

Cystoid macular oedema and cytomegalovirus retinitis in patients with HIV disease treated with highly active antiretroviral therapy

Nathalie Cassoux, Livia Lumbroso, Bahram Bodaghi, Lydie Zazoun, Christine Katlama, Phuc LeHoang

Abstract

Background—Although cystoid macular oedema (CMO) is a rare cause of visual loss in AIDS related cytomegalovirus (CMV) retinitis, nine cases are reported of CMO occurring in HIV infected patients with a prior diagnosis of CMV who were receiving highly active antiretroviral therapy (HAART).

Methods—Medical and ophthalmological records of nine AIDS patients with inactive CMV retinitis were retrospectively analysed. Ophthalmic examination data, laboratory findings, and the systemic antiviral treatment were studied. Ophthalmic examination included visual acuity, anterior chamber flare measured with the laser flare cell meter (LCFM), vitreous haze quantification according to the Nussenblatt grading system, and fluorescein angiography.

Results—Nine HIV infected patients, eight men and one woman, mean age 39 years (range 29–53 years) presented with inactive CMV retinitis and CMO. On fluorescein angiography, CMO was present only in eyes (14 eyes) with signs of previous CMV retinitis. CMV retinitis was inactive in all of them. Visual acuity ranged from 20/200 to 20/30. In 10 eyes with CMV retinitis, anterior chamber flare measured with the LCFM ranged from 18.5 to 82 photons/ms (mean 35.42 ph/ms). A significant vitreous inflammation (1.5+) was observed in eight eyes. All patients had been treated with anti-CMV drugs for a mean period of 18 months (range 12–36 months). All nine patients received HAART with a combination of two nucleotide analogue reverse transcriptase inhibitors and one protease inhibitor for a mean period of 14 months (range 9–18 months). The HIV viral load was below detectable levels (<200 copies/ml) in eight patients and low (3215 copies/ml) in one. At the time of CMO, the median CD4+ lymphocyte count was 232 cells $\times 10^6/l$ (range 99–639).

Conclusion—In AIDS patients, the usual absence of intraocular inflammation in eyes affected by CMV retinitis has been tentatively explained by the profound cellular immunodeficiency. In these patients, treated with HAART, CD4+ counts were increased for several months (mean 14 months). In their eyes, CMV retinitis was

associated with significant ocular inflammation and CMO. These findings could be related to the restoration of immune competence after HAART as recently shown. (Br J Ophthalmol 1999;83:47–49)

Cytomegalovirus (CMV) retinitis is the most common retinal infection in patients with AIDS. It usually affects patients with severe immunodeficiency and CD4+ T lymphocyte count below 40 cells $\times 10^6/l$.¹

In AIDS patients, eyes with CMV retinitis have a mild inflammatory reaction in the anterior segment and in the vitreous. Cellular reaction in the vitreous has been reported in the course of chronic CMV retinitis, but is usually insufficient to induce visual loss.¹

Recently, the use of a combination therapy, including protease inhibitors, has profoundly changed the management of HIV infection. The combination of two nucleotide analogues with a protease inhibitor can increase CD4+ cell counts, reduce HIV load, and improve certain opportunistic infections.²

Several months of highly active antiretroviral therapy (HAART) delays the progression of CMV retinitis, despite stopping all anti-CMV treatment, suggesting a certain immune restitution.³ This concept is also suggested by the appearance of a posterior segment inflammation in some patients treated by HAART.⁴

We describe nine AIDS patients treated with HAART with inactive CMV retinitis who developed cystoid macular oedema (CMO) in the course of their disease.

Materials and methods

The records of patients referred to our ophthalmology department presenting with inactive CMV retinitis and visual loss due to CMO were retrospectively reviewed. CMO was confirmed by fluorescein angiography. Ophthalmic examination data, which included visual acuity, slit lamp examination, anterior chamber flare measured with the laser cell flare meter (LCFM, Kowa 1000), funduscopy, vitreous cell quantification according to the Nussenblatt grading system and fluorescein angiography were reviewed. Laboratory investigations (CD4+ lymphocyte counts and HIV-1 load) and the systemic antiviral treatment of the patients were recorded.

Results

The features of our CMV retinitis cases are summarised in Table 1.

Department of
Ophthalmology,
Pitié-Salpêtrière
Hospital, Paris, France
N Cassoux
L Lumbroso
B Bodaghi
L Zazoun
P LeHoang

Department of
Infectious Diseases,
Pitié-Salpêtrière
Hospital, Paris, France
C Katlama

Correspondence to:
Professor P LeHoang,
Service d'Ophtalmologie,
Hôpital Pitié-Salpêtrière,
47–83 boulevard de
l'Hôpital, 75651 Paris Cedex
13, France.

Accepted for publication
29 July 1998

Table 1 Summary of cases

Patient	Age/sex	HAART	Duration of HAART (months)	Baseline CD4+ (cell $\times 10^6/l$)	CD4+ at CMO diagnosis	Anterior chamber inflammation: LCFM (ph/ms)	Ophthalmological findings	Anti-CMV therapy
1	42/M	stavudine lamivudine indinavir	12	5	180	R: 22.6 L: 5.1	IR R CMO Vitritis +	IV then oral GCV
2	29/M	stavudine lamivudine ritonavir	18	4	109	R: 82.0 L: 55.3	IR both eyes CMO both eyes Vitritis ++ both eyes	Oral GCV
3	43/M	stavudine lamivudine saquinavir	18	3	146	R: 39.0 L: 21.2	IR both eyes CMO both eyes Vitritis ++ both eyes	IV GCV
4	32/F	stavudine lamivudine indinavir	9	9	99	R: 3.0 L: 20.1	IR L CMO L Vitritis ++ L	IVT GCV
5	30/M	Zidovudine zalcitabine ritonavir	12	3	639	ND	IR both eyes CMO both eyes	Oral GCV
6	34/M	stavudine lamivudine indinavir	17	4	280	R: 5.3 L: 28.3	IR L CMO L Vitritis ++	IVT GCV
7	48/M	stavudine lamivudine saquinavir	12	20	100	R: 38.0 L: 29.5	IR both eyes CMO both eyes Vitritis ++ both eyes	IV GCV
8	39/M	stavudine lamivudine indinavir	16	5	175	ND	IR both eyes CMO both eyes Vitritis ++ both eyes	IV GCV
9	53/M	stavudine lamivudine indinavir	18	1	144	R: 3.6 L: 18.5	IR L CMO L Vitritis + L	NONE

HAART = highly active antiretroviral therapy; IR = inactive retinitis; ND = not determined; CMO = cystoid macular oedema; IV = intravenous; IVT = intravitreal; GCV = ganciclovir; LCFM = laser cell flare meter; ph/ms = photons per millisecond.

All our patients were infected by HIV-1 virus (mean time 10 years: range 9–14 years). CMV retinitis was diagnosed earlier at a mean time of 18.6 months (range 14–36 months). All patients but one received CMV maintenance therapy with systemic or intravitreal ganciclovir. None was treated with systemic or local cidofovir. For all patients CMV retinitis was inactive at the time of diagnosis of CMO. It was unilateral in four patients and bilateral in five. In the affected eyes, the extent of the retinal area involved by CMV infection varied from less than a quadrant (five eyes) to more than three quadrants (three eyes). The posterior pole (not including the macular area) was affected in only four eyes.

Visual acuity (VA) ranged from 20/200 to 20/30. Five eyes presented with severe VA decrease of less than 20/100, three eyes maintained a VA of 20/50 or better.

When the disease was bilateral, vision was approximately the same in both eyes. The anterior chamber flare measured with the LCFM in seven patients, was significantly higher in 10 eyes with inactive CMV retinitis (range 18.5–82 photons/ms, average 35.42 ph/ms) than in four unaffected eyes (range 3–5.3 ph/ms, average 4.25 ph/ms).

A significant vitreous inflammation (vitreous haze of 1+ or more) was associated with CMO in 11 eyes (data were not available for two eyes). The five eyes with no CMV retinitis or CMO did not present any vitreous inflammation.

On fluorescein angiography, CMO was present in all eyes with previous signs of CMV involvement. It was absent from the eyes without signs of CMV involvement. Late staining of the optic disc head was present in two eyes associated with the CMO.

All patients received HAART with a combination of two antiretrovirals and one protease inhibitor for a median time of 13.5 months

(range 9–18 months). Before HAART treatment, the median CD4+ lymphocyte count was 14 (range 1–40) and the median HIV-1 viral load was 217 526 copies/ml.

After HAART, the HIV-1 viral load was undetectable in eight patients and low (3215 copies/ml) in one patient. For all patients, CD4+ lymphocyte counts were between 99–639 cells $\times 10^6/l$ (median 208)

All patients were treated with oral acetazolamide and topical steroids for CMO with no significant improvement. Three patients were treated with periocular long acting corticosteroids with encouraging results.

Discussion

CMO is not a classic cause of visual loss in the natural history of AIDS related CMV retinitis. The most common vision threatening complications of CMV retinitis included macular or optic nerve CMV involvement and retinal detachment.⁵ Recently, CMO caused by CMV retinitis has been reported in three patients without HIV infection but treated with immunosuppressive therapy. In these cases CD4+ cell counts were higher than those usually encountered in AIDS related CMV retinitis.⁵

Weinberg *et al* reported a case of CMO associated with inactive CMV retinitis in a patient with AIDS.⁶ In this case, CMO was attributed to chronic intraocular inflammation. Another case of macular oedema associated with AIDS related CMV retinitis was described by Palestine *et al* and attributed to a retinal microangiopathy.⁷ Karavellas *et al* recently described the association of inactive CMV retinitis with vitritis in patients treated by HAART. CMO was presented as an inflammatory complication induced by a recovered immunity.⁴

The results of this study suggest that the natural history of CMV retinitis may be profoundly changed by the introduction of

HAART into the treatment of AIDS patients. Concerning CMV retinitis progression, it usually tended to progress despite maintenance therapy and the median time to relapse with systemic or intravitreal ganciclovir was about 73 days.¹ In our nine patients, CMV retinitis remained inactive for more than 6 months under maintenance therapy and HAART. For one patient, CMV retinitis remained quiescent despite cessation anti-CMV treatment. This beneficial effect of HAART seems to be delayed and CMV retinitis reactivation can appear several weeks after initialisation of the therapy.^{3,8}

On the other hand, intraocular inflammation and CMO were unusual in AIDS patients before the use of HAART. CMO has been recently described in three patients affected by CMV retinitis but without HIV infection. The development of CMO in these patients with immunodeficiency related to immunosuppressive therapy is attributed to more pronounced intraocular inflammation observed in these eyes.⁵

The recent paper by Karavellas *et al* presents five patients with vitritis associated with HAART. CMO was in some of the patients a complication of ocular inflammation. In our series, all patients had an increase in CD4+ cell counts and had relatively restored immune competence.⁴

Indeed, HAART combining two nucleotide analogues with a protease inhibitor, may suppress HIV replication, increase CD4+ cell counts, and improve certain opportunistic infections.³

Recently, Autran *et al* have reported positive effects of HAART on CD4+ cell functions.² Therefore, our hypothesis to explain the increased intraocular inflammatory reaction in our patients and CMO appearance is the presence of an immune reaction to CMV antigens after restoration of the CD4+ T cell counts. CMO is a classic complication of chronic intraocular inflammation in immunocompetent patients presenting with an uveitis. In our AIDS patients treated with HAART unusual increased intraocular inflammation could explain the presence of CMO.

However, intraocular inflammation is a side effect of certain therapies such as cidofovir.⁹ A case of possible zidovudine induced CMO and

a case of indinavir induced uveitis have been described.^{10,11} A possible side effect due to an antiprotease or to a combination of several antiretroviral drugs cannot be excluded.

Nevertheless, while in our hospital approximately 700 patients have received protease inhibitors with half of them being severely immunosuppressed and regularly followed ophthalmologically, we have so far not observed such CMO in these patients in the absence of CMV retinitis.

Conclusion

Intraocular inflammation and CMO can be a complication of CMV retinitis in AIDS patients receiving HAART. These findings seem to be associated with the restoration of a certain immune competence.

Prospective natural history studies are needed to identify risk factors for developing CMO in patients with AIDS related CMV retinitis, in order to better understand the pathophysiology of this new complication that potentially affects visual acuity.

- Holland GN, Tufail A, Jordan MC. Cytomegalovirus diseases. In: Holland GN, Pepose JS, Wilhelmus KR, eds. *Ocular infection and immunity*. S Louis: Mosby, 1996:1088.
- Autran B, Carcelain G, Li S, *et al*. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science* 1997;277:112-16.
- Reed JB, Schwab IR, Gordon J, *et al*. Regression of cytomegalovirus retinitis associated with protease-inhibitor treatment in patients with AIDS. *Am J Ophthalmol* 1997;124:199-205.
- Karavellas MP, Lowder CY, Macdonald JC, *et al*. Immune recovery vitritis associated with inactive cytomegalovirus retinitis. *Arch Ophthalmol* 1998;116:169-75.
- Maguire AM, Nichols CW, Crooks GW. Visual loss in cytomegalovirus retinitis caused by cystoid macular edema in patients without the acquired immune deficiency syndrome. *Ophthalmology* 1996;103:601-5.
- Weinberg DV, Moorhy RS. Cystoid macular edema due to cytomegalovirus retinitis in a patient with acquired immune deficiency syndrome. *Retina* 1996;16:343-44.
- Palestine AG, Frisberg B. Macular edema in acquired immunodeficiency syndrome-related microvasculopathy. *Am J Ophthalmol* 1991;111:770-1.
- Jacobson MA, Zegans M, Pavan PR, *et al*. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet* 1997;349:1443-5.
- Kuppermann BD. Therapeutic options for resistant cytomegalovirus retinitis. *J Acq Imm Defic Syndr Hum Retrovirol* 1997;14(Suppl 1):13-21.
- Lalonde RG, Deschênes JG, Seamone C. Zidovudine-induced macular edema. *Ann Intern Med* 1991;114:297-8.
- Gariano RF, Cooney EL. Uveitis following administration of the protease inhibitor indinavir to a patient with AIDS. *Clin Infect Dis* 1997;24:529.