Letters

OBSERVATION

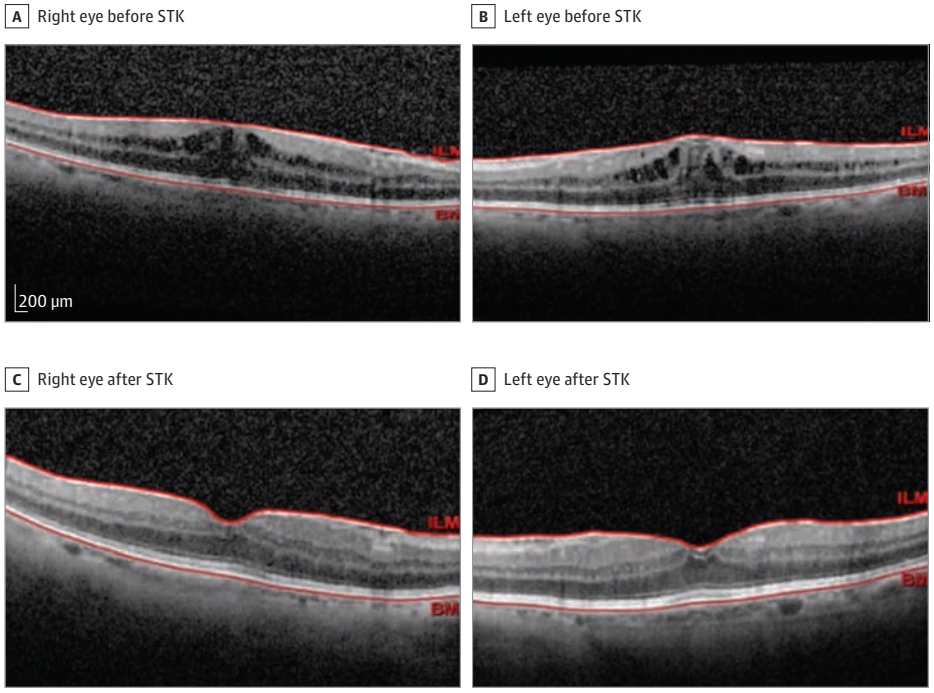
Sub-Tenon Triamcinolone and Anti-HIV Medication–Induced Cushing Syndrome

We describe a patient who developed Cushing syndrome associated with periodic sub-Tenon triamcinolone injections in the setting of using ritonavir (Norvir [AbbVie]) and darunavir (Prezista [Janssen]), 2 protease inhibitors used to treat HIV.

Report of a Case | We report a patient with a severe adverse effect associated with periodic sub-Tenon triamcinolone injections (STK). The patient is an 82-year-old male with a longstanding history of hereditary chorioretinopathy and pseudophakia for 6 years, who initially presented with a visual acuity with correction of 20/150 OD and 20/60 −2 OS. There was no cell in the anterior or posterior segment. Optical coherence tomography (OCT) showed cystoid macular edema (CME) (**Figure 1**). Fluorescein angiography demonstrated retinal vascular leakage in the macula with fluorescein accumulation in a petaloid pattern surrounding the fovea, consistent with postsurgical CME (Irvine-Gass) syndrome in both eyes. There was some consideration that the CME was associated with ellipsoid-zone or retinal pigment epithelial disruption associated with his hereditary chorioretinopathy, but there was no evidence of ellipsoid-zone-retinal pigment epithelial disruption (Figure 1). Medical history included type 1 diabetes, congestive heart failure, hypertension, and HIV infection. Medications included darunavir, ritonavir, furosemide, insulin, and apixaban. There was no change in CME after 3 months of topical ketorolac, 0.5%, administered 6 times daily and topical prednisolone acetate, 1%, administered 4 times daily. He then received STK, 20 mg, in each eye, which resulted in improvement in visual acuity to 20/40 OD and 20/40 OS and reduced OCT CME thickness. Within 2 months of starting STK, the patient started having progressively worsening exercise tolerance, dyspnea on exertion, lower extremity weakness, increased fat in his face and abdomen, easy bruising, muscle wasting, and confusion. He continued to receive STK, 20 mg, in each eye every 3 months, for a total of 3 doses in each eye. One month after the third dose of STK, the patient was seen in the emergency department for progression of all his symptoms including skin atrophy (**Figure 2**) and admitted for further evaluation.

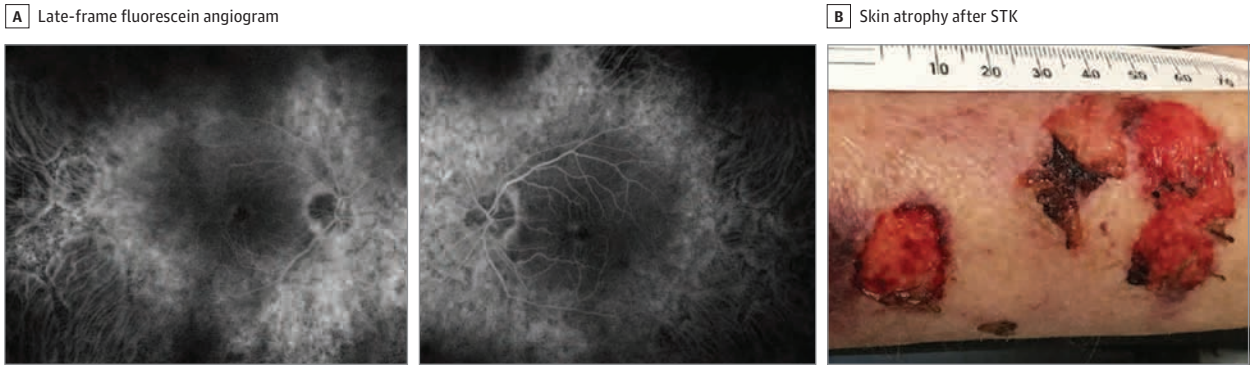
Corticotropin level was low at 3.2 pg/mL (normal, 7-63 pg/mL; to convert to picomoles per liter, multiply by 0.22) and early morning cortisol level was low at 2.0 µg/dL (normal, 3.7-19.4 µg/dL; to convert to nanomoles per liter, multiply by 27.588). Magnetic resonance imaging of the pituitary gland, and computed tomography of the adrenal glands were unremarkable. Cosyntropin (Cortrosyn [Amphastar Pharma]) stimulation test was normal. The patient received dexamethasone, 1 mg, orally at 11 PM and serum dexamethasone at 8 AM the following day was 855 ng/dL (reference range, 140-295 ng/dL), indicating that glucocorticoid metabolism was substantially

Figure 1. Sub-Tenon Triamcinolone Injection (STK)



Optical coherence tomography images of the right and left eye before (A and B, respectively) and after (C and D, respectively) STK.

Figure 2. Findings on Fluorescein Angiography and Physical Examination



A, Late-frame fluorescein angiography of the right and left eye demonstrating mild perifoveal leakage. B, Skin atrophy after sub-Tenon triamcinolone injection (STK).

inhibited and supported the diagnosis of iatrogenic Cushing syndrome caused by high circulating glucocorticoid level, presumably from STK, despite the low serum corticotropin and cortisol levels. The patient had subsequent resolution of Cushingoid symptoms with discontinuation of STK therapy and initiation of glucocorticoid replacement therapy for adrenal insufficiency. We hypothesize that his findings were related to inhibition of cytochrome P450 3A4 (CYP3A4), which is the most abundant cytochrome P450 and is responsible for glucocorticoid metabolism. As part of his HIV treatment, he was taking ritonavir and darunavir, both of which cause strong inhibition of CYP3A4, which is responsible for glucocorticoid metabolism. Other HIV medications have similar inhibitory effects. Additionally, he was taking amiodarone, which further inhibits CYP3A4.

Discussion | These findings support the possibility of iatrogenic Cushing syndrome caused by periocular injections of corticosteroids in the setting of CYP3A4 inhibition by HIV medications. Local corticosteroids injections have often been understood as causing less systemic adverse effects when compared with systemic corticosteroids owing to decreased systemic circulation.[1] However, cases have been reported of topical corticosteroids associated with iatrogenic Cushing syndrome.[2] Additionally, cases have also been reported with orbital floor triamcinolone[3] and a pediatric case related to topical and sub-Tenon triamcinolone.[4] In cases of substantially inhibited corticosteroid metabolism, these levels can rise dramatically. In our case, ritonavir (and to a lesser degree darunavir and amiodarone) caused strong inhibition of CYP3A4. Other substances known to strongly inhibit CYP3A4 include grapefruit, voriconazole, and ketoconazole. The US Food and Drug Administration maintains a list of significant modulators of the cytochrome P450 system.[5]

However, in the setting of metabolic inhibition, even lower doses of corticosteroids can become problematic. Ophthalmologists should be aware of the possibility of hypothalamic-pituitary-adrenal axis suppression with local use of corticosteroids. This case highlights the need for physicians to remain cognizant of patients' medication use and the potential for serious drug interactions, especially those affecting drug metabolism.

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1. Shen L, You Y, Sun S, Chen Y, Qu J, Cheng L. Intraocular and systemic pharmacokinetics of triamcinolone acetonide after a single 40-mg posterior subtenon application. *Ophthalmology*. 2010;117(12):2365-2371. doi:10.1016/j.ophtha.2010.03.033

2. Decani S, Federighi V, Baruzzi E, Sardella A, Lodi G. Iatrogenic Cushing syndrome and topical steroid therapy: case series and review of the literature. *J Dermatolog Treat*. 2014;25(6):495-500. doi:10.3109/09546634.2012.755252

3. McConkey HZ, Williams H, Kulasegaram R, Graham E. Orbital floor triamcinolone causing Cushing syndrome in a patient treated with Kaletra for HIV 1. *BMJ Case Rep*. 2013;2013:bcr0220125849. doi:10.1136/bcr.02.2012.5849

4. Ozerdem U, Levi L, Cheng L, Song MK, Scher C, Freeman WR. Systemic toxicity of topical and periocular corticosteroid therapy in an 11-year-old male with posterior uveitis. *Am J Ophthalmol*. 2000;130(2):240-241. doi:10.1016/S0002-9394(00)00501-8

5. US Food and Drug Administration. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. Accessed June 5, 2023. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

COMMENT & RESPONSE

Myopic Maculopathy in Children and Adolescents With High Myopia

To the Editor I read with interest the article "Four-Year Progression of Myopic Maculopathy in Children and Adolescents With High Myopia" by Jiang et al.[1] In this study, the authors investigated the progression of myopic maculopathy and associated factors in highly myopic children and adolescents. In univariable and multivariable analyses, myopic maculopathy progression was associated with younger age, longer axial length with faster elongation, and more serious maculopathy. The study used the International Photographic Classification and Grading System for myopic maculopathy, and with fundus photographic changes being correlated with visual acuity, axial length, and other eye metrics, the risk factors for myopic maculopathy progression were determined.

However, myopic maculopathy can be a complex disease. Existing classification systems may lack sensitivity, particularly in younger patients. In the present study, each eye was treated as an independent subject and was counted individually rather than collectively per person. In clinical practice, some patients develop asymmetric myopic maculopathy with different severity in each eye. Under this circumstance, if any asymmetric myopic maculopathy–related changes in each eye of an individual were particularly analyzed, the asymmetry of myopic maculopathy development[2] might not provide insight into systemic aspects of risk factors for myopic maculopathy progression. Therefore, in this study, it might not be possible to compare the clinical characteristics between the eyes of the same patient with different degrees of severity during follow-up.

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1. Jiang F, Wang D, Xiao O, et al. Four-year progression of myopic maculopathy in children and adolescents with high myopia. *JAMA Ophthalmol*. 2024;142(3):180-186. doi:10.1001/jamaophthalmol.2023.6319

2. Takahashi H, Tanaka N, Shinohara K, et al. Ultra-widefield optical coherence tomographic imaging of posterior vitreous in eyes with high myopia. *Am J Ophthalmol*. 2019;206:102-112. doi:10.1016/j.ajo.2019.03.011

In Reply We appreciate the comments by Asensio-Sánchez on our study[1] exploring the 4-year progression of myopic maculopathy in children and adolescents with high myopia.

We agree that myopic maculopathy is a complex disease. The challenges of classifying numerous myopic maculopathy findings are reflected, for example, by the frequently cited International Photographic Classification and Grading System for Myopic Maculopathy.[2] This system uses fundus photographs to grade myopic macular degeneration, demonstrating relatively high sensitivity when applied in clinical studies, including those involving younger age groups.[3]

We acknowledge that some patients develop highly asymmetric myopic maculopathy with substantially different severity in each eye. However, in our experience, the vast majority of patients with bilateral high myopia exhibit relatively symmetric fundus lesions. The analysis of the severity of myopic maculopathy between right and left eyes in our study found no meaningful differences. Additionally, when we performed a logistic regression analysis using only 1 eye per participant, while the smaller dataset led to wider confidence intervals, the findings appeared consistent with the results of our original findings, including myopic maculopathy progression associated with worse best-corrected visual acuity (odds ratio [OR], 11.33; 95% CI, 0.60-213.80), longer axial length (OR, 1.74; 95% CI, 1.19-2.54), faster axial length elongation (OR, 607.86; 95% CI, 20.41-18 100.37), and more severe myopic maculopathy (diffuse atrophy: OR, 5.23; 95% CI, 1.49-18.40; patchy atrophy: OR, 5.57; 95% CI, 1.63-19.09).

Furthermore, when reviewing the article referenced by Asensio-Sánchez regarding asymmetric myopic maculopathy between eyes of the same participant,[4] that study appeared to focus on the morphology of posterior vitreous detachments (PVDs) in highly myopic eyes, without specifically addressing changes related to myopic maculopathy. Current classifications do not generally include PVDs as part of myopic maculopathy.[2,5] Nevertheless, the characteristics of PVDs may provide insights into the pathogenesis of myopic traction maculopathy, which may be associated with various risk factors. These include the presence of an epiretinal membrane, vitreomacular traction syndrome, remnants of cortical vitreous, and the inherently less elasticity of the retina and the inner limiting membrane compared with the surrounding tissues, which are unable to accommodate the scleral outpouching of the posterior pole.[5] Also, that study[4] found that PVDs commonly were more asymmetric relative to the fovea in highly myopic eyes than in eyes that were not highly myopic, without exploring differences of PVDs between the left and right eyes of the same patient.

Of course, further research with more participants evaluated and potentially more precise categorization would be of