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## Clinical Case Report

### Transient anterior corneal deposits in a human immunodeficiency virus-positive patient

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#### ABSTRACT

**Purpose:** To report findings of pigmented anterior corneal deposits in a human immunodeficiency virus (HIV)-positive patient.

**Methods:** Case report. A 49-year old HIV-positive patient was examined following the appearance of pigmented corneal deposits. Slit-lamp biomicroscopy, fundus photography, and laser-scanning in-vivo confocal microscopy were performed to visually document the ocular condition.

**Results:** The patient had a history of mycobacterium avium infection and was suspected to have recovery uveitis from a cytomegalovirus infection. Small, rounded, light brown-coloured deposits were distributed across the anterior cornea from limbus to limbus, bilaterally. In-vivo confocal microscopy revealed the deposits to be confined to the basal epithelium and Bowman's layer, while the posterior stroma, Descemet's membrane, and the endothelium appeared normal. Systemic steroid treatment was administered and two weeks later, the deposits had vanished on slit lamp examination, while remnants were observed at the microscopic level.

**Conclusions:** The deposits were unusual for their anterior corneal location and pan-corneal distribution. The response to systemic steroid treatment remains unexplained and illustrates

the complexity of the underlying conditions, their treatment, and the associated pathways of ocular manifestation.

Key Words: cytomegalovirus, HIV, mycobacterium avium, corneal deposit, Bowman's layer

## Introduction

In patients with human immunodeficiency virus (HIV), an immunocompromised state is accompanied by an increased susceptibility to opportunistic infections such as cytomegalovirus (CMV) and mycobacterium avium complex (MAC). Corneal involvement in such cases is not uncommon. A number of reports have documented the presence of corneal deposits in HIV patients with CMV retinitis<sup>1-3</sup> or in patients with systemic CMV infection.<sup>3-5</sup> The deposits in these cases have been variably-pigmented (ranging from white to yellow and brown), were located predominantly in the peripheral cornea,<sup>4</sup> and have been invariably confined to the level of Descemet's membrane<sup>4</sup> or corneal endothelium,<sup>1</sup> with the exception of peripheral stromal involvement in one case.<sup>2</sup> Rare epithelial and stromal manifestations of CMV infection have been reported,<sup>5,6</sup> with patients presenting a range of symptoms and exhibiting corneal findings of stromal scarring, edema, and enlarged, infected epithelial cells and stromal keratocytes, with a progressive worsening of the condition.

Similarly, a number of reports have described pigmented corneal deposits or precipitates associated with rifabutin treatment for MAC in HIV-positive<sup>3,4,7,8</sup> and negative<sup>9,10</sup> patients. Deposits in these cases have varied in pigmentation from light brown<sup>4</sup> to yellow-brown or golden<sup>4,8,10</sup> to yellow-white,<sup>9</sup> white,<sup>11</sup> or gray-white.<sup>4</sup> In all cases, however, rifabutin-associated corneal deposits were localized to the endothelium, Descemet's membrane, or the posterior stroma, and were present predominantly in the peripheral cornea. Additionally, an increase in density and size of rifabutin-associated corneal deposits over time has been noted by some investigators,<sup>8,9</sup> while others have noted a static behaviour.<sup>3,4,10</sup>

Here we report a case of an HIV-positive patient who had received rifabutin treatment for MAC, and was additionally suspected to have had CMV retinitis. The patient developed corneal deposits with an unusual appearance and location, while the known corneal manifestations of these conditions were conspicuously absent. Remarkably, the deposits resolved at a macroscopic level upon initiation of systemic steroid treatment.

### Case report

The patient, a 49-year-old woman, was diagnosed with HIV infection 15 years ago following intravenous drug abuse. The infection was initially treated with nucleoside analogues, thereby stabilizing the condition. Methadone hydrochloride has since been given continuously to avoid relapse of drug abuse. In 2007, hepatitis C was diagnosed and treatment with interferon and ribavirin was continued for six months without apparent effect on the condition.

In February 2008 the patient developed high fever, fatigue and night sweats. Investigations revealed high serum titres of cytomegalovirus (CMV), with RT-PCR > 150,000 copies/ml, and blood culture was positive for *Mycobacterium avium* complex (MAC). Treatment with clarithromycin, ciprofloxacin, rifabutin, ethambutol and amikacin was initiated for MAC infection. For the HIV infection, raltegravir, ritonavir, atazanavir and emtricitabine/tenofovir disoproxil (later changed to abacavir/lamivudine) was given. Due to oral mycosis, fluconazole was also administered. Valaciclovir was given for perianal herpes infection and trimethoprim-sulfamethoxazole as prophylactic treatment for pneumocystis carinii. The HIV virus count decreased from 5.9 million to 957, and CD4+ lymphocytes increased from 57 cells/ $\mu$ l to 186 cells/ $\mu$ l . The patient slowly recovered but developed a skin reaction, which later disappeared

after ceasing the MAC treatment for a few days and thereafter changing clarithromycin to azithromycin. Rifabutin 150 mg, taken every other day, was continued for two months and ethambutol 800 mg daily, was continued for six months for the MAC infection. Although CMV was found in the blood, ophthalmic examinations excluded uveitis and retinitis. No specific treatment for CMV was given.

Seven months later the patient developed bilateral visual disturbances and floaters. Best-spectacle corrected visual acuity was RE: 20/50 and LE: 20/33. Clinical eye examination revealed bilateral granulomatous anterior uveitis, vitritis, and retinitis with vasculitis. Intraocular pressure was normal. Topical treatment with dexamethasone 1mg/ml was initiated, and CMV retinitis was suspected. New investigation revealed a normalized CD4+ lymphocyte count (> 200). RT-PCR for CMV showed 3900 copies/ml, thereby excluding active CMV infection. The ocular condition was diagnosed as recovery uveitis and topical steroids were continued, calming down the intraocular inflammation. In November 2008, while still under topical steroid treatment, bilateral, round, brown-coloured, subepithelial corneal deposits developed in the exposed part of the cornea, extending from limbus to limbus (Fig 1A). On suspicion of Herpes simplex infection, topical and systemic aciclovir was given, but without apparent effect.

In January 2009, the patient was referred for detailed ophthalmic examination. Her symptoms included bilateral blurring of vision and floaters. A complete clinical examination was performed including slit lamp biomicroscopy, fundus examination, and in vivo confocal microscopy. The bilateral subepithelial corneal deposits persisted, while further ophthalmic examination revealed calm anterior chambers, bilateral vitritis, retinitis and vasculitis with a CMV appearance, with more pronounced findings in the LE (Fig 2). Intraocular pressure was

10 mmHg in both eyes. In-vivo confocal microscopy (IVCM; HRT3-RCM, Heidelberg Engineering, Heidelberg, Germany) revealed normal epithelial cell morphology, but with an abnormally reflective basal epithelium and Bowman's layer, laden with rounded focal opacities up to several hundred micrometers in diameter (Fig 3). The opacities did not extend into the anterior stroma, however, the most anterior stromal cells immediately beneath Bowman's layer exhibited irregularly-shaped nuclei, and reflective 'microdot' opacities were present in the extranuclear space. The deeper stroma, endothelium, and Descemet's membrane appeared normal both by IVCM and under slit lamp illumination. Anterior chamber tap RT-PCR and blood examination was negative for CMV/Herpes simplex and varicella zoster virus. As RT-PCR sensitivity can be low, a CMV origin of the condition could not be excluded, therefore treatment with ganciclovir 900 mg twice daily in combination with bilateral dexamethasone 1 mg/ml five times daily was started and continued for three weeks, but with minimal effect on the condition. Ganciclovir was thereafter reduced to 450 mg twice daily and prednisone 40mg daily was added to reduce the immunologic response. Two weeks later, in late February 2009, the corneal deposits had vanished (Fig 1B) and the intraocular inflammation had calmed down. Visual acuity in both eyes was 20/30. At a microscopic level, the focal opacities in Bowman's layer had subsided (Fig 4) although some residual reflectivity and the anterior stromal microdots remained.

## Discussion

The patient had a complex history of conditions, both systemic and ocular, for which numerous medications had been administered. While a corneal manifestation of one or more of these conditions or the administered treatments in this situation cannot be regarded as extraordinary, we believe the particular form of corneal involvement in this case, combined with its subsequent resolution, to be unique.

Although the patient did not have detectable CMV retinitis, the earlier presence of CMV systemically, and the history of rifabutin use suggest that either or both of these factors may have contributed to the observed corneal deposits. The major findings in this case, however, are in stark contrast with previously reported descriptions of corneal involvement in association with CMV or rifabutin. In this case, a low dose of rifabutin was given for only a short duration. Deposits were localized to the basal epithelium and Bowman's layer, and were distributed across the cornea from limbus to limbus. The posterior corneal stroma, Descemet's membrane, and endothelium appeared normal and unaffected. Shortly after initiation of systemic steroid treatment, the deposits were noted to have disappeared on slit lamp examination, but without any apparent effect on the patient's ocular symptoms. IVCN revealed the persistence of microdot deposits and abnormal anterior stromal cells. The microdots were similar in appearance to microdot deposits noted in long-term contact-lens users.<sup>12,13</sup> The abnormally-shaped, reflective anterior stromal cell nuclei may represent keratocytes in an activated state (possibly inflammation-induced), where the normally-transparent cytoplasm is rendered visible.<sup>14</sup>

We cannot ascertain the specific reasons for development of the corneal deposits in this case, nor can we suggest why the deposits appeared to respond to systemic steroid treatment. The bilaterality of the deposits suggests a pharmacological or inflammatory origin, however, to our knowledge no similar corneal findings have been reported. The observed deposits may have arisen from either a combination of the various treatments or may be an unusual presentation of ocular inflammation in an immunocompromised patient.

As HIV patients are living longer with the advent of modern antiretroviral therapy, reports of ocular complications of HIV are increasing. Side effects of systemic and ocular treatments, cross-reactivity between medications, and the mechanisms of corneal involvement in HIV, however, are still poorly understood. Documentation and reporting of corneal abnormalities in HIV patients may therefore aid in our understanding of the treatment, the immune system, and possibly even the virus itself. For this purpose, in-vivo confocal microscopy can be a valuable tool for documenting the specific depth location and morphology of corneal deposits and following their clinical course.

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### Figure Captions

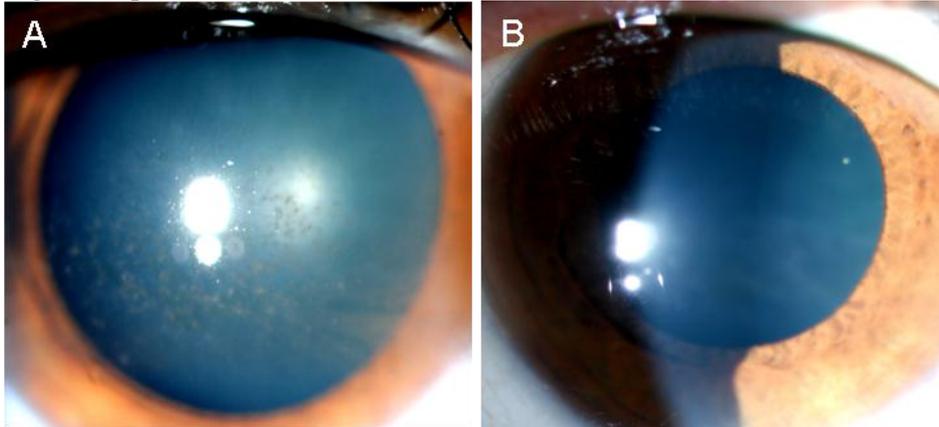


Figure 1. Appearance of the same cornea (RE) in an HIV-positive patient before and after systemic steroid treatment. (A) Rounded, light brown-colored deposits distributed across the corneal surface. (B) Close-up view of corneal deposits. (C) Slit lamp examination one month later demonstrating clear cornea without deposits.

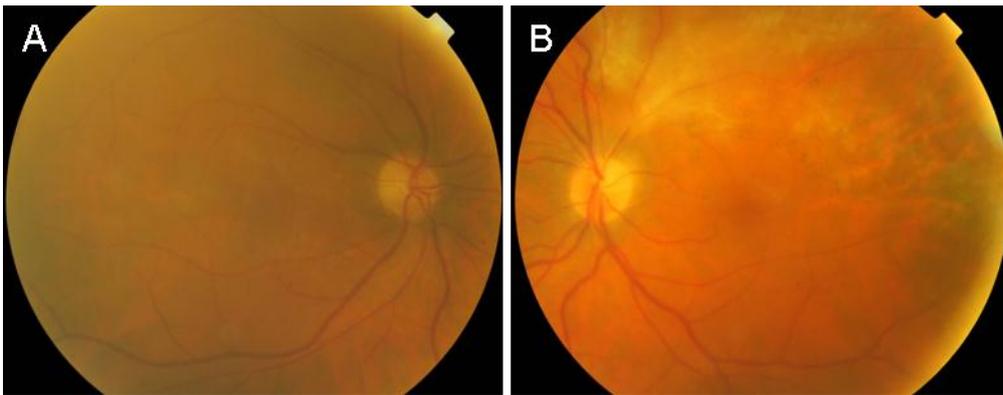


Figure 2. Fundus images (Topcon TRC 501X retinal camera) of (A) RE and (B) LE at the time of referral. The RE image was blurred due to vitritis. Signs of retinitis and vasculitis were found in the periphery, and were more pronounced in the LE.

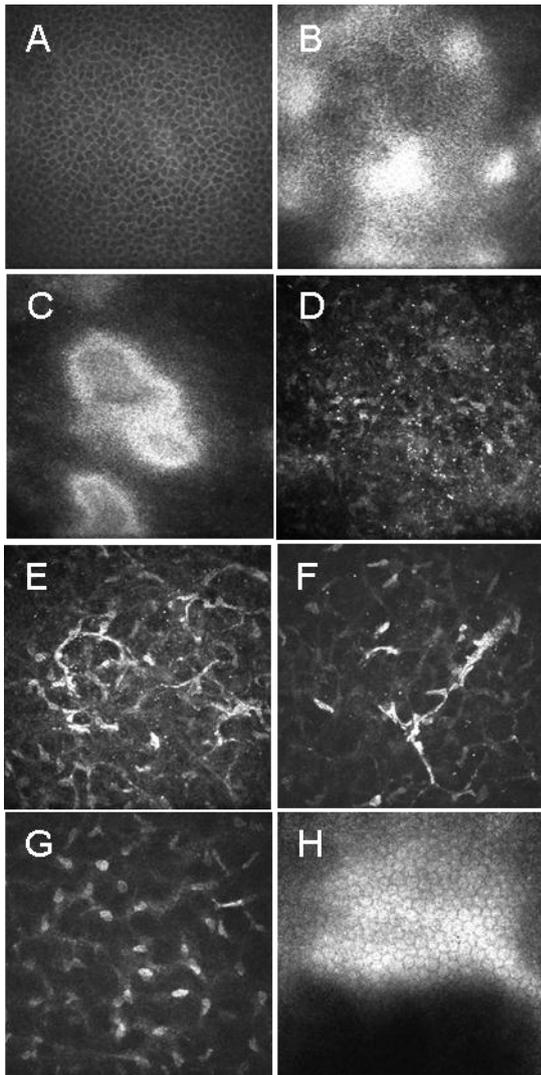


Figure 3. In-vivo confocal microscope images from HIV-positive patient with corneal deposits. (A) epithelial wing cell layer with normal cell morphology. (B) basal epithelium with localized, highly reflective opacities. (C) focal opacities in Bowman's layer. (D) appearance of the anterior stroma immediately beneath Bowman's layer, with reflective microdots visible. (E) anterior stroma with irregularly-shaped, abnormally reflective cells. (F) abnormal, elongated anterior stromal deposit with surrounding stromal cells. Note the lower density of microdots. (G) normal appearance of posterior keratocyte nuclei. (H) normal-appearing endothelium. All images are  $400 \times 400\mu\text{m}$ . Depth of images from the corneal surface (in  $\mu\text{m}$ ) A – H: 17, 40, 48, 55, 79, 122, 531, 594.

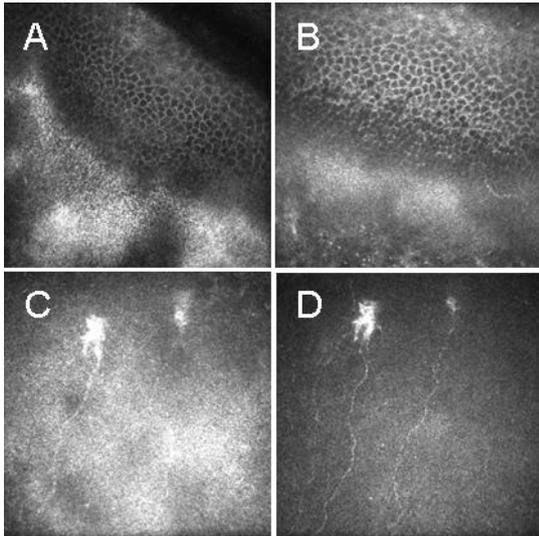


Figure 4. In-vivo confocal microscope images before and after initiation of systemic steroid treatment. (A) oblique section demonstrating focal opacities present at the level of the basal epithelium and Bowman's layer. (B) after treatment, opacities decreased in size and intensity but were not completely absent at the microscopic level. (C) nerve sprouts at the basal epithelium are obscured by an intense reflectivity of the corneal deposits. (D) after treatment, the same nerve sprouts were located, demonstrating reduced reflectivity at the basal epithelium and Bowman's layer. Note the improved visibility of subbasal nerves. Images C and D are  $400 \times 400\mu\text{m}$ .