Summary Statement

To the best of our knowledge, this is the first case report of Ritonavir-associated toxicity mimicking retinitis pigmentosa in a HIV infected patient on Highly-Active Antiretroviral Therapy.

Abstract

**Purpose:** To report Ritonavir-associated retinal pigment epithelium toxicity in a patient infected with the human immunodeficiency virus (HIV) on Highly-Active Antiretroviral Therapy (HAART) including ritonavir.

**Methods:** Retrospective single case report. We describe a case of gradual-onset of blurry vision in both eyes in a HIV-positive male. Visual acuity, clinical examination findings, and functional testing (electroretinogram and Goldmann perimetry) were reviewed. Diagnostic imaging including fundus photography, spectral domain optical coherence tomography (SD-OCT), fluorescein angiography (FA) and fundus autofluorescence (FAF) were assessed.

**Results:** 59-year-old HIV-infected male, treated with ritonavir for eight years, presented with a history of decreased night vision and peripheral field loss. Ophthalmologic examination confirmed the diagnosis of retinal toxicity. Goldmann perimetry showed areas of central and para-central scotomas. ERGs demonstrated mild to moderate photoreceptor dysfunction. Fundus examination revealed a diffuse pattern of RPE mottling in both eyes. SD-OCT confirmed the presence of choroidal thinning while FAF showed mottled hypoautofluorescence.

**Conclusions:** Although ritonavir-associated retinal toxicity is clinically uncommon, the clinical features of our findings support this diagnosis. Consideration of HAART-associated retinal toxicity should be given to the differential diagnosis in HIV-positive patients with retinopathy of unclear etiology. This report also highlights the need for constant monitoring of patients using the ritonavir for early detection of possible retinal toxicity.
Introduction

Many medications have been associated with retinal toxicity. The retinal pigment epithelium is a likely target for systemically administered compounds, since the underlying choroid is highly vascularized. The blood-retinal barrier prevents many systemically administered drugs from entering the eye via the circulatory system. Yet many medications that are administered systemically may still gain access to the eye and evoke degeneration of the RPE, and have been associated with toxic retinopathy, optic neuritis, anterior uveitis and cystoid macular edema.

We report a case of an HIV positive patient, who presented ritonavir-associated toxicity mimicking retinitis pigmentosa after 8 years of continuous treatment.

Case report

A 59-year-old HIV-infected male, presented with a history of slowly progressive decreased night vision in both eyes and peripheral visual field loss of two years duration. He had been placed on antiretroviral therapy with protease inhibitors ritonavir (Norvir, Abbott Laboratories) 100mg/day and atazanavir (Reyataz) 300mg/day, and a nucleoside reverse transcriptase inhibitor tenofovir/emtricitabine (Truvada, Gilead Sciences International Limited) 245/200mg/day starting 8 years prior, and other medications such as: reosuvastatin 10mg/day, amlodipine 5mg/day and aspirin 75mg/day. CD4+ T cell count was 330 cells per microliter, viral load was undetectable, and there was no previous history of AIDS-defining illness. There was no record of previous didanosine use, nor of anti-tuberculous drugs. The patient refers no family history of retinal disorders and has no history of HIV retinopathy or CMV retinitis.

Best-corrected visual acuity measured 6/15 in the right eye and 6/9.5 in the left eye. Anterior segment examination and intraocular pressures were normal in both eyes. Dilated fundoscopic examination revealed scattered bone specule-like pigment changes on the mid-peripheral retina of both eyes (Figure 1 a. and b) while wide-field FAF revealed more extensive retinal involvement than stereo fundus biomicroscopy alone, highlighting mottled hypofluorescence, and sparing the macula area in the left eye (Figure 1 c. and d.).

A fluorescein angiogram was performed, which showed bilateral bright punctate window defects resulting in a speckled appearance throughout the fundus and pigmentary clumping mostly in the mid-periphery. (Figure 2 a. and b.)

SD-OCT demonstrated thinning of the retina, especially in the outer nuclear layer, which corresponds to loss of photoreceptors (Figure 2 c. and d.) Visual field test (Goldmann perimetry) showed areas of paracentral scotomas. The patient subsequently underwent
electroretinogram (ERG) testing. Pattern ERG P50 was undetectable bilaterally. Rod ERGs were severely subnormal bilaterally. Bright flash ERG a-waves were markedly subnormal and waveforms electoronegative bilaterally. Photopic 30Hz flicker ERGs were markedly delayed and of subnormal amplitude bilaterally. Single flash cone ERGs have an abnormal broad a-wave and sharply rising b-wave without oscillatory potentials and both a- and b-wave amplitudes were subnormal bilaterally. These ERG features were consistent with a rod-cone dystrophy with an additional inner retinal involvement suggestive of retinal toxicity.

The diagnosis of toxic retinopathy associated with ritonavir was made based on clinical history, examination and ophthalmologic exams.

**Discussion**

Many etiologies can cause retinopathy phenocopying RP (pseudoretinitis pigmentosa). Correctly differentiating these conditions from RP is imperative because these conditions are generally treatable, unlike RP. The causes of pseudoretinitis pigmentosa, based on etiology, include infection such as congenital rubella, toxoplasmosis, syphilis, Lyme disease; inflammation (retinal vasculitis, old posterior uveitis); autoimmunity (autoimmune retinopathy, cancer-associated retinopathy, acute zonal occult outer retinopathy); trauma (intraocular foreign bodies such as siderosis, or blunt trauma, such as severe commotio retinae); and drug toxicity to chloroquine/hydroxychloroquine, phenothiazides, or thioridazine. In the present case, the combination of a good clinical history and a complete ophthalmic examination contributed significantly to diagnosis.

Three drugs used in the treatment of AIDS-related disorders have previously been linked with retinal epitheliopathy: the protease inhibitor ritonavir; clofazimine, used in the management of atypical mycobacterial infections, and the reverse transcriptase inhibitor didanosine. The only agent common to our patient and previous cases is ritonavir, a HIV protease inhibitor, which exhibits anti-neoplastic effects independent from its ability to inhibit HIV protease.

Ocular complications resulting from ritonavir are rare and can include blepharitis, conjunctivitis, iritis, and uveitis. Roe et al. reported the occurrence of a retinal pigment epitheliopathy associated with macular telangiectasis and intraretinal crystal deposits in HIV-positive patients receiving long-term ritonavir as part of highly active antiretroviral therapy. Both hypertrophic and atrophic changes were seen; and these did not involve the fovea. Intraretinal crystalline deposits and other features reminiscent of idiopathic parafoveal telangiectasis were also seen, in all 3 patients. However, none of these cases involving ritonavir toxicity described fundus appearance mimicking a pseudo-retinitis pigmentosa fundus. Retinitis pigmentosa-like fundus has been reported by Muccioli et al. in a HIV positive patient and it was attributed to didanosine use; however, this patient was on ritonavir therapy too.
It is not yet known the mechanism by which ritonavir injures the RPE, the neurosensory retina and the choriocapillaris, but it appears to be related to the drug's effect on mitochondrial DNA. Based on rodent studies, the proposed mechanism of ritonavir retinal toxicity has been phospholipidosis.\textsuperscript{13}

Besides the retina, liver, thyroid and kidney have also been described as targets for dose-related ritonavir toxicity.\textsuperscript{13} Liver dysfunction was one characteristic common to the 3 patients in Roe's report;\textsuperscript{11} whereas our patient had normal liver serum enzymes, thyroid hormone blood tests and blood and urine kidney function tests.

FAF is a useful tool as it displayed a more extensive disruption of the RPE than stereo fundus biomicroscopy alone. The involvement of the macula of the right eye explains the poorer vision in that eye compared to the left eye, where the macula appears to have normal FAF.

This report shows the need for ophthalmological screening and constant monitoring of patients using the ritonavir for early detection of possible retinal toxicity. Identification of this is important, especially if a reasonable alternative is available. Our case report may represent further evidence toward the retinal toxicity of the protease inhibitor ritonavir. To the best of our knowledge, this is the first case report of ritonavir toxicity with fundus appearance mimicking a pseudo-retinitis pigmentosa fundus.