



Tacrolimus induced optic neuropathy in post-lung transplant patients: A series of 3 patients

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ABSTRACT

Purpose: Tacrolimus is a commonly used immunosuppressant medication after lung transplantation. In rare cases, tacrolimus causes a medication-induced optic neuropathy (TON) that can lead to significant vision loss.

Observations: In this series, we describe three cases of TON, 1–10 years after medication use. Two patients were young (22yr and 33yr) females with cystic fibrosis. The last case was a 65yr male with idiopathic pulmonary fibrosis. In 2/3 cases tacrolimus serum levels were normal. Visual acuity ranged from 20/20 to 20/300, and vision loss occurred acutely to sub-acutely, over a span of 2–3 months.

Conclusions and importance: As presented here, TON can be highly variable. MRI findings are often non-specific, from normal brain findings to extensive white matter changes. There remains an unclear association with graft-versus-host disease and reduced kidney function. Visual findings are often subtle, including color vision aberration and peripheral visual field deficits, both of which usually require an ophthalmologic evaluation. When diagnosed in a timely fashion, TON is at least partially reversible in up to half of all cases. While rare, the cases described here support post-lung transplant ophthalmologic evaluation in those taking high-risk medications.

Introduction

Since its approval in 1997 tacrolimus is now used in upwards of 93% of all post-lung transplant patients for maintenance immunosuppression.¹ Tacrolimus induced optic neuropathy (TON) remains an extremely rare and elusive diagnosis, with only 13 cases published in the literature.² Due to its infrequency, it remains a diagnosis of exclusion, after infectious, inflammatory, and neoplastic causes are evaluated. In many cases, the diagnosis remains presumptive. The exact mechanism remains unclear. Some authors support the possibility of an ischemic process, with two studies finding a delay or absence in vascular circulation on fluorescein angiography.^{3–8} In contrast, biopsy of the optic nerve has demonstrated extensive demyelination without ischemic insult, and cortical cultures have shown direct oligodendrocytic toxicity and death.^{9,10} TON is likely distinct from cyclosporine-induced optic neuropathy, as patients who have been switched to cyclosporine due to suspected TON have demonstrated visual improvement.⁶

Clinically, TON usually presents as a slow reduction in visual acuity,

progressive visual field deficits, and/or dyschromatopsia, though acute changes have also been described. MRI can show optic nerve and other white matter lesions, even in the context of normal tacrolimus levels.^{9,11} While tacrolimus can also affect the visual system from posterior involvement of the visual tracts or occipital lobes, due to tacrolimus-induced posterior reversible encephalopathy syndrome (PRES), TON is usually associated with optic nerve edema or pallor.² Through an institutional review board-approved process (AAAS6456), we reviewed all post-lung transplant inpatient consults performed at our institution between 2014 and 2019. Of 65 consultations, 3 patients were found to have tacrolimus-induced optic neuropathy. This report does not contain any personal information that could lead to the identification of these 3 patients.

Abbreviations: ACR, acute cellular rejection; AKI, acute kidney injury; CNS, central nervous system; Cr, creatinine; CT, computed tomography; FLAIR, fluid attenuated inversion recovery; GVHD, graft versus host disease; JC, John Cunningham; MRI, magnetic resonance imaging; OCT, optical coherence topography; PET, positron emission tomography; PRES, posterior reversible encephalopathy syndrome; TON, tacrolimus optic neuropathy; VZV, varicella zoster virus.

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Findings

Case 1

A 33-year-old female with a past medical history of diabetes and cystic fibrosis, status post double lung transplant 11 years prior, presented to the neurology service for non-specific headache, vision loss (blurriness, darkness, loss of peripheral vision), weakness, and lethargy. She had several prior admissions for headache, neck pain, and subjective fever. During these admissions, repeat lumbar punctures, along with extensive encephalitis panels, were unremarkable. A previous MRI, however, demonstrated new T2/FLAIR abnormalities along the optic chiasm and proximal optic tracts, hypothalamus, and cerebellum. Based on these findings her tacrolimus dose of 0.5mg/day was discontinued, even though she had remained within therapeutic range (5–20ng/ml). Her creatinine (Cr) function at that time was consistent with acute kidney injury (AKI) of 2.51.

3 months later, on presentation to our institution, she reported continued worsening of her visual symptoms over the course of 2–3 months. On exam, her visual acuity was 20/300 in the right eye and 20/200 in the left eye. She had severe dyschromatopsia on Hardy-Rand-Rittler color plates (0/12 in both eyes). A 24–2 visual field (Fig. 1) demonstrated poor reliability, but suggested bitemporal field loss with significant field constriction. Dilated fundus examination was notable for optic nerve pallor and atrophy. This was confirmed on optical coherence tomography (OCT), which demonstrated diffuse ganglion cell layer loss.

During this admission she was diagnosed and treated for a superficial cellulitis of the hand, which improved after intravenous vancomycin. A broader infectious examination - including coccidiomycosis, syphilis, tuberculosis, John Cunningham virus, cytomegalovirus, and bartonella - was negative. Inflammatory and neoplastic evaluation, including a PET scan, were unremarkable. Kidney function improved from her prior admissions (Cr of 1.50) and she underwent a repeat brain, orbit, and spinal MRI. Her MRI abnormalities remained unchanged, with persistent hyperintensity of the optic chiasm (Fig. 2). Her visual symptoms, which persisted after treatment of her cellulitis, along with her neuroradiologic findings, were deemed most consistent with a severe and atypical tacrolimus-induced toxicity.

Case 2

A 65-year-old male with a history of idiopathic pulmonary fibrosis complicated by pulmonary hypertension, underwent a single left lung

transplantation 2 years prior to admission. His immediate post-transplant course was complicated by cryptococcal meningitis, which resolved after treatment, with no residual deficits. His immunosuppressive regimen included tacrolimus at an alternating dose of 0.5mg and 0.25mg twice a day, prednisone 10mg daily, and cellcept 500mg three times a day. On admission, he presented with an acute change in mental status and slurring of speech and was found to have maculopapular lesions respecting the midline, consistent with varicella zoster virus (VZV) in the trigeminal V1 distribution.

At the time the patient also complained of blurry vision in his left eye, which warranted an ophthalmology consultation. On exam, vision was 20/50 in both eyes and was otherwise unremarkable, notable only for tilted optic discs, a benign finding. CT imaging was negative for stroke, but a lumbar puncture was VZV polymerase chain reaction positive, confirming CNS involvement. MRI brain revealed diffuse pachymeningeal enhancement. His titers resolved on intravenous antiviral treatment with acyclovir, yet he remained lethargic and deconditioned. On treatment, he had a persistently mild AKI (Cr of 1.30–1.60). After several weeks, his condition improved and the patient returned to baseline.

One month later, however, he was reexamined for a subjective worsening of vision, now in the right eye. At this point, there was a decrease in right eye vision, from 20/50 to 20/70, a new right afferent pupillary defect, and a new temporal visual field deficit. Optic nerve exam demonstrated newfound pallor in both eyes, consistent with a sub-acute to chronic process. Color vision was reduced on Ishihara color plates, 1.5/14 right eye and 11.5/14 left eye. Optic nerve atrophy was confirmed on OCT, which demonstrated diffuse, asymmetric, nerve fiber layer loss (right > left) (Fig. 3). There was no evidence of vasculitis, or any MRI findings suggestive of leptomeningeal spread involving the optic nerves. Systemic infectious work-up remained negative and metabolic causes such as folate or vitamin B12 deficiency were excluded. Kidney function had normalized with fluid management, Cr 1.10–1.20, while being maintained on intravenous acyclovir 500mg twice a day. The interdisciplinary teams agreed that these findings were most consistent with TON, and his tacrolimus dosing was discontinued.

Case 3

A 23-year-old female with cystic fibrosis, status post bilateral lung transplant one-year prior, was transferred to our medical intensive care unit due to acute on chronic respiratory failure. Prior to admission, her home dose of tacrolimus was 0.5mg daily and prednisone 10mg daily. On admission, she was intubated for acute respiratory distress

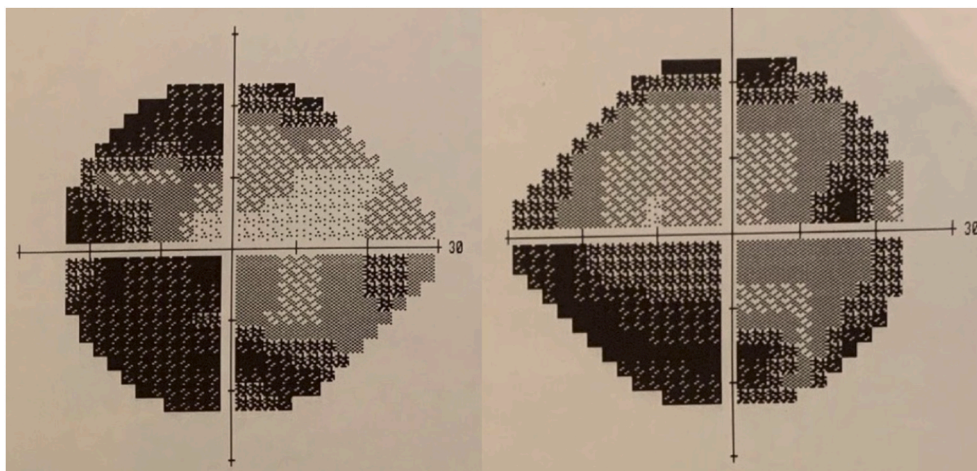


Fig. 1. Bitemporal hemianopia on an automated 24–2 visual field in Case 1.

Legend: Left = Right Eye, Right = Left Eye. Black and grey are regions of reduced sensitivity to visual stimuli when compared to normative data. Note the right worse than left visual field deficits. This visual field demonstrates an incongruent bitemporal hemianopia with additional infero-nasal deficits in both eyes.

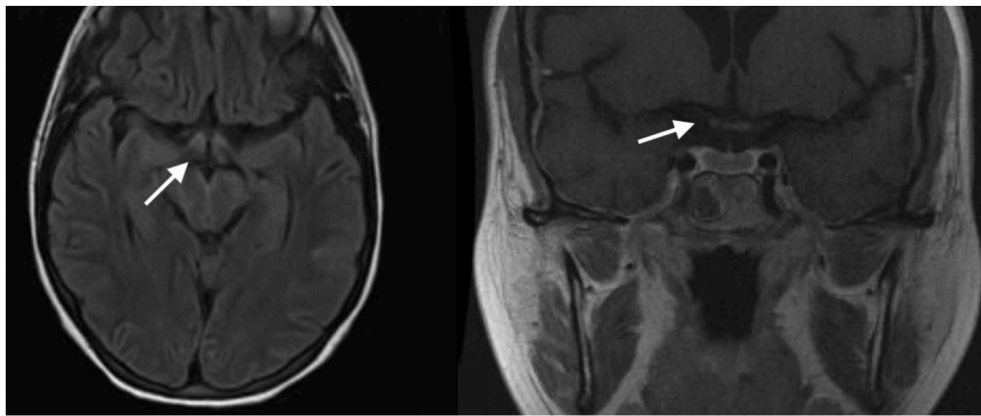


Fig. 2. FLAIR hyperintensity of the optic chiasm in Case 1.

Legend: Left = an axial image with hyperintensity (arrow) over the optic chiasm consistent with TON. Right = a coronal image highlighting the same persistent hyperintensity (arrow).

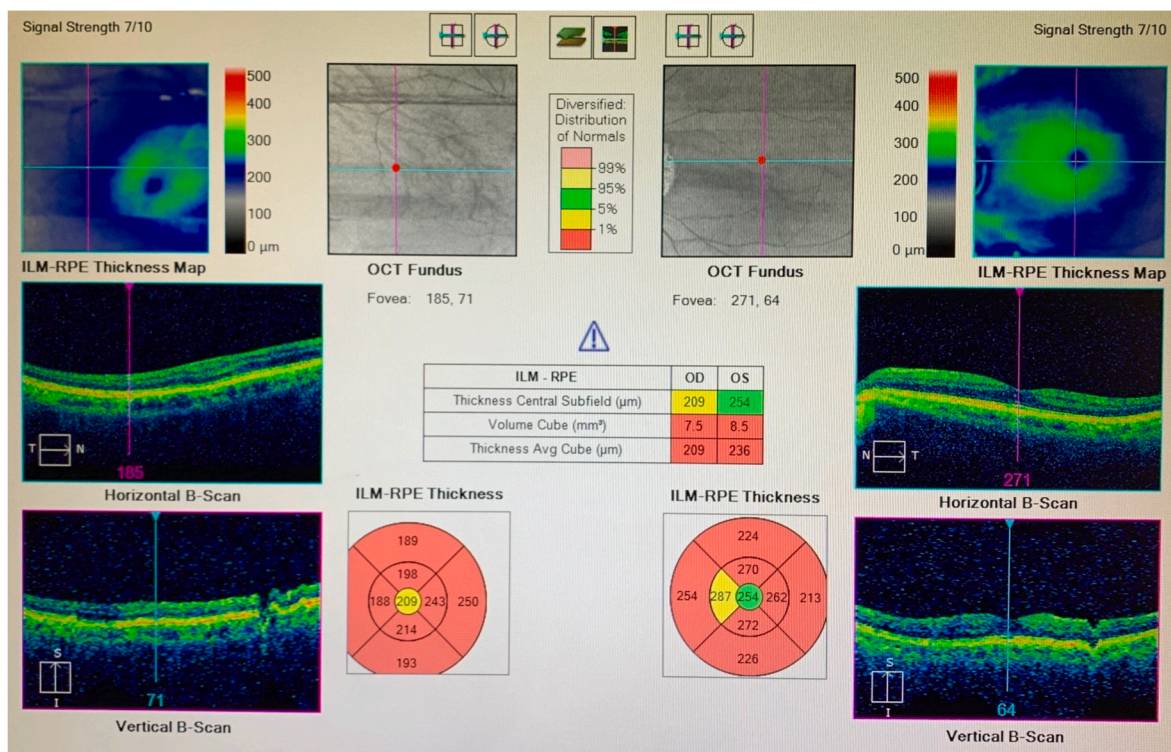


Fig. 3. Macular thickness on optical coherence tomography in Case 2.

Legend: Optical coherence tomography provides a detailed view of each layer of the retina. A thin retina is noted by the ‘red’ values in the two quantitative circles, when compared to normative data. While the right eye is off-center (see top box, left side), a qualitative assessment of the retinal layers in the images provided are consistent with retinal nerve fiber layer loss, which occurs in tacrolimus-induced nerve damage. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

syndrome. Infectious work up (including bronchoalveolar lavage cultures) remained negative, prompting a diagnosis of acute cellular rejection (ACR). Her tacrolimus level rose from 17 to 53 ng/ml acutely and was held. Of note, she’d had a prior admission one year ago for acute tacrolimus toxicity resulting in AKI, which had resolved. Creatinine on this admission was 2.37, consistent with AKI.

She was treated with pulse dose steroids, intravenous immunoglobulin and plasma exchange, and Thymoglobulin with eventual clinical improvement. She was extubated 5 days later. At one month, she reported a new right temporal visual field deficit. On exam, vision was 20/20 in both eyes. Visual field was full (Fig. 4A–B). Her dilated exam demonstrated temporal nerve pallor in the right eye and diffuse optic

atrophy in the left eye. This was confirmed on optical coherence tomography, which demonstrated asymmetric nerve loss (left > right) and appeared consistent with TON (Fig. 4C–D).

She was scheduled for a wider visual field test (Goldmann) to assess for far temporal visual field deficits but developed bifrontal seizures and altered mental status requiring admission to the neuro-intensive care unit. MRI brain demonstrated white matter changes consistent with PRES. Tacrolimus was discontinued with eventual improvement in both her symptoms and brain lesions. She remained hospitalized for another month due to the re-development of ACR requiring further medication management. She was subsequently discharged home on cyclosporine 375mg twice a day and oral prednisone 50mg daily, after a 3-month

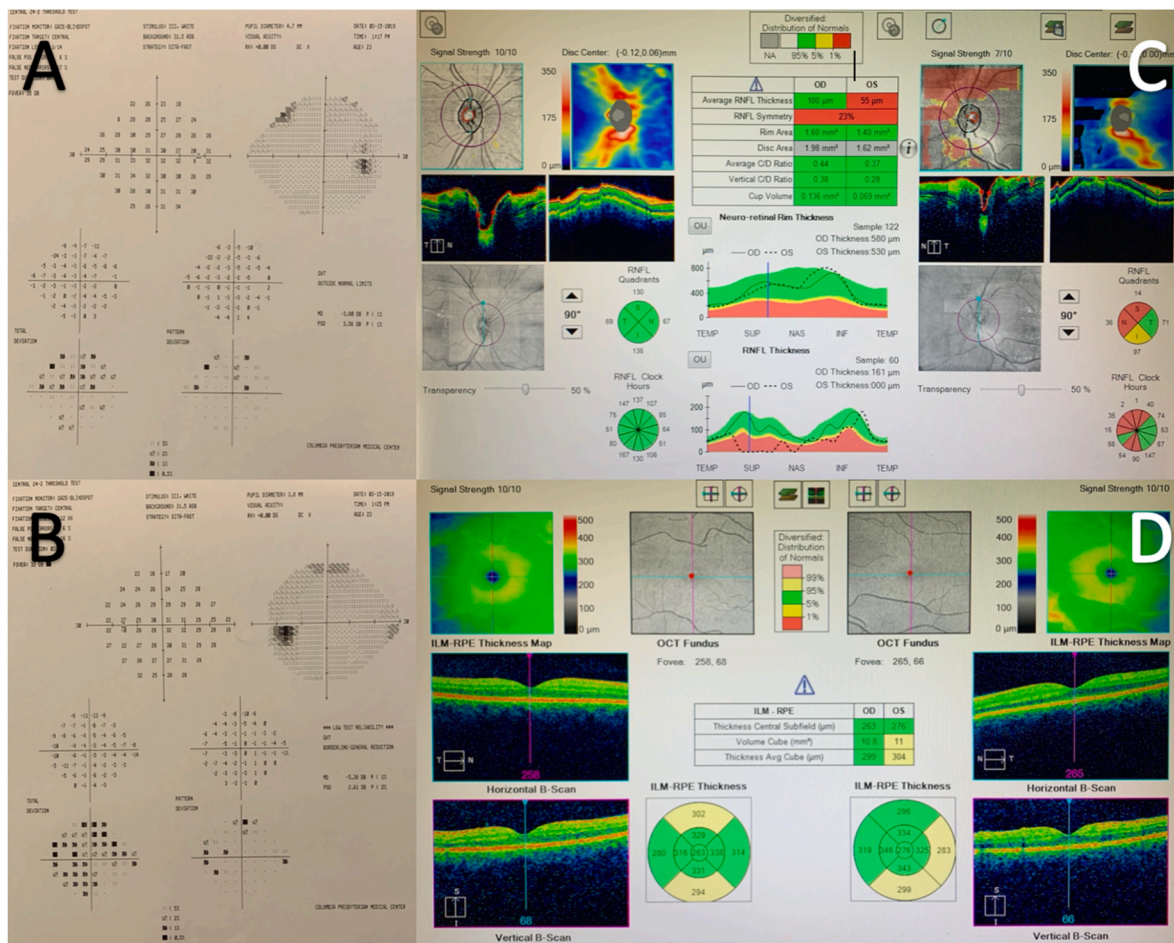


Fig. 4. 24–2 visual fields and optical coherence tomography in Case 3. Legend: Panel A–B demonstrates a normal right and left visual field. This would not capture any far temporal peripheral field deficits, since a 24-2 measures only the central 24° of the visual field. In Panel C are quantitative measures of optic nerve health. The left eye (OS) is in red, indicating nerve fiber layer loss. While the left eye was convoluted by artifact (black components of the top right picture), thinning is further confirmed in Panel D which demonstrates a reduced average thickness of the macula. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

hospital stay.

Discussion

The diagnosis of tacrolimus induced optic neuropathy is clinically challenging. Previous cases report the development of TON anywhere from 2 months to 5 years after initiation.² Toxicity usually occurs at a plasma level >20 ng/ml but can occur at normal or even sub-therapeutic levels (Table 1).¹² Vision loss can be sudden, over a few days, or gradual (>1 year). Like the cases described herein, in which one patient maintained 20/20 vision while another declined to the 20/200–300 range, prior studies have reported 20/20 to light perception vision. Usually, TON is a bilateral process, but can affect one optic nerve prior to the other, as with case 2.² Similar to case 1, visual deterioration can continue, even after tacrolimus discontinuation.⁵

MRI findings also vary considerably between patients, from extensive white matter changes to normal brain findings.² Only 35.7% of patients with neurologic symptoms from tacrolimus have white matter abnormalities. Isolated cases of brain stem involvement have also been reported.^{13,14} In one study, 2/5 patients with tacrolimus toxicity had no reversal of white matter abnormalities upon discontinuation, even in the context of clinical improvement.¹⁵ This appears similar to case 1 in which white matter lesions persisted after medication discontinuation.

Tacrolimus, even after its metabolism by the liver, can maintain biologic activity. Combined with a wide range in half-life (3.5–40.5

hours), normal plasma levels may not accurately reflect a patient’s tacrolimus burden.^{14,16} Studies have also found different genetic predispositions to drug pharmacokinetics that may increase susceptibility to CNS penetration, and presumably, optic nerve damage.¹⁷ One case series suggested that transient breakdown in the blood-brain barrier due to graft-versus-host disease (GVHD) may also allow for increased CNS penetration.² This concept has been previously considered in other instances of rare medication toxicity, such as eye-drop induced visual hallucinations.¹⁸ GVHD is also known to reduce tacrolimus clearance by 20% due to hepatic dysfunction and by 40% from acute kidney injury in patients post hematopoietic transplantation.¹⁰ The second case in this series was diagnosed with VZV meningitis, which can also result in blood brain barrier disruption. This mechanism may be fundamentally similar to that of GVHD.¹⁹ Case 3 was particularly interestingly due to the subsequent development of PRES after a diagnosis of TON. Shao et al. describes a similar case, in which TON pre-dated the development of PRES.⁸ TON may be an early sign of vascular dysregulation and blood brain barrier dysfunction, and suggestive of impending posterior involvement.

Case 3 was also convoluted by a history of significant nephrotoxicity and elevated serum tacrolimus level on presentation. The relationship between tacrolimus toxicity and renal function remains unclear, as tacrolimus is not cleared by the kidney. However, several studies have suggested an association between rising creatinine levels and the subsequent development of TON, even with AKI that occurs months prior to

Table 1
Published Cases of Tacrolimus-Induced Optic Neuropathy (including the present study).

Source	Age/ Sex	Duration	Dose	Plasma Level	Onset	Visual Acuity	Color Vision	Visual Field	Pupils	Eye	Transplant
Brazis et al., 2000	58/M	2mo	4mg QD	NR	~3mo	OD: 20/ 20 OS: 20/ 100	OD: 9.5/ 10 OS: 3/10	OD: Superior arcuate OS: Infe- ro- altitudinal	Left APD	OU	Liver
Venneti et al., 2010	63/M	5yr	NR	8.8 µg/L	~2mo	OD: 20/ 70 OS: HM	Reduced	OD: Inferonasal OS: Unable	Sluggish	OU	Renal
Lake et al., 2003	38/M	NR	4mg QD	NR	~12mo	OD: 3/60 OD: 2/60	NR	OD: Normal OS: Normal	No APD	OU	Pancreas
Ascaso et al., 2012	56/F	6mo	1.5mg QD	1.9 ng/ml	Sudden	OD: 20/ 20 OS: LP	OS: None	NR	Left APD	OS	Liver
Akers et al., 2009	47/F	NR	NR	5.7ng/ml	~4 days	OD: 20/ 25 OS: 20/40	OD: 5/10 OS: 1/10	OD: Normal OS: Inferonasal	NR	OS	Renal
Canovai et al., 2019	51/M	3.5yr	2mg BID	4.4 µg/L	~2wks	OD: CF OS: CF	NR	OD: Central scotoma OS: Central scotoma	No APD	OU	Multi-visceral
Shao et al., 2012	30/M	3mo	NR	13.9ng/ml	~5 days	OD: HM OS: HM	NR	NR	Sluggish No APD	OU	Small Bowel
Yun et al., 2010	54/M	6mo	2.5mg BID	6.2mg/L	~3mo	OD: CF OS: CF	NR	OD: Cecocentral scotoma OS: Cecocentral scotoma	Left APD	OS	Liver
Kessler et al., 2006	51/F	5mo	2mg QD	12.9ng/ml	“gradual”	OD: 20/ 100	NR	NR	NR	OD	Pancreas
Gupta et al., 2012	35/F	2yr	1mg BID	NR	~2wks	OD: 6/6 OS: 6/6	NR	OD: Normal OS: Inferonasal	Left APD	OS	Nephrotic Syndrome
Rasool et al., 2018	55/M	4yr	2mg BID	8ng/ml	~ few days	OD: 20/ 200 OS: 20/25	OD: Normal OS: Reduced	OD: Diffuse depression OS: Superior/ Inferior nasal	Right APD	OU	BMT
Rasool et al., 2018	66/M	5yr	0.5mg BID	10ng/ml	~3mo	OD: 20/ 25 OS: 20/ 100	OD: Reduced OS: Reduced	OD: Temporal- inferior OS: Inferior arcuate	No APD	OU	PBSCT
Rasool et al., 2018	63/M	4mo	0.5mg QD	5ng/ml	~3 days	OD: 20/ 20 OS: 20/50	OD: NR OS: Reduced	OD: Diffuse OS: Nasal loss	Left APD	OU	BMT
Current Study	33/F	10yr	0.5mg QD	12.2ng/ml	~2-3mo	OD: 20/ 300 OS: 20/ 200	OD: 0/12 OS: 0/12	OD: Temporal field loss OS: Temporal field loss	No APD	OU	Lung
Current Study	65/M	2yr	0.5mg/ 0.25mg BID	8.3ng/ml	~few days	OD: 20/ 50 OS: 20/50	OD: 1.5/ 14 OS: 11.5/ 14	OD: Temporal defect OS: Normal	Right APD	OU	Lung
Current Study	23/F	1yr	0.5mg QD	53ng/ml	Sudden	OD: 20/ 20 OS: 20/20	OD: 6/6 OS: 6/6	OD: Normal OS: Normal	No APD	OU	Lung

symptom development.² While the other two cases did not present with elevated serum levels or significant nephrotoxicity, both had transient AKI, prior to or during the development of visual symptoms.

Conclusions

To our knowledge, this is the first series to report TON in lung transplant recipients (Table 1). These three cases occurred out of 65 consults, suggesting a higher incidence than expected. Our tertiary care center, however, may be biased towards a higher degree of comorbidity amongst the post-transplant population. Risk stratification is hampered by a wide range of reported doses, duration of use, and normalcy of plasma levels (Table 1). Unlike haemopoietic stem cell transplantation, there are no set guidelines for routine post-lung transplant ophthalmology follow-up.²⁰ In the context of several other medical concerns, continued ophthalmologic follow-up after discharge is likely overlooked by the primary team. This series emphasizes the need for lung transplant services to consider establishing guidelines for outpatient post-transplant ophthalmic follow-up. Due to the presumptive nature of

a TON diagnosis, there is likely a subset of patients who remain undiagnosed due to the subtle nature of some early cases, which require a more specialized ophthalmologic approach, including serial color vision and visual field testing. TON may be reversible in ~50% of cases with appropriate care, and immediate discontinuation is necessary to prevent continued visual decline, further highlighting the importance of early detection.²

Patient consent

As per institutional review board approval, written consent to publish this case series was not required. This report does not contain any personal identifying information.

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Authorship

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

Declaration of competing interest

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References

- Adult lung transplantation statistics. Available from: <http://www.isHLT.org/registries/slides.asp?slides=heartLungRegistry>; 2016.
- Rasool N, Boudreaux K, Lessell S, et al. Tacrolimus optic neuropathy. *J Neuro Ophthalmol*. 2018 Jun 1;38(2):160–166.
- Bouvier N, Flinois JP, Gilleron J, et al. Cyclosporine triggers endoplasmic reticulum stress in endothelial cells: a role for endothelial phenotypic changes and death. *Am J Physiol-renal*. 2009 Jan;296(1):F160–F169.
- Stein DP, Lederman RJ, Vogt DP, et al. Neurological complications following liver transplantation. *Ann Neurol*. 1992 Jun;31(6):644–649.
- Brazis PW, Spivey JR, Bolling JP, et al. A case of bilateral optic neuropathy in a patient on tacrolimus (FK506) therapy after liver transplantation. *Am J Ophthalmol*. 2000 Apr 1;129(4):536–538.
- Wilson SE, Aksamit AJ, Wiesner RH, et al. Cyclosporin A-induced reversible cortical blindness. *J Clin Neuro Ophthalmol*. 1988 Dec;8(4):215–220.
- Yun J, Park KA, Oh SY. Bilateral ischemic optic neuropathy in a patient using tacrolimus (FK506) after liver transplantation. *Transplantation*. 2010 Jun 27;89(12):1541–1542.
- Shao X, He Z, Tang L, Gao L. Tacrolimus-associated ischemic optic neuropathy and posterior reversible encephalopathy syndrome after small bowel transplantation. *Transplantation*. 2012 Nov 15;94(9):e58–60.
- Venneti S, Moss HE, Levin MH, et al. Asymmetric bilateral demyelinating optic neuropathy from tacrolimus toxicity. *J Neurol Sci*. 2011 Feb 15;301(1-2):112–115.
- McDonald JW, Goldberg MP, Gwag BJ, et al. Cyclosporine induces neuronal apoptosis and selective oligodendrocyte death in cortical cultures. *Ann Neurol*. 1996 Nov;40(5):750–758.
- Akagi T, Manabe S, Ishigooka H. A case of cyclosporine-induced optic neuropathy with a normal therapeutic level of cyclosporine. *Jpn J Ophthalmol*. 2010;54(1):102.
- Jacobson P, Ng J, Ratanatharathorn V, et al. Factors affecting the pharmacokinetics of tacrolimus (FK506) in hematopoietic cell transplant (HCT) patients. *Bone Marrow Transplant*. 2001 Oct;28(8):753–758.
- Wu Q, Marescaux C, Qin X, et al. Heterogeneity of radiological spectrum in tacrolimus-associated encephalopathy after lung transplantation. *Behav Neurol*. 2014;2014.
- Saadi A, Schmahmann JD. Pearls & Oysters: tacrolimus neurotoxicity presenting as an isolated brainstem lesion. *Neurology*. 2016 Mar 15;86(11):e109–e111.
- Appignani BA, Bhadelia RA, Blacklow SC, et al. Neuroimaging findings in patients on immunosuppressive therapy: experience with tacrolimus toxicity. *AJR Am J Roentgenol*. 1996 Mar;166(3):683–688.
- Jain AB, Abu-Elmagd K, Abdallah H, et al. Pharmacokinetics of FK506 in liver transplant recipients after continuous intravenous infusion. *J Clin Pharmacol*. 1993 Jul;33(7):606–611.
- Yamauchi A, Ieiri I, Kataoka Y, et al. Neurotoxicity induced by tacrolimus after liver transplantation: relation to genetic polymorphisms of the ABCB1 (MDR1) gene. *Transplantation*. 2002 Aug 27;74(4):571–572.
- Nanda T, Rasool N, Callahan AB, et al. Ophthalmic timolol hallucinations: a case series and review of the literature. *J Glaucoma*. 2017 Sep 1;26(9):e214–e216.
- Hoyer C, Eisele P, Ebert AD, et al. Blood-CSF-barrier dysfunction is a marker for encephalitic involvement in patients with aseptic meningitis/meningoencephalitis. *J Clin Virol*. 2016 Nov 1;84:82–86.
- Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Hemtol Oncol Stem Cell Ther*. 2012 Jan 1;5(1):1–30.