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A case of reversible toxic optic neuropathy from tacrolimus (FK506)

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ABSTRACT

Purpose: To report a rare case of reversible vision loss from tacrolimus-associated toxic optic neuropathy.
Observations: A 30-year-old man with cystic fibrosis requiring bilateral lung transplantation developed painless, bilateral, gradual onset central vision loss with dyschromatopsia two years after starting tacrolimus. Visual fields revealed bilateral cecocentral scotomas. Fundoscopy demonstrated bilateral temporal pallor of the optic nerves. Testing for nutritional deficiencies was unremarkable. Tacrolimus was switched to cyclosporine and the patient was started on idebenone. Two months later, the patient demonstrated marked improvement in his visual acuity and dyschromatopsia.
Conclusionsand Importance: Neurotoxicity is a rare but major potential side effect of tacrolimus. Idebenone should be considered as a potential, low-risk supplement for transplant patients who are immunosuppressed in whom toxic optic neuropathy is a concern.

1. Introduction

Tacrolimus (FK506) is an effective, widely used immunosuppressive agent in transplant patients. Isolated from *Streptomyces tsukubaenis*, it is thought to suppress graft rejection by inhibiting cytokine synthesis, particularly IL-2, IL-3 and IFN-α, thereby blocking T-cell activation and T-cell dependent B cell proliferation.[1]

Neurotoxicity is a rare but major potential side effect of tacrolimus. Tacrolimus-associated posterior reversible encephalopathy syndrome (PRES), optic nerve demyelination, and ischemic optic neuropathy have been reported in the literature.[2–6](Demontes, 2019 #1657) Here, we present a case of a patient whose vision loss is suggestive of a toxic optic neuropathy syndrome. Remarkably, after cessation of medication and supplementation with idebenone, his visual acuity and dyschromatopsia improved significantly. Our case underscores the potential heterogeneity in the clinical characteristics of vision loss and potential mechanisms of injury that underlie tacrolimus-associated vision loss.

1.1. Case report

A 30-year-old man with cystic fibrosis requiring bilateral lung transplantation in 07/15/14 was administered mycophenylate mofetil, tacrolimus, and prednisone for immunosuppression. His course was complicated by Type 1A rejection and accelerated bronchiolitis obliterans syndrome necessitating a second bilateral transplant in 12/11/15. In January of 2016, he was found to have mild A2 rejection for which he was started on monthly IVIG and photophoresis. By June 2016, he was found to be rejection free. He continued on the same dose of tacrolimus since starting the drug in 2014. On 9/26/16, the patient underwent a bronchoscopy with balloon dilation of his proximal airways as well as Argon beam assisted removal of granulation tissue. During this hospitalization, his tacrolimus levels were found to be below target which prompted the team to adjust his dosage. He had no known personal or family history of inherited vision loss.

An ophthalmological evaluation was sought on 10/05/16 for complaints of progressive, bilateral blurring of vision starting 4–6 months prior. He denied associated pain, flashes of light, floaters, or focal neurological deficits. Records revealed a visual acuity of 20/40 OD, 20/60 OS, without a relative afferent pupillary defect. Sensorimotor exam demonstrated full ocular motility. Dilated exam revealed a cup to disc ratio of 0.4 OU, no evidence of optic nerve pallor. Macula and peripheral retina were unremarkable. Refraction with optometry was recommended.

Two weeks later, optometric exam revealed best corrected visual acuity of 20/200 OD and 20/400 OS with a manifest refraction of −3.50 + 0.75 × 008 OD and −4.00 + 0.75 × 004 OS, similar to his original spectacle correction. At this point, the neuro-ophthalmology service was consulted. No relative afferent pupillary defect was noted. Patient did demonstrate marked dyschromatopsia: 3/10 Ishihara plates OD, 2/10 OS. Exam of the posterior pole demonstrated bilateral temporal pallor of

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the optic disc associated with mild elevation of the disc margins OU (Fig. 1). The arcuate fibers appeared mildly edematous OU. Macular reflex was blunted OU. Papillomacular atrophy was seen on optical coherence tomography (OCT, Fig. 2) An MRI of the brain and orbits was recommended but the patient declined.

Given his presentation of painless, progressive bilateral symmetric loss vision associated with atrophy of the papillomacular bundle, toxic and nutritional optic neuropathies were considered most likely. His medications at the time included azithromycin 100mg M/W/F, bupropion 75mg BID, diltazam 720mg daily, folic acid 1mg daily, gabapentin 300mg TID, insulin, ipratropium, levalbuterol, lubiprostone 24mcg BID, magnesium 400mg daily, metoprolol tartrate 12.5mg BID, multivitamin, pancrelipase, pantoprazole 40mg daily, pravastatin 10mg QHS, prednisone 10mg daily, tacrolimus 2.5mg PO BID, valganciclovir 450mg q48hrs, voriconazole 200mg BID, and zolpidem 5mg QHS. Tacrolimus level at that time was 8.9ng/ml (goal 8–10ng/ml) but was elevated for multiple days, reaching as high as 25.0ng/ml, in the preceding weeks. The elevation in tacrolimus levels was a consequence of the team adjusting his dosing as his levels had dropped below target. Creatinine was 1.37 mg/dL which was his baseline.

Testing for nutritional deficiencies was unremarkable: vitamins B1, B6, B12, RBC folate, methylmalonic acid, Zn, and Cu levels were found to be within normal limits. Hereditary optic neuropathies such as Lebers Hereditary Optic Neuropathy (LHON) were also considered but testing not performed secondary to financial constraints.

The decision was made to switch his tacrolimus to cyclosporine 100mg BID on 11/08/16 and to start idebenone 300mg TID. As there was concern that voriconazole could be contributing to his visual decline and was replaced with isavuconazonium sulfate 186mg daily.

Our patient noted subjective improvement in vision within two months of the above-mentioned interventions. On follow-up exam 6 months later, visual acuity was 20/30 OD, 20/25 OS, with improvement in dyschromatopsia (6/8 plates OD, 5/8 OS). Posterior pole exam was remarkable for marked temporal pallor OU, OD worse than OS, with drop out of the papillomacular bundle. Cup to disc ratio was 0.4 OU without excavation. Progressive atrophy of the papillomacular bundle was noted on OCT (Fig. 2) which correlated with visual fields (Fig. 3), demonstrating cecocentral scotomas bilaterally.

2. Discussion

Toxic optic neuropathies generally present as painless, insidious, bilateral vision loss. On exam, patients can be found to have dyschromatopsia, cecocentral scotomas on visual field testing, and temporal pallor of the optic nerve with minimal excavation with subsequent atrophy of the papillomacular bundle. Although many medications (e.g. ethambutol, amiodarone, methanol, phosphodiesterase-5 inhibitors) have been associated with optic nerve dysfunction, it is difficult to prove direct causality.[7] Here, we present a case of a patient who developed bilateral optic neuropathy with improvement in optic nerve function after cessation of tacrolimus and initiation of idebenone.

Neurotoxicity is a rare but known major complication of tacrolimus. The underlying mechanism through which tacrolimus damages the central nervous system, however, is unknown. Early reports of tacrolimus-associated vision loss described patients who suffered from cortical blindness, without evidence of optic nerve damage. Shutter et al. described the first patient who developed severe, painless bilateral vision loss eight days after starting tacrolimus.[6] Fundoscopic exam was normal, but magnetic resonance imaging (MRI) demonstrated diffuse, non-enhancing subcortical white matter lesions with a posterior predilection. Visual acuity improved three days after the patient was switched to cyclosporine. Importantly, her fundus exam remained normal, with no evidence of optic nerve pallor in the ensuing weeks. These white matter lesions resolved on repeat imaging one month later, suggestive of PRES. Similar cases of tacrolimus-associated cortical blindness have been reported by others,[8] all of which demonstrated improvement in vision after drug cessation.

Tacrolimus-associated vision loss, however, has also been reported in patients without evidence of PRES, suggesting that non-cortical mechanisms may be possible. These patients differed from those described above in that they demonstrated direct evidence of optic nerve dysfunction on examination. Brazis et al. reported the first presumed case of tacrolimus-associated optic neuropathy. Their patient suffered from painless, sudden onset altitudinal vision loss two months after starting tacrolimus.[2] No progression was noted after tacrolimus was stopped. Yun et al. reported a similar case of sudden onset, bilateral optic neuropathy that improved in the less severely affected eye one month after cessation of tacrolimus.[9] Interestingly, on fluorescein angiography, the authors noted an absence of filling of either optic disc. This finding, taken together with the sudden onset of symptoms suggested an ischemic etiology. Shao et al. proposed that tacrolimus, which has been shown to interact with the prostacyclin-thromboxane pathway, could predispose patients to ischemic optic neuropathy by increasing thromboxane A2 levels, leading to vasoconstriction.[10] Rasool and colleagues described three patients suspected of tacrolimus-associated optic neuropathy, all presenting with arcuate and altitudinal visual field changes similar amiodarone-associated optic neuropathy.[3,11]

Venneti et al. proposed an alternative hypothesis. Their patient had been immunosuppressed with tacrolimus for five years prior to onset of vision loss after orthotropic heart and kidney transplant for ischemic cardiomyopathy and diabetic nephropathy. Visual acuity was 20/70 OD and hand motions (HM) OS. MRI demonstrated enhancement of the left optic nerve on post-gadolinium T1 weighted imaging. Extensive rheumatologic and infectious work-up were unremarkable. Visual acuity declined to HM OD and no light perception OS. Biopsy of the left optic nerve revealed prominent loss of myelin with preserved axonal elements

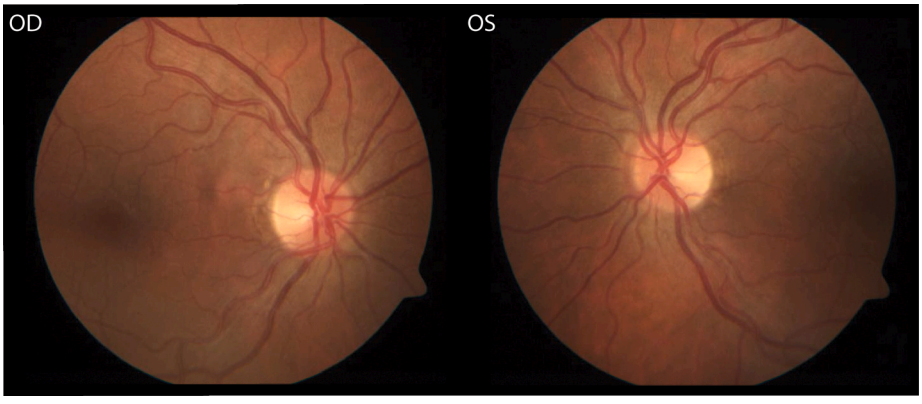

Fig. 1. Disc photos.

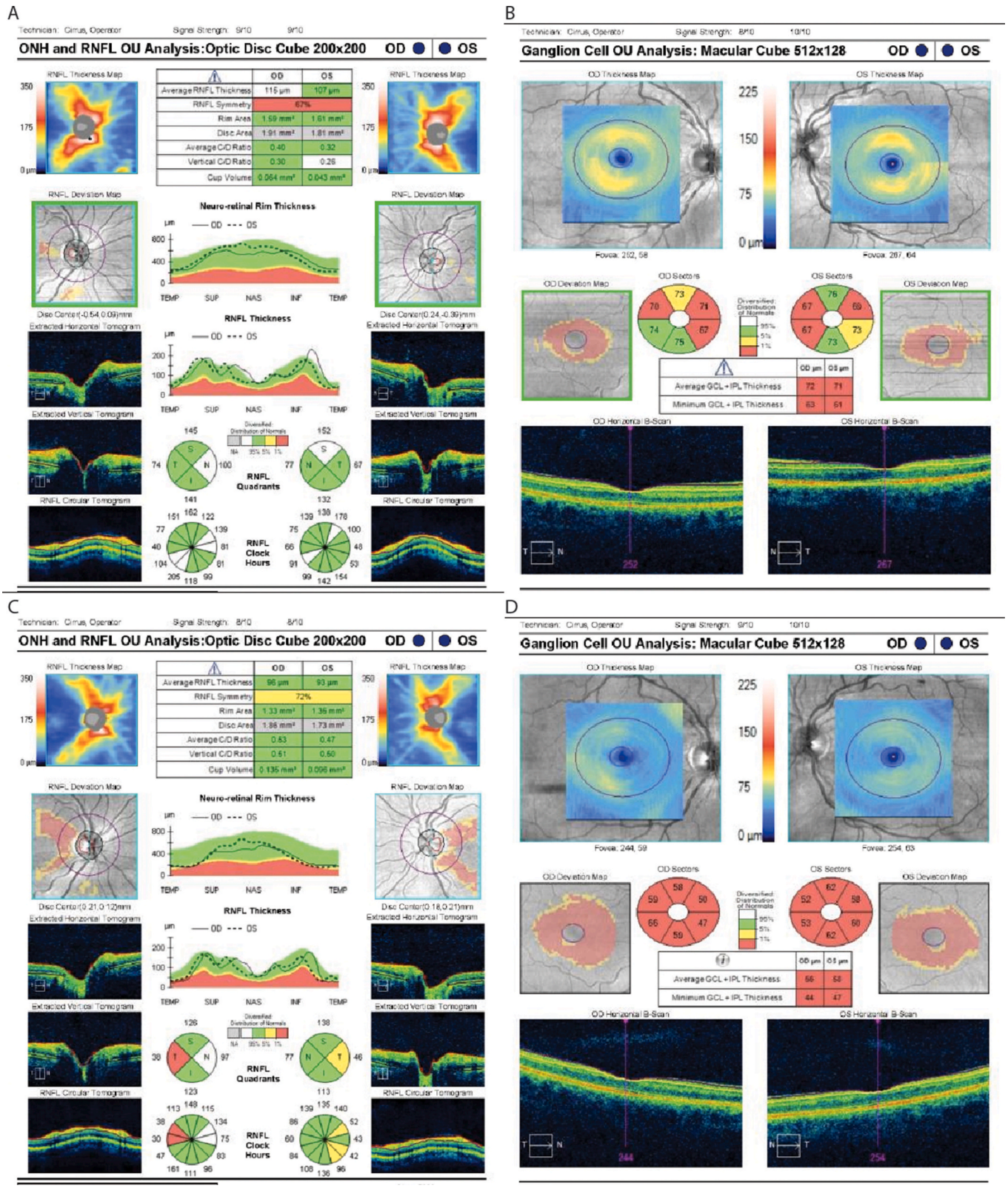

Fig. 2. Spectral domain optic coherence tomography.

and no evidence of infectious, vasculitic, or neoplastic process. This case raises the question of whether tacrolimus can induce optic nerve demyelination and is supported by a recent case by Demontes et al. who reported improvement with acute administration of intravenous corticosteroids. (Demontes, 2019 #1657).

Here, we present a case of a patient who developed bilateral optic neuropathies two years after initiation of tacrolimus. His insidious onset of vision loss coupled with his cecocentral scotomas and atrophy of the papillomacular bundle were consistent with a metabolic, toxic, or nutritional etiology. Work up for nutritional etiologies was

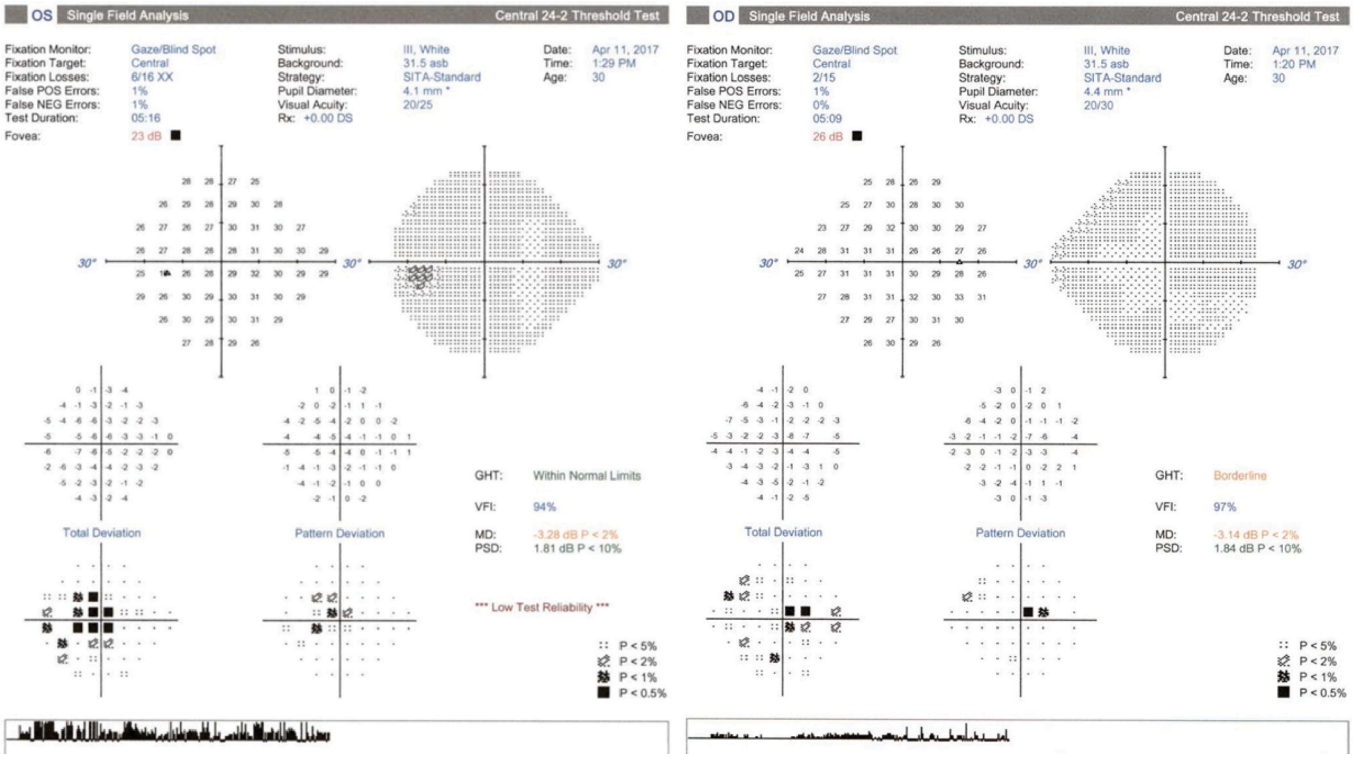

Fig. 3. Automated visual fields, 24-2Automated visual fields demonstrate central scotomas OU, OS worse then OD.

unremarkable, and we could not definitively exclude the possibility of a hereditary optic neuropathy such as Lebers Hereditary Optic Neuropathy (LHON) as mitochondrial gene testing was not performed. That being said, metabolic deficiencies may underlie many cases of toxic optic neuropathy as nerves with ailing mitochondria are less equipped to cope with the metabolic stress induced by toxins. This may explain why only a subset of patients who are exposed to a toxin become symptomatic. Moreover, insidious bilaterally simultaneous loss of vision, followed by the remarkable degree of visual recovery in this case, would be highly unusual for the large majority of LHON patients. Taking together the concomitant elevation of tacrolimus levels and temporal sequence of improvement of visual dysfunction following cessation of tacrolimus, we feel this provides robust evidence to support a causal link.

Our patient demonstrated improvement in central visual acuity and dyschromatopsia after cessation of tacrolimus as well as initiation of idebenone, which is a co-enzyme Q10 derivative with good blood brain barrier penetration and inhibits lipid peroxidation. It has been found to portend some visual benefit in a subset of patients with underlying metabolic optic neuropathies such as LHON.[12] Given that our patient suffered from severe vision loss due to a suspected metabolic etiology, the decision to start idebenone was motivated by a desire to minimize oxidative stress to the optic nerve, further supported by idebenone's low risk profile. Although our patient recovered from 20/200 vision OD and 20/400 vision OS to 20/30 OD and 20/25 OS, we cannot exclude the possibility that cessation of tacrolimus alone was responsible for the improvement.

3. Conclusions

Although anecdotal, this case offers two important considerations to the clinician that cares for patients chronically immunosuppressed by tacrolimus. First, tacrolimus should be considered as a potential causative agent for vision loss in transplant patients. Visual compromise may occur due to posterior cortical dysfunction as in PRES, or may be the result of an optic neuropathy. Further, when contrasted with previously reported cases of optic neuropathy, our case underscores the potential heterogeneity in the clinical characteristics of vision loss and potential mechanisms of injury. Second, idebenone should be considered as a potential, low-risk supplement for transplant patients who are immunosuppressed in whom toxic optic neuropathy is a concern.

Patient consent

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

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Authorship

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

Fundus disc photography demonstrates temporal pallor with atrophy of the papillomacular bundle OU. Note the fairly prominent demarcation between the relatively normal arcuate bundles and the atrophic papillomacular bundle (arrows).

SD-OCT demonstrates full RNFL OU (A) but early papillomacular bundle atrophy OU can be appreciated on GCC (B). Six months later, progressive papillomacular atrophy ensues and can be detected on both RNFL (C) and GCC (D) imaging, with relative sparing of the arcuate projections.

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