Case Report

Tacrolimus Optic Neuropathy Mimicking Papilledema

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Abstract
Tacrolimus (FK506) is a potent and effective immunosuppressive agent, mainly utilized after solid organ transplantation. We report the clinical features of tacrolimus optic neuropathy (TON) in a patient on tacrolimus therapy that had an exhaustive workup not revealing any additional cause. The patient was a 60-year-old man post-cardiac transplantation who presented with a 5-month history of vision loss OD and 10 days of vision loss OS. Dilated exam showed significant optic disc edema in both eyes (OCT RNFL 442 μm OD and 330 μm OS). Multiple lumbar punctures showed a normal opening pressure. After discontinuation of tacrolimus, he noticed gradual improvement in his vision and 10-month follow-up revealed significantly improved visual function and resolved optic disc edema. This case report adds significant optic disc edema to the clinical characteristics of TON. TON should be suspected in any patient on this medication with a new optic neuropathy and negative workup for infectious or inflammatory causes. Discontinuation of the medication and change to cyclosporine can result in improvement in vision.
Introduction

Tacrolimus, also known as Fujimycin or FK506, is a potent and effective immunosuppressive agent produced from the fungus Streptomyces tsukbensis. Although tacrolimus has several off-label uses, it is mainly utilized after solid organ transplantation to reduce the risk of organ rejection [1–3]. Similar to cyclosporine, through the inhibition of calcineurin phosphatase, tacrolimus inhibits cytotoxic lymphocytes, which are primarily responsible for graft versus host disease [1, 4, 5]. There are a number of cytokines and interleukins that are reduced due to tacrolimus, further dampening the immune response [1, 5]. Tacrolimus has several well-known side effects, but tacrolimus optic neuropathy (TON) is rare. We report a patient status post-cardiac transplantation on tacrolimus therapy who developed severe optic disc edema with progressive asymmetric visual loss. Optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) confirmed the most severe optic disc edema ever reported for this condition. Our patient illustrates that visual loss associated with tacrolimus toxicity can be accompanied by significant optic disc edema and a visual field that simulates papilledema.

Case Report

A 60-year-old man presented with a 5-month history of gradual-onset, progressive blurred vision in his left eye and a 10-day history of blurred vision in his right eye. He denied any symptoms suggestive of raised intracranial pressure including no headache or pulsatile tinnitus. He had a past medical history of a cardiac transplant 6 months prior to presentation for ischemic cardiomyopathy, chronic kidney disease secondary to cardiorenal syndrome. His oral medications included tacrolimus 3 mg BID, prednisone 7.5 mg PO daily, mycophenolate sodium 360 mg BID, voriconazole 200 mg BID, pantoprazole 40 mg daily, pravastatin 20 mg daily, bisoprolol 2.5 mg daily. Ophthalmological examination revealed a visual acuity of 20/30 in the right eye (OD) and 20/50 in the left eye (OS) and a left relative afferent pupillary defect. Humphrey visual field testing revealed a constricted visual field OD and an enlarged blind spot and nasal step OS (Fig. 1b). Dilated fundus examination showed significant bilateral optic disc edema that was more pallid OS (Fig. 1a). OCT RNFL demonstrated an average thickness of 442 μm OD and 330 μm OS (Fig. 1c). The top differential diagnosis considered was chronic papilledema given the characteristic visual field changes, medication-toxicity, or infection.

He underwent magnetic resonance imaging of the brain, magnetic resonance venography, which was normal and showed no signs of raised intracranial pressure including no distal transverse sinus stenosis (Fig. 2). He underwent a lumbar puncture in the left lateral decubitus position, which demonstrated an opening pressure of 12 cm of water, 3 nonerythroid cells, normal glucose and protein. Cerebrospinal fluid was negative for cryptococcal antigen, varicella zoster virus, VDRL and fungal culture was negative. A repeat lumbar puncture 2 weeks later showed an opening pressure of 14 cm of water with normal cerebrospinal fluid contents. Blood work revealed a hemoglobin of 114, creatinine of 181, negative VDRL, tacrolimus level of 13.4 μg/L. Given the exhaustive negative workup, TON was suspected, and the medication was discontinued, and he was transitioned to cyclosporine 150 mg BID. He noticed gradual improvement in his vision and 12-month follow-up revealed improved visual fields (Fig. 1c) and a visual acuity of 20/25 in both eyes. Dilated examination revealed bilateral optic disc pallor without edema and OCT RNFL thickness was 62 μm OD and 61 μm OS (Fig. 3).
Discussion

There are several ocular side effects associated with tacrolimus therapy, but TON is a rare cause of vision loss in patients on this medication. This is often a diagnosis of exclusion since patients on this medication are immuno suppressed and infectious causes must be ruled out. The diagnosis becomes even more challenging when the presentation is unilateral or asymmetric. This case stood out for a number of reasons. The first is the significant optic disc edema with peripapillary hemorrhages. Humphrey 24-2 SITA-Fast visual fields showed an enlarged blind spot OD and significant constriction OS. OCT of the RNFL at presentation revealed a significantly elevated average thickness of 442 μm OD and 330 μm OS.

![Fig. 1](image1.png)

**Fig. 1.** Sixty-year-old man presented with a 5-month history of bilateral vision loss and dilated fundus examination showed bilateral optic disc edema with peripapillary hemorrhages. Humphrey 24-2 SITA-Fast visual fields showed an enlarged blind spot OD and significant constriction OS. OCT of the RNFL at presentation revealed a significantly elevated average thickness of 442 μm OD and 330 μm OS.

![Fig. 2](image2.png)

**Fig. 2.** Magnetic resonance venography (left) was normal without distal transverse sinus stenosis. Magnetic resonance of the brain (right) was normal without tortuosity of the optic nerves/optic nerve sheath or flattening of the posterior globes.
edema at presentation with an OCT RNFL thickness 442 μm OD and 330 μm OS, which is the highest ever reported in this condition. His left eye had worse visual function, but less optic disc edema, which was likely due to optic atrophy given more pallor evident on the optic disc. This was likely why his left eye did not have as much recovery as the right eye. The second is that the patient’s visual fields were highly characteristic of papilledema in that he had a very constricted visual field in the left eye and an enlarged blind spot and nasal step in the right eye. However, we do not believe that this patient’s presentation could be accounted for by papilledema for the following reasons: he had no headache, pulsatile tinnitus, or other symptoms or raised intracranial pressure, he had no signs of raised intracranial pressure on MRI/MRV and it has been stated that almost all cases of papilledema and raised ICP are associated with distal transverse sinus stenosis, which he did not have [6]. He also had two good-quality lumbar punctures in the left lateral decubitus position that showed an opening pressure within the normal range. The only intervention that was introduced was discontinuation of tacrolimus and initiation of cyclosporine and this would not be expected to result in resolution of papilledema. If anything, cyclosporine is known to cause raised intracranial pressure [7]. He also had improvement of his visual function with this medication change.

Currently, 12 cases of TON have been reported in the literature [1–3, 5, 8–14]. Like in our patient, tacrolimus was mainly used in post-transplant patients as an immunosuppressive agent to reduce the risk of graft versus host disease. There was only 1 case reported in a nontransplant patient, where tacrolimus was being used off-label to treat nephrotic syndrome [10]. There was a wide range of treatment doses; however, all reported cases of TON, including our patient, are notable for the absence of toxic blood levels of tacrolimus. Tacrolimus is largely metabolized by cytochrome P4503A in the liver and intestinal mucosa and subsequently excreted in the bile [15]. Despite this, elevated creatinine levels have been associated with higher plasma concentrations of the drug. Nephrotoxicity is typically associated with plasma tacrolimus concentrations of greater than 20 ng/mL. The association between increased creatinine and higher blood concentrations of tacrolimus remains unclear [16].

Our patient developed optic nerve toxicity within 6 months of treatment initiation, which is consistent with other reported cases. The interval between treatment initiation and

**Fig. 3.** Final follow-up at 12 months showing resolved optic disc edema and residual pallor (a). Humphrey 24-2 SITA-Fast visual fields showed improved visual fields (b). OCT of the RNFL showed a reduced overall average thickness due to optic atrophy (c).
symptom onset is highly varied between 2 months and several years. It is unclear whether toxicity is associated with accumulated dose; however, there is no evidence that tacrolimus is stored in the fat or liver [1]. Rasool et al. [1] reported 2 cases with elevated tacrolimus levels associated with elevated creatinine levels months before symptom onset, although the drug levels were still in normal range with the onset of visual dysfunction. This suggests that the drug may be stored and may cause subclinical damage over time.

As in our patient, most cases are bilateral, with some showing a sequential pattern. Kessler et al. [8] could not confirm bilaterality in their report as the patient had severe diabetic retinopathy in the left eye. Three of the 12 previously reported cases are unilateral [3, 10, 12]. The degree of vision impairment varies greatly from mild to severe. Of the cases where visual field testing was complete, none resembled papilledema as seen in our patient.

In TON, the optic nerves may appear normal or be edematous and/or pale. Half of the cases in the current literature note optic disc edema in at least one of the optic nerves, with a few also noting hemorrhage [1, 10–13]. Most notable in our patient is the significant optic disc edema at presentation. Although 2 cases reported had OCT RNFL performed, only one of these cases was in the context of optic disc edema. Demontes et al. [12] reported a patient with unilateral TON presenting with right optic disc edema. OCT RNFL showed thickness of 198 µm in the right eye and 108 µm in the left eye. Rasool et al. [1] also reported a case of unilateral TON with optic disc pallor in the left optic nerve and no edema. OCT RNFL demonstrated evidence of optic nerve atrophy with a reduced thickness in the left optic nerve. The appearance of the optic nerve at presentation is likely influenced by the timing of the examination relative to the development of visual symptoms. Of the cases that preformed MRI, none showed a partially empty sella.

When TON is suspected, tacrolimus is usually discontinued and the patient is placed on an alternative immunosuppressive agent, unless the risk of discontinuing tacrolimus outweighed the benefits. Tacrolimus was not stopped in 2 of the 12 cases, although high-dose corticosteroids were administered [3, 5]. The outcome after tacrolimus discontinuation is varied. However, improvement in vision is not necessarily indicated by the visual acuity alone. Demontes et al. [12], reported improvement in visual fields without significant improvement in visual acuity, suggesting that follow-up on visual fields is important. Early intervention appears to yield more favorable patient outcomes.

The pathophysiological mechanism of tacrolimus toxicity is not well known. There are, however, two main theories proposed: an inflammatory mechanism and a vascular mechanism. Similar to cyclosporine, tacrolimus may have direct neurotoxic effects, which may result in axonal swelling, increased water content, and neural tissue edema [1, 3, 5, 10, 13]. With this, there may be blood-brain barrier breakdown, allowing for the increased passage of lipophilic drugs like tacrolimus [1, 10]. Specifically, due to the high lipid content of the myelin sheath, it becomes an attractive binding site for lipophilic agents, leading to oligodendroglial toxicity [1–3, 10–12]. Rasool et al. [1], reporting a case of TON, confirmed significant myelin loss with preserved axonal elements and no marked vascular changes through an optic nerve biopsy. Cases that show a lack of improvement following tacrolimus discontinuation may be explained by severe oligodendroglial cell damage [1]. The degree of toxicity may be further influenced by CNS pharmacokinetics. Elimination of tacrolimus from the CNS may be impacted by polymorphisms in the ABCB1 protein gene. ABCB1 is a P-glycoprotein multidrug efflux pump expressed on endothelial cells and individuals with these polymorphisms seem to have a greater susceptibility to CNS tacrolimus toxicity independent of plasma drug levels [2]. Vascular mechanisms hypothesized to explain the neurotoxic effect of tacrolimus are consistent with a subacute clinical presentation [12, 13]. They involve modifications to the interactions between prostacyclin and thromboxane A2, including an augmentation of thromboxane A2 levels and resulting in vasoconstriction and relative tissue ischemia [1, 2, 5, 8, 12, 13].
In conclusion, clinicians should be aware that, although rare, patients on tacrolimus therapy face a risk of vision loss from tacrolimus toxicity. Our case demonstrates that significant optic disc edema can be seen in this context and the timely dose reduction or discontinuation of tacrolimus can revert the sight-threatening complication.

Statement of Ethics

This report was reviewed by the University of Toronto Research Ethics Board and ethics approval exemption was provided. The patient has given their written informed consent to publish this case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Conception and design (Jonathan A. Micieli), data collection (Isra M. Hussein), drafting of the manuscript (Isra M. Hussein), critical revisions (Jonathan A. Micieli), and final approval (Isra M. Hussein and Jonathan A. Micieli).

Data Availability Statement

All data generated and analyzed in this case report are included in the manuscript. Additional questions regarding data can be directed to the corresponding author.

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