CASE REPORT

Immune recovery uveitis in a patient with previously undiagnosed cytomegalovirus retinitis

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SUMMARY

A 40-year-old man presented to the emergency service of the Department of Ophthalmology, Fundación Oftalmológica de Santander, Floridablanca, Colombia, with blurred vision in his right eye. Anamnesis revealed that he also had newly diagnosed stage C HIV. He had recently started highly active antiretroviral therapy (HAART). Examination disclosed intraocular inflammation, along with plain white peripheral non-exudative lesions with sparse haemorrhaging. The differential diagnosis included cytomegalovirus (CMV) retinitis and immune recovery uveitis (IRU). On follow-up, the patient's left eye presented with decreased visual acuity and increased vitreous haze. A vitrectomy with vitreous tap was performed for microbiological studies. PCR for CMV in the vitreous sample was negative. The patient was discharged with the final diagnosis of IRU. In HIV patients with uveitis, the knowledge of characteristic signs and symptoms of particular entities such as opportunistic infections and IRU will enable the clinician to give the appropriate treatment.

BACKGROUND

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical worsening of a treated opportunistic infection or unmasking of a previously subclinical infection after initiation of highly active antiretroviral therapy (HAART).¹ IRIS was initially described most often in cases of *Mycobacterium tuberculosis*, atypical mycobacterium, cytomegalovirus (CMV), varicella zoster virus and *Cryptococcus neoformans*.²

Manifestation of IRIS within the eye is referred to as immune recovery uveitis (IRU). IRU is associated with inactive CMV retinitis,² but a newly reported case of IRU in a patient with inactive toxoplasmic chorioretinitis suggests that inflammation due to other causes may also be responsible for the onset of IRU.³

HAART IRU is one of the most common causes of new vision loss in AIDS patients.⁴ HIV patients are prone to multiple opportunistic infections and IRU. Thus, management is different in each case, and therefore it is of great importance to be aware of the particular signs and symptoms of these entities.

CASE PRESENTATION

A 40-year-old man presented to the emergency service of the Department of Ophthalmology, Fundación Oftalmológica de Santander, Floridablanca, Colombia, with blurred vision in his right eye for two days. He also reported a previous hospitalisation that occurred 5 months before due

to cryptococcal meningitis and an episode of diminished vision in both eyes. His best-corrected visual acuity (BCVA) was 20/25 (Snellen annotation) in both eyes. On slit-lamp examination, his eyelids, conjunctiva and cornea were unremarkable. Anterior and vitreous chamber cellularity were each graded as ++ (SUN Working Group Grading),⁵ no iris nodules were evident and the pupils had normal photomotor and consensual responses. Intraocular pressure (IOP) was 15 mm Hg. On posterior segment examination, the vitreous was turbid, and plain white, non-exudative lesions with no clear borders on the superotemporal periphery in both eyes were evident. A haemorrhage near the lesions was present in the left eye, but none was found in the right eye. The optic nerve was normal and no vasculitis was observed. A peripapillary nevus was present in the left eye.

On questioning, the patient revealed that he had stage C HIV, diagnosed 5 months before. HAART instituted at that time consisted of lamivudine 150 mg two times a day, abacavir 300 mg two times a day and efavirenz 600 mg once daily. Opportunistic prophylaxis included fluconazole 200 mg once daily, trimethoprim sulfamethoxazole 160/800 mg once daily and valganciclovir 450 mg two times a day.

Laboratory results from the patient's hospitalisation 5 months earlier showed the following: ELISA HIV positive, western blot HIV-positive, HIV RNA load of 224 000 copies/mL, CD4+ count of 3 cells/ μ L, CMV positive in cerebrospinal fluid of 1046 copies/mL, CMV positive in serum of >1 000 000 copies/mL, IgG CMV of 18.43 IU/mL and IgM CMV of 0.265 IU/mL.

Following his consultation in our clinic, the laboratory results show HIV RNA load of 154 copies/mL and a CD4+ count of 74 cells/ μ L.

Based on the laboratory results, including the low CD4+ count before HAART and the increasing count afterwards, along with the immunosuppression, we diagnosed IRU associated with CMV retinitis.

INVESTIGATIONS

Macular optical coherence tomography (OCT) of both eyes revealed no evidence of cystoid macular oedema or epiretinal membranes. OCT of the left eye revealed a posterior shadow as an artefact of the vitreous opacities (figure 1).

DIFFERENTIAL DIAGNOSIS

In patients who are immunosuppressed due to HIV/AIDS and who present with uveitis, opportunistic infections should be suspected as the leading

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Figure 1 Funduscopy and optical coherence tomography (OCT) of the patient's right and left eyes. (A) Colour photo of right eye shows no alterations on posterior pole. (B) Macular OCT of right eye revealed no evidence of cystoid macular oedema or epiretinal membrane. (C) Colour photo of left eye shows media opacity (red arrow), peripapillary subretinal pigmented lesion (blue arrow), and an intraretinal haemorrhage on the superotemporal periphery (green arrow). (D) Left eye OCT revealed posterior shadows (blue arrows) as artefacts from vitreous opacities. No evidence of cystoid macular oedema or epiretinal membrane was detected.

cause of intraocular inflammation.⁶ For our patient, the infection by *Cryptococcus neoformans* was one of the principal diagnoses to consider because of the history of meningeal cryptococcosis. However, this diagnosis was ruled out by the microbiological studies of the vitreous, and, in addition, the patient had received therapy with amphotericin B and was being treated with antifungal prophylaxis. Ocular toxoplasmosis also affects immunosuppressed individuals with CD4 counts below 150 cells/ μ L;⁷ however, this infection was ruled out clinically and with PCR analysis of the vitreous. The most common presentation of tuberculosis in patients with immunosuppression secondary to HIV/AIDS is ocular choroiditis;⁸ however, ophthalmological examination did not disclose ocular lesions typical of tuberculosis.⁹ Progressive outer retinal necrosis is characterised by the presence of confluent necrotic lesions distributed throughout the fundus, with preference for the posterior pole and with poor response to management;¹⁰ however, this was not consistent with the ocular fundus findings and the PCR study of vitreous. Endogenous endophthalmitis,¹¹ caused by bacterial or fungal microorganism, was ruled out in the microbiological study of the vitreous.

TREATMENT

Topical steroids were instituted and integral management was started with the Department of Infectious Diseases, Fundación Oftalmológica de Santander-Clinica Carlos Ardila Lülle, Floridablanca, Colombia. During his hospitalisation, our patient's vision decreased and follow-up oral prednisone was instituted at 1 mg/kg, and the maintenance dose of oral valganciclovir 450 mg daily was changed to a therapeutic dose of 900 mg twice daily.

OUTCOME AND FOLLOW-UP

Follow-up was performed every day to detect deterioration in visual acuity or in vitreous haze. On the fourth day of follow-up, the patient's visual acuity declined to 20/40 and vitreous cells and turbidity increased in his left eye. This prompted the decision to perform a vitrectomy with a vitreous tap and to perform PCR analysis for CMV, herpes simplex virus type 1 (HSV-1), HSV-2 and *Toxoplasma gondii*. Additionally, smears with Gram stain, cultures for Gram-positive and Gram-negative bacteria, and cultures for fungi were ordered.

PCR analyses for CMV, HSV-1, HSV-2 and *T. gondii* were negative. Cultures for other pathogens were also negative. In the light of these new results, and after CMV induction therapy was completed, the patient was discharged with a diagnosis of IRU.

Three weeks after vitrectomy, the patient's BCVA was 20/20 in the right eye and 20/25 in the left eye. He expressed recovery of visual quality. No Tyndall effect or vitreous cells were found. Funduscopy revealed plain white diffuse lesions in the superotemporal periphery, which were unchanged from those seen before.

Our final diagnosis was that the patient suffered the sequelae of a previous CMV infection and retinitis that were never diagnosed, and from IRU.

DISCUSSION

IRU is defined by five main criteria:² (1) AIDS patient, (2) HAART therapy instituted, (3) immune reconstitution noted with CD4+ cell count >100 cells/mL for at least 2 months, (4) previous CMV retinitis and (5) presentation of new intraocular inflammation not explained by medication toxicity or a new

opportunistic infection. The occurrence of IRU varies between 3% and 63.3%.²

Diagnosis of IRU should be suspected on the basis of a HIV-positive patient recently on HAART in whom the immune system has been reactivated as demonstrated by reduction of the viral load and a CD4+ cell count >100 cells/mL.^{1 2 12} The presence of blurred vision, floaters, anterior chamber cells and vitreous turbidity characterise IRU. Cystoid macular oedema, epiretinal membranes, frosted branch angiitis, retinal and optic disc neovascularisation and papillitis, are some of the serious sight-threatening inflammatory signs reported.^{2 12 13} Retinal detachment, chronic iritis and vitritis, anterior and posterior subcapsular cataracts, posterior synechiae and inflammatory deposits on intraocular lenses are long-term complications described in cases with IRU.¹³

In our patient, the granular indolent form of CMV retinitis was very important in the differential diagnosis, along with the presence of plain white lesions in the retinal periphery and sparse haemorrhaging. CMV retinitis is not characterised by anterior chamber or vitreous inflammation because of the immunocompromised state of the AIDS patient normally presenting with it. However, taking into account that patients on HAART are elevating their immune state, it is possible that CMV retinitis could present with the above signs.^{14–17} The presence of inflammation in the anterior chamber and vitreous haze made us suspect IRU. Kupperman and Holland stated that the difference between CMV retinitis and IRU is the amount of inflammation encountered.¹²

Prior to the vitreous tap to confirm diagnosis, we instituted anti-CMV therapy based on the fact that CMV is the most frequent cause of blindness in AIDS patients. Additionally, there was a positive serum and cerebrospinal fluid CMV load in his previous hospitalisation, and, most importantly, active CMV retinitis with IRU has been reported.^{18 19} We also thought that anti-CMV therapy should be started to prevent the reactivation of CMV retinitis when using systemic steroids in patients with IRU.

To prevent IRU, most clinicians elect to not start HAART until after anti-CMV induction therapy, and then continue with suppressor anti-CMV therapy for at least 6 months after CD4+

cell counts are above 100 cell/mm³.^{2 12 20} Even though our patient was already on CMV maintenance therapy, IRU developed. Thus, our case does not support the idea that anti-CMV therapy during immune recovery is protective against IRU. Topical, subtenons, intravitreal and systemic use of corticoids has been described for the treatment of IRU, depending on the severity of the anterior chamber and vitreous inflammation.²

Vision loss in patients with IRU is due to macular pathology, cystoid macular oedema and epiretinal membranes. Accurate observation and examination of the macula by slit lamp or OCT is of primary importance to assess the state of the macula. This would allow a timely surgical approach when necessary.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Always evaluate the immune status of your patient when the diagnosis of HIV positive or AIDS is made. Determine how long the patient has been on highly active antiretroviral therapy (HAART), and, if possible, determine CD4+ count and viral load.
- Before initiating HAART in a patient with CD4+ count under 50 cells/μL, serum analysis for cytomegalovirus (CMV) and other opportunistic infections must be carried out. Prophylaxis treatment to prevent unmasking previously latent infections must be instituted.
- It is important to be familiar with the different presentations of active CMV retinitis and with immune recovery uveitis (IRU) because IRU treatment may worsen CMV retinitis.
- Since IRU treatment is based on steroids, patients should have recovered from CMV before systemic steroid therapy is begun.
- Patients with inactive CMV retinitis should be evaluated on a regular basis. Some have recommended 1–3-month intervals for follow-up evaluations.^{21 22}

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