depending on the changes in CMV DNA load and immunologic profile of AqH.

Keywords: Frosted branch angiitis, Anti-cytomegalovirus treatment, Unmasking immune reconstitution inflammatory syndrome, Case report

Background
Frosted branch angiitis (FBA) is a special form of vasculitis, affecting the entire retina. The funduscopic findings of FBA include bilateral widespread retinal vasculitis with severe sheathing of the retinal vessels, resembling frosted branches of a tree, especially at the periphery, and mild to moderate iritis or vitritis. In this article, we reported a case of FBA secondary to cytomegalovirus (CMV) infection-associated unmasking immune reconstitution inflammatory syndrome (IRIS).

Case presentation
A 27-year-old young man, who previously had sexual contact with other men, was diagnosed with human immunodeficiency virus (HIV) infection 2 months ago. His
CD4+ T cell count was 33 cells/μL. His serum anti-cytomegalovirus immunoglobulin M (IgM) was 23.6 U/mL (normal range: 0–18 U/mL), and CMV IgG was 139.0 U/mL (normal range: 0–12 U/mL). His serum CMV DNA load was $4.54 \times 10^3$ copies/mL. The patient had no ocular symptoms and signs. No abnormalities were found on funduscopic screening examination (Fig. 1A). The preemptive anti-CMV treatment was not performed. His acid-fast smear of sputum, interferon-gamma release assay for *Mycobacterium tuberculosis*, and tuberculin skin test were negative. The IgM antibodies of rubella virus, herpes simplex virus (HSV),

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Fig. 1 Changes observed in the patient’s eye examination. A Normal bilateral eyes appearance before antiretroviral therapy (ART). B After 5 weeks of ART, the left eye showed sheathing of the retinal vessels appearing like frosted branches of a tree without haemorrhages, necrosis, and occlusion. C Eye ultrasound revealed mild vitreous haze in the left eye after 5 weeks of ART. D No oedema in the macular area by optical coherence tomography were seen after 5 weeks of ART. E After 6 weeks of anti-CMV treatment, frosted branch angiitis in the left eye had significantly improved. F After 6 months of anti-CMV treatment, the retinal perivenous exudate in the left eye had resolved.
varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) were all negative. The IgM and IgG antibodies to toxoplasma gondii, mycoplasma, and legionella were all negative. The specific antibody of syphilis was negative. The blood sugar level was normal. Abdominal ultrasound screening, chest computed tomography, and brain magnetic resonance imaging were normal. Then, the patient received antiretroviral therapy (ART), including tenofovir, lamivudine, and efavirenz as well as oral cotrimoxazole, two tablets daily, for primary prophylaxis of Pneumocystis jirovecii pneumonia.

On the 35th day of ART, the patient complained of floaters and blurred vision in the left eye and was admitted to our hospital due to worsening of eyesight. No other systemic abnormal symptoms and signs had been found, such as fever, rashes, cough, watering nose, sneeze, sore throat, parotid enlargement, mouth ulcer, diarrhoea, and bloody stool, etc. His CD4+ T cell count rapidly increased to 172 cells/μL. The HIV RNA load was 1.80 × 10^3 copies/mL. The left and right eyes were not red and swollen. His visual acuity was 20/20 in the right eye and 20/30 in the left eye. Bilateral intraocular pressures were normal. Slit-lamp examination showed diffuse punctate keratic precipitates and positive aqueous flare in the left eye. The size of the pupils and the light response were normal. The lens was transparent. Fundal examination revealed extensive retinal perivascular exudate, forming frosted branch vascular sheathing in the left eye (Fig. 1B). At the lower border of the right eye, peripheral retinitis, characterized by white granular exudates with minimal haemorrhage, was detected. Eye ultrasound revealed a slightly vitreous haze (Fig. 1C). Optical coherence tomography did not reveal macular oedema (Fig. 1D). The serum CMV DNA became negative (< 1.0 × 10^3 copies/mL). The level of C-reactive protein was 5.60 mg/L (normal range: 0.00–5.00 mg/L). The levels of antistreptolysin O and rheumatoid factor were normal. Blood screening results of autoantibodies were all negative. A 100 μL sample of Aqueous humour (AqH), collected by anterior chamber puncture, was sent to Beijing Zhi De medical laboratory science finite company. CMV DNA in the left AqH was 6.54 × 10^5 copies/mL. Using BD-Pharmingen cytometric bead array, the interleukin (IL)-6 and IL-8 levels in the AqH were 2845.0 pg/mL (normal range: 1–50 pg/mL) and 967.8 pg/mL, respectively. His CD4+ T cell count was 131 cells/μL, and HIV RNA load was 30.3 copies/mL. His serum CMV IgM was negative, and CMV IgG exceeded 180.0 U/mL.

Discussion and conclusion

This was the first case that met the criteria for diagnosing early unmasking IRIS-FBA [1]. His condition was classified as a re-activation of a latent CMV infection. Short-term ART decreased the CMV DNA in his blood to undetectable levels [2]. However, subacute visual loss and floaters developed in his left eye. Detectable CMV DNA in the intraocular fluid is crucial for CMV retinitis diagnosis and differentiation from primary FBA or other infections. The elevated levels of IL-8 and IL-6 (principal cellular sources from monocytes and macrophages) in the AqH, as an indicator of active retinitis, obviously decreased following the anti-CMV treatment [3–5]. In this case, anti-CMV treatment monotherapy decreased the CMV DNA load as well as IL-8 and IL-6 levels in the AqH. Along with this, the patient’s eyesight improved, and perivascular exudation regressed. Thus, systemic steroid treatment was not required.

CMV retinitis is an important cause of blindness in individuals with advanced HIV infection and is characterized by intraretinal haemorrhages, white zones of retinitis, retinal oedema, and vasculitis. FBA is a special form of retinal vasculitis. This may be primary FBA or secondary to ocular infectious diseases, such as CMV, syphilis, HSV, VZV, tuberculosis, toxoplasmosis, and non-infectious diseases, such as autoimmune diseases and haematological malignancies in the non-HIV-infected population [6]. Antigen-antibody complex deposition and direct CMV infection of the vessel wall are the underlying pathogeneses [7, 8]. In the setting of HIV infection, FBA is an uncommon sign. Apart from the syphilis-related case [9], reported cases were exclusively associated with CMV retinitis [7, 8, 10–16] (summarised in Table 1). Currently, only two cases of FBA were associated with paradoxical IRIS [10, 12]. The time from ART initiation to IRIS development was 7 days [12] and 6 months [10], respectively. Anti-CMV treatment without steroid treatment was beneficial in ART-naive HIV-infected patients [7, 16]. However, some individuals responded well to steroid treatment, especially in the presence of CMV-associated IRIS [12, 13].

In conclusion, FBA could be a sign of CMV-associated unmasking IRIS. In HIV-infected patients with oral ganciclovir (3 g/day). During the sixth-month follow-up, the peripheral granular lesion in his right eye subsided, and the vascular sheath-like exudates in the left eye resolved (Fig. 1F). His visual acuity became 20/25 in the left eye. His serum CMV DNA was undetectable. CMV DNA in the left AqH was also negative (< 1.0 × 10^3 copies/mL), and the levels of IL-6 and IL-8 in the left AqH decreased to 28.5 pg/mL and 5.6 pg/mL, respectively. His CD4+ T cell count was 131 cells/μL, and HIV RNA load was 30.3 copies/mL. His serum CMV IgM was negative, and CMV IgG exceeded 180.0 U/mL.
asymptomatic CMV viremia, preemptive anti-CMV therapy was not recommended by the guideline. However, some trials assessing preemptive anti-CMV therapy in advanced HIV-infected patients documented its efficacy [17, 18]. CMV retinitis can be prevented by taking early ART and maintaining a CD4 + T cell count > 100 cells/μl. Recognising the early manifestations of the disease and initiating proper therapy are crucial. Anti-CMV treatment with or without steroid treatment can be administered for FBA depending on the changes in CMV DNA load and immunologic profile of the AqH. In patients with no response to anti-CMV medications, systemic corticosteroids are recommended.

Abbreviations

AqH: Aqueous humour; ART: Antiretroviral therapy; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; FBA: Frosted branch angiitis; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; Ig: Immunoglobulin; IL: Interleukin; IRIS: Immune reconstitution inflammatory syndrome; VZV: Varicella-zoster virus

Acknowledgements

None.

Authors’ contributions

TS and WY participated in the drafting of the manuscript. ZN participated in the management of the patient. All authors revised the article critically for important intellectual content. All authors read and approved the final manuscript.

Funding

This work was supported by “double first class” university and discipline construction funds of China Medical University(3110119068 to W.Y.). The funder had no role in writing the manuscript or in the decision to publish the results.

Table 1 Summary of reported cases with HIV-infection and cytomegalovirus-associated frosted branch angiitis

| Case | Age (years) | Gender | CD4 cell count(μl) | Eyes with FBA | Duration post-ART | ART | Outcome | Treatment |
|------|-------------|--------|-------------------|--------------|-----------------|-----|---------|-----------|
| Mansour AM et al. 1993 [7] | 27 | M | NM | Left | NM | NM | R | Gancyclovir |
| | 39 | M | NM | Right | NM | NM | R | Gancyclovir |
| | 24 | M | NM | Left | NM | NM | NM | Gancyclovir |
| | 35 | M | NM | Left | NM | NM | R | Gancyclovir |
| | 35 | M | NM | Both | NM | NM | R | Introvenous gancyclovir |
| | 32 | M | NM | Both | NM | NM | R | Gancyclovir |
| R F Spaide et al. 1992 [8] | 36 | M | 10 | Both | NM | NM | R | Introvenous gancyclovir |
| | 50 | M | 10 | Both | NM | NM | R + retinal detachment | Gancyclovir, vitrectomy, intravenous foscarnet |
| | 28 | M | 20 | Right | NM | NM | R | Intravenous foscarnet |
| Mehmet Numan Alp et al. 2010 [10] | 36 | F | From 9 to 20 | Both | 6 m | Y | R + retinal detachment | Introvenous gancyclovir, Periocular and topical steroids, ART continuation |
| Aguilar Lozano et al. 2016 [11] | 41 | M | 31 | Left | 8 m | Y | NM | DR | Intravenous gancyclovir, ART adjustment |
| Supinda Leeam-ornsiri et al. 2013 [12] | 40 | F | From 53 to 107 | Right | 1 W | Y | R | NDR | Intravitreal ganciclovir injections, Oral prednisone ART continuation |
| H F Fine et al. 2001 [13] | 7 | M | 30 | Both | NM | NM | R | Intravenous gancyclovir and foscarnet, Oral prednisone |
| Biswas et al. 1999 [14] | 39 | M | 69 | Both | 5 m | Y | DR | R +retinal detachment | Intravenous gancyclovir, Vitrectomy, Intravitreal injections of gancyclovir |
| S A Geier et al. 1992 [15] | 49 | M | NM | Right | NM | NM | R | Intravenous gancyclovir, Oral fluocortolone |
| Feifei Mao et al. 2016 [16] | 26 | M | 11 | Right | 3 W | Y | R | NDR | Oral prednisone, Intravitreal foscarnet injections, ART continuation |
| Our patient | 27 | M | From 33 to 172 | Left | 5 W | Y | R | NDR | Intravitreal ganciclovir injection, Intravenous gancyclovir, Intravenous foscarnet ART continuation |

M male, F female, NM not mentioned or not done, DR drug resistance of ART, NDR non-drug resistance of ART, R regression of FBA, Y yes, FBA frosted branch angiitis, ART Antiretroviral therapy
Availability of data and materials
Not applicable (no datasets were generated or analyzed during the current study).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The informed consent for being written and published was provided by the patient.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Infectious Diseases Department, The First Affiliated Hospital of China Medical University, No. 155, Nanjing North Street, Heping District, Shenyang 110001, Liaoning Province, China. 2 Department of Ophthalmology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, China. 3 Department of Gastroenterology, The sixth People’s Hospital of Shenyang, Shenyang, Liaoning Province, China.

Received: 31 December 2020 Accepted: 10 June 2021

Published online: 26 June 2021

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