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Case report

Cytomegalovirus retinitis after treatment with topical difluprednate in an aphakic eye of an immunocompetent patient

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ABSTRACT

Purpose: To report a case of an immunocompetent 64-year-old man who developed cytomegalovirus (CMV) retinitis after using topical difluprednate.

Observations: A 64-year-old man with type 2 diabetes developed hemorrhagic retinitis while using topical difluprednate after penetrating keratoplasty. Polymerase chain reaction of the vitreous was positive for CMV DNA. Complete blood count was within normal limits and 4th generation human immunodeficiency virus assay was negative. The retinitis resolved with oral valgancyclovir and intravitreal foscarnet injections.

Conclusion and importance: CMV retinitis may occur after topical difluprednate in an immunocompetent patient.

1. Introduction

Cytomegalovirus (CMV) retinitis is a known complication in immunocompromised patients, including those with acquired immune deficiency syndrome (AIDS) and those on systemic immunosuppression or chemotherapy. Several cases of CMV retinitis have been reported in immunocompetent patients after treatment with intravitreal triamcinolone acetonide (ITA).[1–7] We describe a case of CMV retinitis after topical difluprednate therapy in an aphakic eye of a diabetic man that was human immunodeficiency virus (HIV)-negative without any other evidence of systemic immunosuppression.

1.1. Case report

A 64-year-old man with well-controlled type 2 diabetes mellitus presented with decreased vision and pain in his right eye. Past ocular history was complex in the right eye and consisted of two corneal transplants following complicated cataract extraction without intraocular lens (IOL) implant two years prior. The patient was using topical difluprednate four times daily in the right eye for about one year, started after his first corneal transplant.

Prior cataract surgery in the right eye was complicated by a dropped nucleus and post-operative hyphema and vitreous hemorrhage. During the initial cataract surgery iris hooks were used and a pars plana vitrectomy (PPV) and pars plana lensectomy were performed for dislocated lens fragments. No intraocular lens was placed since the surgeon noted inadequate capsular support during the initial surgery. An additional PPV with posterior hyaloid removal and anterior chamber washout was performed 10 days after the cataract surgery for a non-clearing hyphema and vitreous hemorrhage noted one day after the surgery; no retinal breaks were found. The source of the intraocular hemorrhage appeared to be the posterior iris.

The patient was using an aphakic soft contact lens after the surgery with a best-corrected vision of 20/40 in the right eye. Despite tolerating the aphakic contact lens, the patient developed two sight-threatening contact lens-related bacterial corneal ulcers during the subsequent two years (1st: *pseudomonas aeriginosa;* 2nd *serratia marcescens)* requiring two penetrating keratoplasties (PKP). They occurred about one year and one and half years after the cataract surgery. The second corneal ulcer was associated with a corneal perforation and graft failure requiring repeat PKP. Ocular hypertension during this time was managed with topical medications alone.

On current presentation, visual acuity was counting fingers in the right eye and 20/200 in the left eye. The pupil in the right eye was of irregular shape consistent with prior surgery. Anterior segment examination revealed a lack of conjunctival injection, a clear corneal transplant graft with epitheliopathy, a quiet anterior chamber and aphakia in the right eye. The left eye had a normal pupil with clear corneal and lenticular cortical changes. Funduscopic examination of the right eye revealed a clear vitreous cavity and a large area of granular

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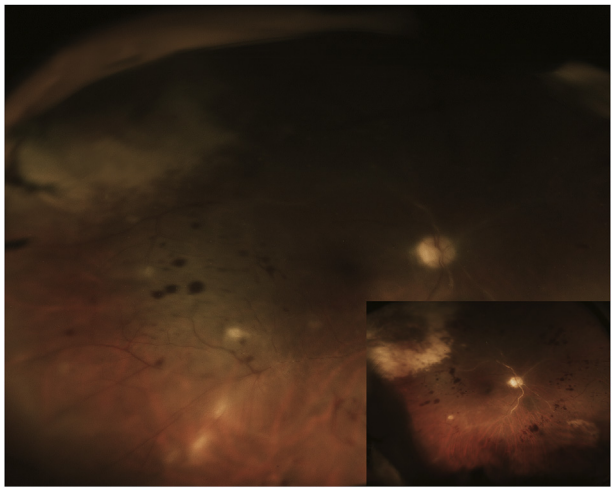

Fig. 1. Wide field fundus photo of the right eye in a 64-year-old man on topical difluprednate therapy showing a large area of granular retinitis superotemporally with a leading edge just anterior to the superior temporal vascular arcade; segmental retinal periarteritis involving the retinal arterioles with other areas of retinal whitening resembling cotton wool spots with multiple dot and blot retinal hemorrhages; and non-proliferative diabetic retinopathy. Inset: One month after starting therapy, consolidation of the retinitis is observed, as well as increased dot-blot hemorrhages.

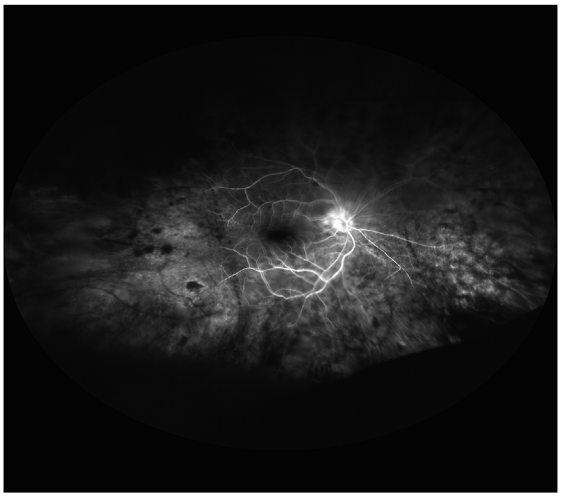

Fig. 2. Wide field fluorescein angiogram of the right eye, 29 seconds after injection, in a 64-year-old man on topical difluprednate therapy showing peripheral nonperfusion with blockage in areas of retinal hemorrhage and retinitis.

retinitis superotemporally with a leading edge just anterior to the superior temporal vascular arcade. The anterior retina behind the retinitis was atrophic with mottled pigmentation. There was segmental retinal periarteritis (Kyrieleis) involving the retinal arterioles with other areas of retinal whitening resembling cotton wool spots with multiple dot and blot retinal hemorrhages and non-proliferative diabetic retinopathy. The optic nerve was pale with a flat choroidal nevus inferior to it (Fig. 1). The left eye had mild non-proliferative diabetic retinopathy without macular edema or any signs of inflammation. Fluorescein angiogram (FA) revealed peripheral non-perfusion with blockage in the areas of retinal hemorrhage and retinitis (Fig. 2).

The patient underwent a vitreous cavity needle biopsy and was given intra-vitreal foscarnet (2.4 mg/0.1 mL) injections. Qualitative polymerase chain reaction (PCR) of the vitreous specimen was positive for CMV and was negative for Herpes Simplex virus 1 and 2, Varicella Zoster virus, and Toxoplasma gondii. Systemic work-up was negative for evidence of any immunosuppression, except for diabetes, with a

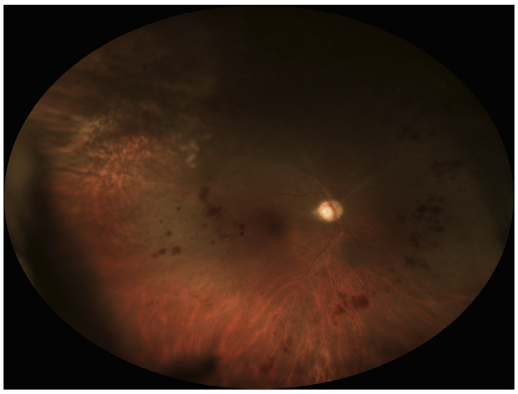

Fig. 3. Wide field fundus photo of the right eye in a 64-year-old man on topical difluprednate therapy showing resolution of retinitis with a superotemporal area of atrophy and persistent areas of hemorrhage.

normal complete blood count and negative 4th generation HIV assay. The patient was started on oral valgancyclovir 900mg twice daily. The retinitis completely resolved on oral valgancyclovir, leaving a superotemporal area of chorioretinal atrophy (Fig. 3). Although the retinitis resolved, an increase in mid-peripheral dot-blot hemorrhages was noted in the right eye with FA revealing persistent peripheral non-perfusion. His ischemic retinopathy was thought to be a consequence of the prior vasculitis, as well as some acceleration of diabetic retinopathy.

The patient was maintained on prophylactic dose valganciclovir and had no recurrence of his retinitis on topical prednisolone acetate twice daily. He subsequently underwent uncomplicated cataract extraction with intraocular lens placement in the left eye. One year following treatment the patient's vision remained stable at hand movement in the right eye and was 20/30 in the left eye.

2. Discussion

Cytomegalovirus (CMV) is a ubiquitous DNA virus infection, which is generally asymptomatic. The virus usually remains latent within many tissues of the host and may reactivate if host immunity is compromised. In the eye, CMV causes a necrotizing retinitis which is most commonly seen in immunocompromised patients with acquired immunodeficiency syndrome (AIDS), or in individuals on immunosuppressive medications. Several cases of CMV retinitis in immunocompetent patients have been reported after intravitreal or sub-Tenon injection of triamcinolone acetonide.[1–7] Of these, the majority of cases occurred in diabetics,[1–6] most of whom had undergone either cataract extraction, vitrectomy, or both.[1–4] There are no published reports of CMV retinitis associated with diabetes in the absence of other immunosuppression. To our knowledge, this is the first report of CMV retinitis associated with topical difluprednate.

Both steroids and diabetes may increase the risk for CMV retinitis. As has been pointed out by Radwan and colleagues,[5] diabetes, like HIV retinopathy, results in endothelial damage and reduced retinal blood flow. With reduced retinal blood flow, diabetic rats demonstrate increased leukocyte entrapment in the retina,[8] which may include CMV infected cells. In mice, corticosteroid-induced immunosuppression leads to reactivation of CMV in the eye including within the retina and RPE.[9] Our patient suffered from diabetes, demonstrated non-proliferative diabetic retinopathy, and was exposed to corticosteroids.

After treatment for CMV retinitis, our patient demonstrated persistent non-perfusion on FA and increasing number of dot-blot hemorrhage, suggesting worsening ischemic retinopathy. Findings from multimodal imaging appear to localize Kyrieleis plaques to the vascular endothelium (endothelitis) versus the arteriolar wall (periarteritis).[10] This vascular pathology, in addition to the endothelial damage caused by diabetes, may explain the worsening of this patient's ischemic

retinopathy in the context of CMV retinitis.

Studies suggest that difluprednate can achieve significant concentrations in the retina. Nakano et al. compared topical difluprednate to sub-Tenon's injection of triamcinolone acetonide.[11] After three months of treatment, they found comparable reductions of retinal thickness between the groups. The authors concluded that difluprednate effectively reached the macula. This conclusion is supported by animal research. Tajika et al. studied the ocular distribution of tritium-labeled difluprednate in rabbit eyes.[12] They detected radioactivity in the retina and choroid, also concluding that difluprednate effectively reaches the posterior segment.

Our patient's aphakic status may have further increased the concentration of difluprednate in the posterior segment. Green et al. compared the vitreous concentration of indomethacin after topical administration in phakic and aphakic rabbit eyes.[13] The aphakic eyes demonstrated vitreous concentrations more than 500 times that of the phakic eyes 1 hour after administration. While indomethacin and difluprednate differ in certain pharmacodynamic properties, both drugs reach the anterior chamber and achieve concentrations in the retina. As such, we suspect that difluprednate also achieves greater vitreous concentration in aphakic eyes.

We believe that our patient's chronic treatment with topical difluprednate significantly altered the local immunity within the posterior segment of his right eye, precipitating his CMV retinitis, especially considering the absence of systemic immunosuppression.

3. Conclusions

Cytomegalovirus retinitis in an immunocompetent patient may be associated with topical difluprednate therapy. Ophthalmologists should be aware of this possible treatment complication.

Patient Consent

Consent to publish this case report was not obtained. The report does not contain any personal information which could lead to the identification of the patient.

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Disclosure statement

Drs. Kedhar, Gentile, Do and Kaplan have nothing to disclose.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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