DRUG-INDUCED UVEITIS IN AIDS PATIENTS: TWO CASE REPORTS

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ABSTRACT

Patients with acquired immunodeficiency syndrome (AIDS) can develop severe uveitis. Although infectious and autoimmune causes must always be considered, drug induced uveitis is also an important etiology. Herein, we present two case reports illustrating the classical presentation of rifabutin and cidofovir induced uveitis.

The first case was a 33 year old woman with AIDS treated with anti-protease and anti-tuberculosis drugs (including rifabutin). She presented with a red painful right eye. There was a strong anterior segment inflammation with fibrinous exudates and a dense vitritis. Rifabutin was stopped and topical steroids and mydriatics were given. Intraocular inflammation and symptoms rapidly resolved.

The second patient was a 36 year old woman who presented with a painful decrease of vision in her left eye. She was followed for bilateral CMV retinitis in the setting of AIDS and had recently received 2 systemic injections of cidofovir. Anterior segment inflammation with posterior synechiae in both eyes and folds of Descemet membrane in the left eye were noted. Intraocular pressure was 0 mmHg in the left eye and 10 mmHg in the right eye. Fundus examination disclosed CMV retinitis scars in the right eye and choroidal folds in the macula of the left eye. Cidofovir was discontinued and topical steroids and mydriatics started. Progressively the inflammation decreased and the intraocular pressure returned to normal levels.

In conclusion, rifabutin and cidofovir are classical examples of drug induced uveitis with distinct characteristic clinical presentation. Recognition of those entities in AIDS patients can avoid useless and potentially invasive interventions in those fragile people.

KEY WORDS

AIDS, cidofovir, complication, drug-induced uveitis, rifabutin, tuberculosis

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INTRODUCTION

Patients with acquired immunodeficiency syndrome (AIDS) are a specific group of patients because of their immunodeficiency, complicated medical history and very intensive treatment. While being on highly active anti-retroviral therapy (HAART) accompanied with prophylactic and therapeutical anti-opportunistic drugs they can present in emergency with severe uveitis of various origins.

Like in immunocompetent patients, infectious uveitis is frequently found and common pathogens (herpes, toxoplasmosis, syphilis, tuberculosis) can cause uveitis in AIDS patients (1). However infectious uveitis might also be related to opportunistic infections such as cytomegalovirus (CMV) retinitis and cryptococcal or *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) choroiditis.

AIDS patients can as well have non infectious uveitis and autoimmune diseases must always be considered in the differential diagnosis. Furthermore, patients well responding to HAART therapy and with history of CMV retinitis can develop a specific immune recovery uveitis (IRU) which occurs in 18 to 63% of patients (2).

Moreover, uveitis in AIDS patients can also be the result of a drug reaction (3, 4). Drug induced uveitis is most frequently associated with rifabutin and cidofovir. The former is used both in prophylaxis and in antimycobacterial therapy and the latter in CMV and other herpesviruses infections.

Depending on the etiology of uveitis the treatment will be different (1, 5). Therefore it is crucial to make the right diagnosis based on complete medical history and detailed ocular examination. In this paper we present two case reports illustrating the characteristic presentation of drug induced uveitis in AIDS patients.

CASE REPORTS

Case 1

A 33 year old woman presented with a 2 days history of a red painful right eye. Her medical history was significant for AIDS and active pulmonary tuberculosis. She was treated with 4 anti-retroviral drugs: abacavir 600 mg and lamivudine 300mg (Kivexa®), lopinavir 800 mg and ritonavir 200 mg (Kaletra®) per day, and 3 antituberculous drugs: pyrazinamide 1000 mg (Tebrazid®), isoniazide 300 mg (Nicotibine®) and rifabutin 150 mg (Mycobutin®).

Best-corrected right visual acuity was reduced to 1/10 in the right eye. Slit lamp examination revealed a strong anterior segment inflammation (Tyndall ++) with fibrinous exudates. The fundus was barely visible because of vitritis (Figure 1a). B-scan ultrasonography of the globe excluded retinal detachment. A presumptive diagnosis of rifabutin uveitis was made. Rifabutin was replaced by moxifloxacine (Avelox®) and the patient was treated with topical steroids and mydriatics. Intraocular inflammation and symptoms rapidly resolved. After 2 weeks, her vision returned to 9/10, the anterior segment was normal and the vitreous was clear (Figure 1b).

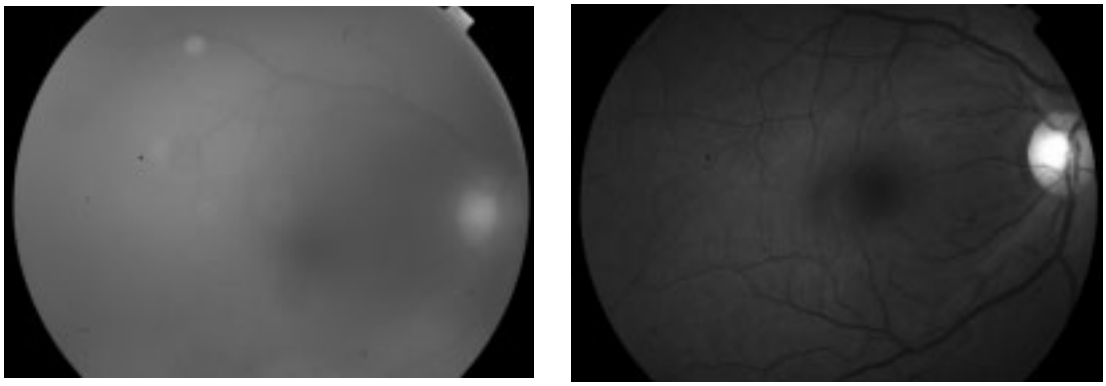

Fig 1. Posterior pole of the right eye in redfree photograph: **a**, Posterior pole barely visible because of vitritis in patient with rifabutin induced uveitis, **b**, posterior pole clearly visible 2 weeks after rifabutin discontinuation.

Case 2

A 36 year old woman presented in emergency for a painful decrease of vision in her left eye. She was followed in our department for bilateral CMV retinitis in the setting of AIDS. She was treated with HAART (but was poorly compliant) and had received 2 systemic injections of cidofovir and several intraocular injections of foscarnet and ganciclovir. She was also treated with ethambutol (Myambutol®), isoniazide (Nicotibine®), pyrazinamide (Tebrazid®) and rifabutin (Mycobutin®) for pulmonary active tuberculosis. The current CD4 count was 10 cells/μl. Best-corrected vision for the left eye was reduced to counting fingers and for the right eye to 8.5/10. Slit lamp biomicroscopy revealed anterior segment inflammation (Tyndall +) with posterior synechiae in both eyes and folds of Descemet membrane in the left eye (Figure 2). Intraocular pressure was 0 mmHg in the left eye and 10 mmHg in the right eye. Fundus examination disclosed CMV retinitis scars in the right eye. The fundus in the left eye fundus was barely visible but disclosed choroidal folds in the macula. A diagnosis of cidofovir induced hypotensive uveitis was made and cidofovir was discontinued. Ganciclovir with topical steroids and mydriatics were started. The rest of the treatment was not changed. After 2 weeks the IOP in the left eye had increased to 5 mmHg and no folds of Descemet were observed. Best-corrected vision for the left eye was 5/10 after 3 weeks. Intraocular inflammation resolved slowly and was absent after 7 weeks of follow-up. However, synechiae persisted over 360° in the left eye.

DISCUSSION

Drug induced uveitis is an uncommon adverse reaction to medication that accounts for less than 1% of uveitis (4). According to the WHO Causality Assessment Guide, biphosphonates are the only drugs certainly associated with uveitis while cidofovir, rifabutin, topical metipranolol, and sulfonamides are considered as 'probable' causes of uveitis (4). Many other

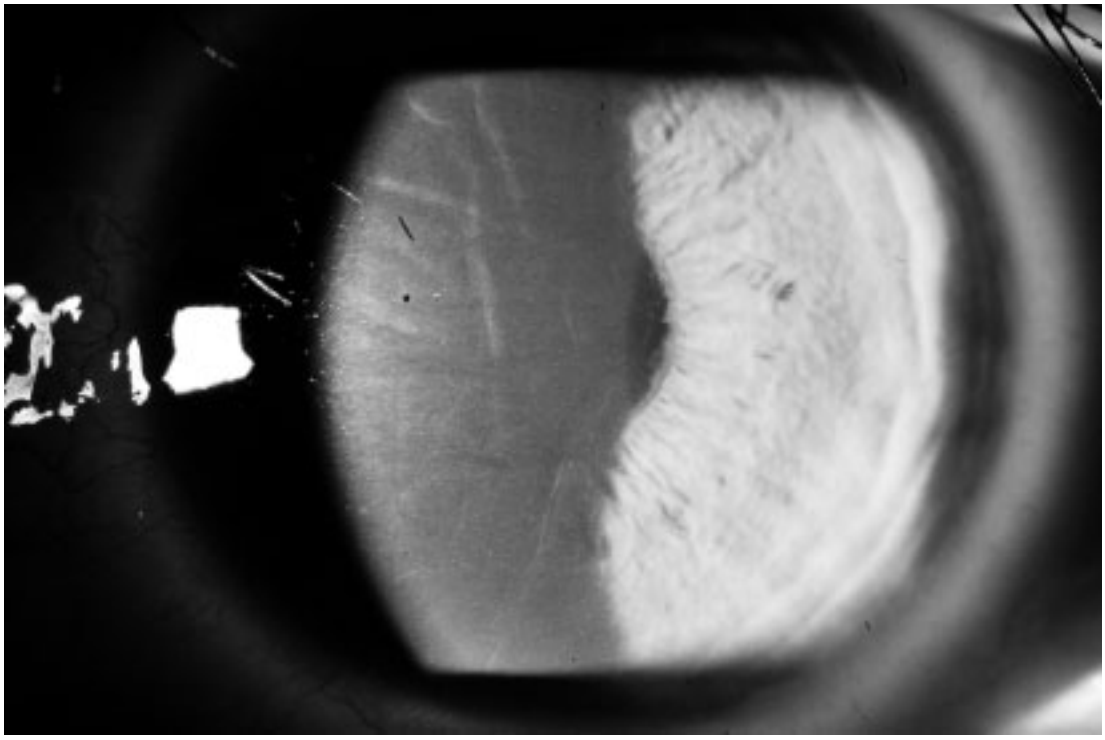

Fig 2. Folds of Descemet membrane in a patient with cidofovir induced hypotensive uveitis.

drugs have also been associated sporadically with the development of uveitis, but those associations should be considered with caution (3).

In this paper, we present two case reports that illustrate the clinical presentation of rifabutin and cidofovir induced uveitis in AIDS patients. Rifabutin is a semi-synthetic derivative of rifamycin and is widely used in the treatment and prophylaxis of *Mycobacterium avium* complex (MAC) infection. After introduction of rifabutin it became more popular than rifamycin in first-line treatment of tuberculosis although recent analysis did not prove any difference in efficacy between rifabutin and rifampicin (6). However, rifabutin is probably better for HIV positive patients due to its lack of interactions with antiretroviral drugs, mainly protease inhibitors (6). Nowadays, the doses of rifabutin used in treatment are lower than 20 years ago and range from 150 mg to 600 mg. Rifabutin-induced uveitis is also more rarely observed as its occurrence is dose dependent. Rifabutin-induced uveitis incidence is <0.01% for 300 mg/d rifabutin treatment and has a significantly higher incidence (~0.8%) for dosages of > 450 mg/d (in combination with clarithromycin) (7). It has also been observed that coadministration with fluconazole, clarithromycin or some protease inhibitors (indinavir, nelfinavir, or amprenavir) increase serum levels of rifabutin and therefore can increase the risk of rifabutin-induced uveitis (8, 9).
Cidofovir is a nucleotide analog that inhibits viral DNA polymerase. Cidofovir has been proven to delay progression of CMV retinitis (10). High doses (40-100 μg) initially injected intravitreally were invariably associated with sight threatening uveitis (11). Intravitreal injections of lower doses (20 μg) result in fewer (14-32%) cases and less severe uveitis (12). Uveitis with very similar clinical characteristics are also observed frequently (26-59% of patients) following intravenous treatment (13, 14). Patients treated with antiproteases may have a greater risk to develop intraocular inflammation (13). On the contrary, concomitant use of probenicid seems to decrease uveitis frequency (15).

Rifabutin and cidofovir uveitis have a very distinct clinical presentation. Rifabutin induced uveitis is typically - as presented in patient 1 - unilateral, non granulomatous with a mild to moderate cellular reaction of the anterior segment and the vitreous. In some cases, hypopyon and severe vitritis with snowballs opacities can be present (16). Retinal vasculitis and cystoïd macular oedema have also been described (17, 18). Cidofovir uveitis might be uni- or bilateral and is classically anterior with posterior synechias. Low intraocular pressure, which we observed in patient 2, is characteristic and can lead to sever loss of vision (19, 20). The treatment of both rifabutin and cidofovir uveitis is based on drug withdrawal, and topical steroids/mydriatics. However, in mild cases of cidofovir induced uveitis, the drug might be continued and certain authors advocate stopping the drug only in case of hypotony development.

In conclusion, rifabutin and cidofovir are classical examples of drug induced uveitis with distinct characteristic clinical presentation. Recognition of those entities in AIDS patients can avoid useless and potentially invasive interventions.

REFERENCES

(1) Cunningham ET Jr. – Uveitis in HIV positive patients. Br J Ophthalmol 2000; 84: 233-237.
(2) Kestelyn PG, Cunningham ET Jr. – HIV/AIDS and blindness. Bull World Health Organ. 2001; 79: 208-213.
(3) Moorthy RS, Valluri S, Jampol LM. – Drug-induced uveitis. Surv Ophthalmol 1998; 42: 557-70.
(4) Fraunfelder FW, Rosenbaum JT. – Drug-induced uveitis. Incidence, prevention and treatment. Drug Saf 1997;17: 197-207.
(5) Cunningham ET Jr, Margolis TP. – Ocular manifestations of HIV infection. N Engl J Med 1998; 339: 236-244.
(6) Davies G, Cerri S, Richeldi L. – Rifabutin for treating pulmonary tuberculosis. Cochrane Database Syst Rev 2007; 17: CD005159.
(7) Nichols CW. – Mycobacterium avium complex infection, rifabutin, and uveitis- -is there a connection? Clin Infect Dis 1996; 22 Suppl 1:S43-7.
(8) Piscitelli SC, Gallicano KD. – Interactions among drugs for HIV and opportunistic infections. 2001, N Engl J Med 2001; 344: 984-96.
(9) Ebraert H, Salu P. – Toxic uveitis caused by pharmacodynamic interactions of Rifabutin and

protease inhibitors: a case report. Bull Soc Belge Ophtalmol 2007; 303: 57-60.
(10) Lalezari JP et al. – Intravenous cidofovir for peripheral cytomegalovirus retinitis in patients with AIDS. A randomized, controlled trial. Ann Intern Med 1997; 126: 257-63.
(11) Kirsh LS et al. – Phase I/II study of intravitreal cidofovir for the treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 1995; 119: 466-76.
(12) Taskintuna I et al. – Adverse events and autopsy findings after intravitreous cidofovir (HPMPC) therapy in patients with acquired immune deficiency syndrome (AIDS). Ophthalmology. 1997; 104: 1827-36.
(13) Davis JL, Taskintuna I, Freeman WR, Weinberg DV, Feuer WJ, Leonard RE. – Iritis and hypotony after treatment with intravenous cidofovir for cytomegalovirus retinitis. Arch Ophthalmol 1997; 115: 733-7.
(14) Ambati J, Wynne KB, Angerame MC, Robinson MR. – Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. Br J Ophthalmol. 1999; 83: 1153-8.
(15) Chavez-de la Paz E et al. – Anterior nongranulomatous uveitis after intravitreal HPMPC (cidofovir) for the treatment of cytomegalovirus retinitis. Analysis and prevention. Ophthalmology. 1997; 104: 539-44.
(16) Chaknis MJ, Brooks SE, Mitchell KT, Marcus DM. – Inflammatory opacities of the vitreous in rifabutin-associated uveitis. Am J Ophthalmol 1996;122: 580-2.
(17) Skolik S, Willermain F, Caspers LE. – Rifabutin-associated panuveitis with retinal vasculitis in pulmonary tuberculosis. Ocul Immunol Inflamm 2005; 13: 483-5.
(18) Vaudaux JD, Guex-Crosier Y. – Rifabutin-induced cystoid macular oedema. J Antimicrob Chemother 2002; 49: 421-2.
(19) Cochereau I et al. – Uveitis in patients treated with intravenous cidofovir. Ocul Immunol Inflamm 1999; 7: 223-9.
(20) Bainbridge JW, Raina J, Shah SM, Ainsworth J, Pinching AJ. – Ocular complications of intravenous cidofovir for cytomegalovirus retinitis in patients with AIDS. Eye (Lond) 1999;13: 353-6.

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