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Cystoid macular edema in patients with acquired immune deficiency syndrome and cytomegalovirus retinitis

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PURPOSE. *To describe cystoid macular edema in patients with acquired immune deficiency syndrome treated with highly active anti-retroviral therapy, who had or had not already had cytomegalovirus retinitis.*
MATERIALS AND METHODS. *Case report.*
RESULTS. *Five acquired immune deficiency syndrome (AIDS) patients, successfully treated with highly active anti-retroviral therapy, were studied. Two had inactive cytomegalovirus retinitis and cystoid macular edema in both eyes. Two had inactive cytomegalovirus retinitis in both eyes and cystoid macular edema in one eye. One patient had inactive cytomegalovirus retinitis in one eye and cystoid macular edema in both eyes.*
CONCLUSIONS. *Cystoid macular edema may occur in AIDS patients treated with highly active anti-retroviral therapy even in cases without previous retinitis. (Eur J Ophthalmol 2000; 10: 233-8)*

KEY WORDS. *Acquired immunodeficiency syndrome, Cystoid macular edema, Cytomegalovirus, Retinitis*

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INTRODUCTION

Cytomegalovirus retinitis is a common ocular infection in patients with acquired immune deficiency syndrome (AIDS). When the infection is active, macular exudation, lipid star and retinal striae may be present, but they are rare (2). Cystoid macular edema is also a recognized factor leading to visual acuity loss in AIDS, even in patients without active cytomegalovirus retinitis (3).

The objective of this study was to evaluate AIDS patients, with or without inactive cytomegalovirus retinitis, who developed cystoid macular edema.

PATIENTS AND METHODS

We evaluated five patients with AIDS (CDC criteria) and cytomegalovirus retinitis who had a clinical diagnosis of cystoid macular edema confirmed by dynamic fluorescein angiography. There were four men and one woman, age range 29-43 years, mean age 36.2 years. The ocular examination was done every month during follow-up and comprised of measurement of best-corrected visual acuity, binocular indirect ophthalmoscopy and contact lens biomicroscopy. Stereoscopic pairs of color pictures of the posterior pole and wide-angle (50 degrees) fundus photographs of the lesions were obtained at each visit in order to document retinal changes. Fluorescein angiography was done every three months.

Cytomegalovirus retinitis was unilateral in one patient and bilateral in the other four. None of the patients had syphilis. The lesions were classified according to Holland et al (4) by measuring the distance from the most posterior margin to the fovea with the IMAGEnet® Digital System (Topcon - USA): *Zone I*, between 3000 microns from the fovea and 1500 microns from the optic disc; *Zone II*, between zone I and

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the anterior border of the vortex veins; and *Zone III*, between zone II and the ora serrata. The diagnosis of cystoid macular edema was based on the finding of a thickened macula at retinal contact lens biomicroscopy and perifoveal capillary leakage, usually with a cystic stellate or petaloid pattern in fluorescein angiography.

RESULTS

Case 1. A 37-year-old white woman with the diagnosis of AIDS for five years was treated with indinavir, lamivudine and stavudine for five months and intravenous gancyclovir for 40 days. Before that the CD4 count was 59 cells/mm^3. The best-corrected visual acuity was 20/40 in the right eye and 20/20 in the left eye. The right eye showed a healed superotemporal cytomegalovirus retinitis with the most posterior margin of the affected area 2.9 mm from the fovea (Zone I). The left eye showed no signs of cytomegalovirus retinitis. There were no signs of intraocular inflammation, and cystoid macular edema was present in both eyes (Fig. 1). Six months later the CD4 count was 197 cells/ mm^3. Visual acuity and the clinical findings were the same.

Case 2. A 43-year-old white man with the diagnosis of AIDS for three years and cytomegalovirus retinitis for two years had been treated with indinavir, lamiduvine and stavudine for 8 months and intravenous gancyclovir for 16 months. Before the treatment the CD4 count was 50 cells/mm^3. At his first examination best-corrected visual acuity was 20/25 OU.

Ophthalmoscopy revealed healed cytomegalovirus retinitis in the supero and infero-nasal areas of the right eye and in the inferotemporal area of the left eye.

The lesion had its most posterior margin 4.2 mm from the fovea (Zone II) in the right eye and 2.0 mm from the fovea (Zone I) in the left eye. There was no intraocular inflammation but both eyes had cystoid macular edema (Fig. 2).

Case 3. A 29-year-old white man with the diagnosis of AIDS for four years and cytomegalovirus retinitis in both eyes, had been treated with intravenous gancyclovir for 12 months and foscarnet for 10 months. At the time of diagnosis of the cytomegalovirus retinitis the CD4 count was 50 cells/ mm^3. The right eye had received an intravitreous gancyclovir implant two years before and had developed a retinal detachment eight months later, which was successfully treated. The best corrected-visual acuity was 20/200 in the right eye and 20/25 in the left eye. Inactive cytomegalovirus retinitis was present in both eyes, with no intraocular inflammation. The most posterior margin of the lesion was 1.4 mm from the fovea (Zone I) in the right eye and 3.3 mm from the fovea (Zone II) in the left eye. Cystoid macular edema was observed in the left eye (Fig. 3).

Case 4. A 29-year-old white man with the diagnosis of AIDS for three years had been receiving intravenous gancyclovir for two years. The CD4 count was 27 cells/mm^3. The right eye had no light perception (NLP) and the best-corrected visual acuity in the left eye was 20/25. The right eye presented optic atrophy and healed cytomegalovirus retinitis with the posterior margin of the lesion 3.1 mm from the fovea (Zone II). The left eye presented inactive cytomegalovirus retinitis with the most posterior margin of the lesion 5.3 mm from the fovea (Zone II). There was no active intraocular inflammation in either eye but cystoid macular edema was present in the left eye (Fig. 4).

Case 5. A 43-year-old white man with the diagnosis of AIDS for one year presented vision loss in both eyes and a CD4 count of 50 cells/mm^3. Clinical treatment included gancyclovir, zidovudine, indinavir, lamiduvine and stavudine. After six months the best-correct visual acuity was 20/60 in both eyes and lesions were clinically inactive. The posterior margin of the lesion was 2 mm from the fovea (Zone I) in the right eye and 1.2 mm from the fovea (Zone II) in the left. There was no active intraocular inflammation but fundus examination disclosed bilateral cystoid macular edema. Both eyes presented typical leakage in stellate or petaloid pockets on fluorescein angiography.

DISCUSSION

Healed long-standing cytomegalovirus (CMV) retinitis was identified in nine eyes of five AIDS patients. Cystoid macular edema was diagnosed in seven eyes with inactive CMV retinitis (Tab. I), and in one eye without CMV retinitis. There is a possibility that this case had some subclinical level of CMV retinitis or that CMV was present in the retina with no clinical sign of in-

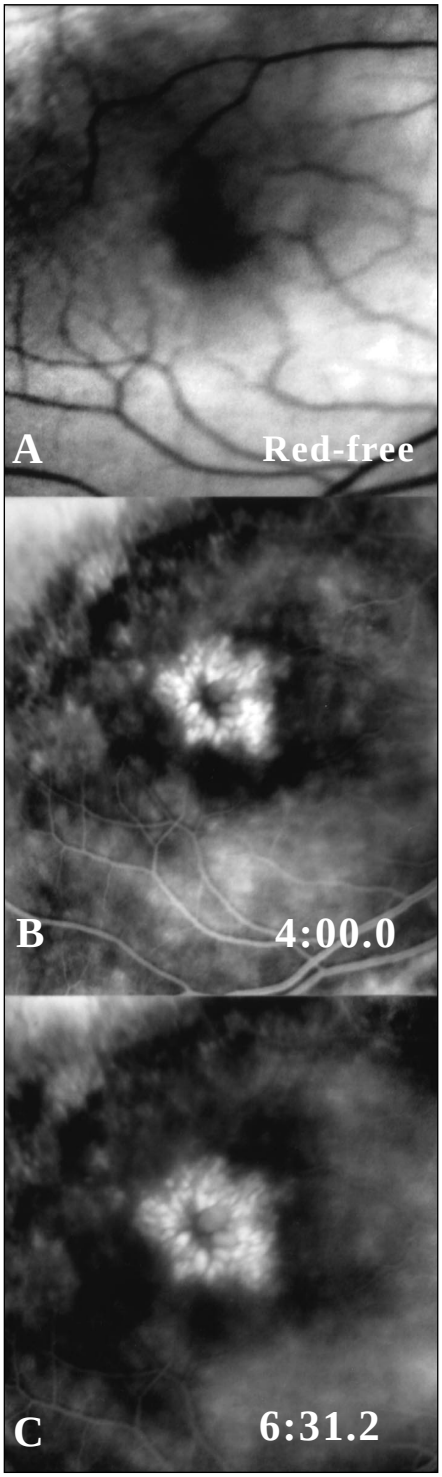

Fig. 1 - A) *Red-free fundus picture of the right eye.*
B) *Early phase of a fluorescein angiogram showing leakage in stellate pockets typical of cystoid macular edema in the center of the macula. In the superotemporal area there is a hyperfluorescent lesion corresponding to the healed cytomegalovirus retinitis.*
C) *Late phase of the same examination.*

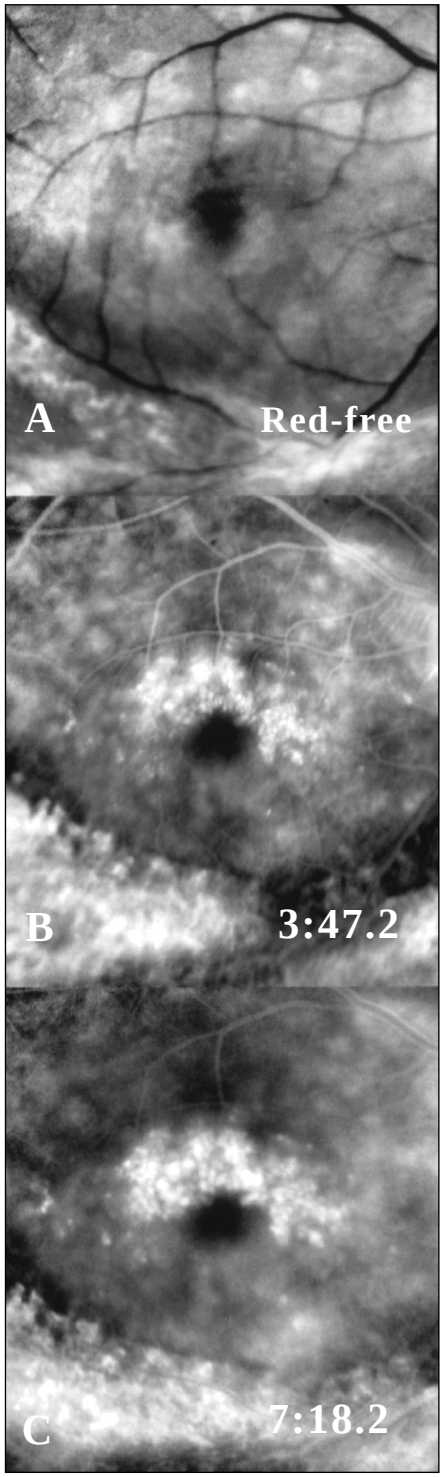

Fig. 2 - A) *Red-free fundus picture of the right eye.*
B) *Early phase of a fluorescein angiogram showing cystoid macular edema, predominantly superior, and infero-temporal healed cytomegalovirus retinitis.*
C) *Late phase of the same examination.*

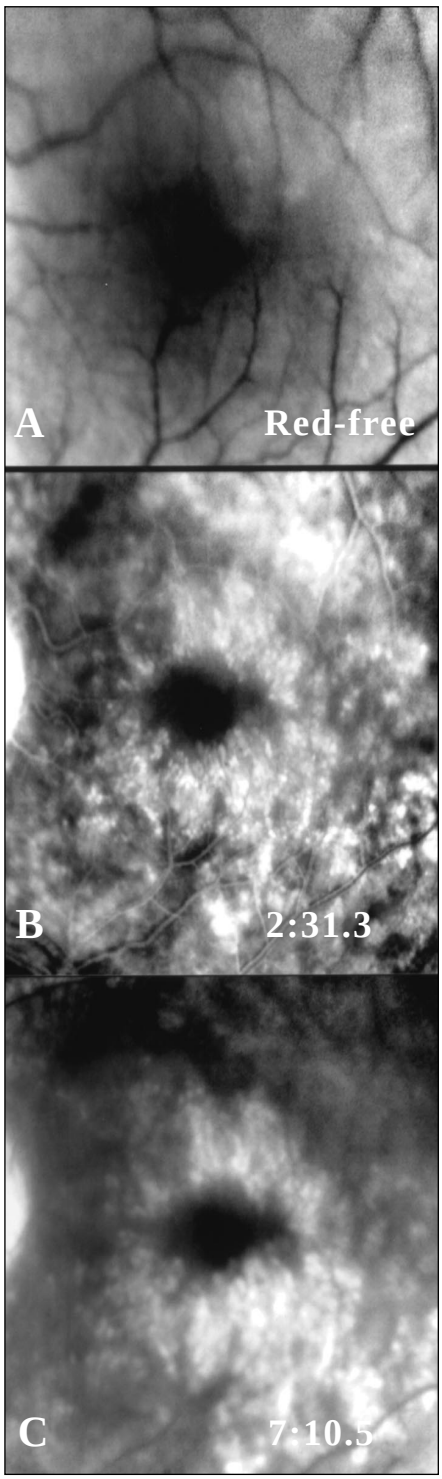

Fig. 3 - A) *Red-free fundus picture of the left eye.*
B) - *Early phase of a fluorescein angiogram showing cystoid macular edema, with healed cytomegalovirus retinitis.*
C) - *Late phase of the same examination.*

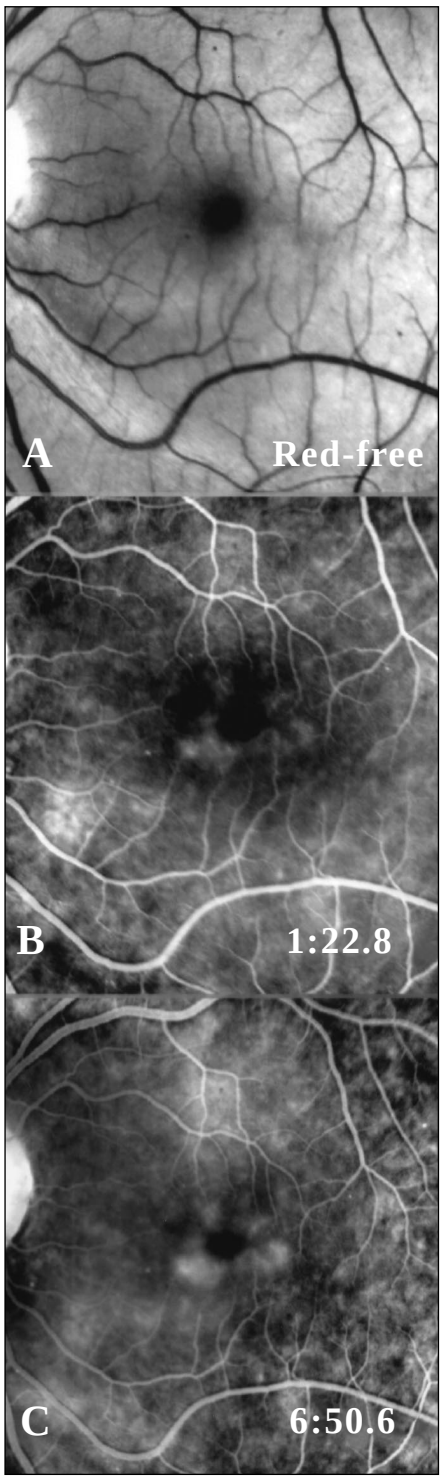

Fig. 4 - A) *Red-free fundus picture of the left eye.*
B) - *Early phase of a fluorescein angiogram showing cystoid macular edema and a hyperfluorescent area in the papillo-macular bundle.*
C) - *Late phase of the same examination.*

TABLE I – MAIN DETAILS OF PATIENTS WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME, CYTOMEGALOVIRUS RETINITIS AND CYSTOID MACULAR EDEMA

Case	Sex race age	CD4 Cells/mm³ before Haart	Right Eye					Left Eye				
			Best VA	CMV retinitis	Distance to the fovea	Zone	CME retinitis	Best VA	CMV retinitis	Distance to the fovea	Zone	CME
1	F/W/37	59	20/40	Inactive	2.9 mm	I	+	20/20	-	-	-	+
2	M/W/43	50	20/25	Inactive	4.2 mm	II	+	20/25	Inactive	2.0 mm	I	+
3	M/W/29	50	20/200	Inactive	3.3 mm	II	-	20/30	Inactive	1.4 mm	I	+
4	M/W/29	27	NLP	Inactive	3.1 mm	II	-	20/25	Inactive	5.3 mm	II	+
5	M/W/43	50	20/60	Inactive	2.0 mm	I	+	20/60	Inactive	1.2 mm	I	+

W - White
F - Female
M - Male
VA - Visual acuity
NLP - No light perception
HAART - Highly active anti-retro-virus therapy

fection. The retinitis had been active several weeks to months before the diagnosis of cystoid macular edema, except in one eye which was otherwise normal. The eight eyes with cystoid macular edema had best-corrected visual acuity ranging from 20/20 to 20/60. Two of these presented with worse visual acuity (20/200 and NLP) due to retinal detachment and optic atrophy associated with the healed CMV retinitis.

Fluorescein angiography were done in all cases to confirm the clinical biomicroscopic diagnosis and to study the retino-choroidal circulation and the microangiopathy. The fluorescein angiogram confirmed cystoid macular edema and showed that it was never associated with microangiopathy and/or subclinical vasculitis.

None of the eyes with cystoid macular edema presented active inflammation. It was not possible to know whether this edema was also present during the active disease and remained despite the successful treatment or whether it appeared *de novo* after the disease abated.

Holland et al (7) reported a case of serous macular detachment in a patient with active CMV infection involving the optic nerve, which responded to therapy. Gangan et al (2) found macular exudation related to the presence of active, zone I CMV retinitis, which resolved after treatment. Karavellas et al (8) described the development of intraocular inflammation and macular edema in patients after treatment with effective drugs against HIV, with an increase in CD4 count and reduction in the HIV load. Our patients presented cystoid macular edema with healed CMV with no signs of active intraocular inflammation; this finding has not been reported before.

The distance from the posterior margin of the lesions to the fovea in the eyes with cystoid macular edema ranged from 1.2 mm to 5.3 mm. Five of the eyes with healed CMV retinitis and cystoid macular edema had lesions in Zone I and two had lesions in Zone II. No relationship was found between the distance from the border of the inactive CMV retinitis and the macula.

Ocular inflammation has been described in patients without signs of previous CMV retinitis after receiving systemic therapy such as zidovudine (9), rifabutin (10,11) or cidofovir (12), but in all those cases there was inflammation.

One of the eyes presented cystoid macular edema but no CMV retinitis or any predisposing condition.

Highly active antiretrovirus therapy could possibly play a role in the occurrence of cystoid macular edema by increasing the CD4 cell count and the immune response. Other possible mechanisms related to the development of cystoid macular edema may be associated with insidious inflammation, cytokine interactions, new drugs, combined therapy. Alternatively,

it may be a long-term manifestation in the natural course of retinal microangiopathy with blood retinal barrier breakdown in HIV-infected patients (13).

These cases present evidence that cystoid macular edema does not have necessarily to be related to clinically active inflammation in AIDS patients successfully treated with anti-HIV and anti-CMV drugs.

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