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Bilateral Optic Neuropathy with Optic Disc Swelling Following Lithium Dose Escalation, Progressing Despite Normalization of Serum Lithium: A Case Report

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Abstract

Background: Lithium is the primary mood stabilizer used in bipolar disorder. Its renal, thyroid and neurological toxicities are well documented, but optic nerve involvement is rare and its mechanism uncertain. **Case summary:** A 37-year-old woman on long-term lithium developed progressive bilateral visual loss and headache after her dose was increased from 400 to 600 mg/day. A 12-hour trough serum lithium of 1.5 mmol/L was recorded at a general hospital, without systemic signs of toxicity. After dose reduction the level fell to 0.5 mmol/L, but three days after discharge her vision deteriorated to hand movements in both eyes, with bilateral Frisén grade 2 optic disc swelling and grossly delayed pattern-reversal visual evoked potentials (VEP). Neuroimaging including magnetic resonance venography was normal, and the infectious and autoimmune screen was negative apart from a weakly positive myelin oligodendrocyte glycoprotein antibody (MOG-IgG). Lithium was stopped and no corticosteroids were given. Tomography improved within three days and reached 6/6 and 6/7.5 by day 22, with resolution of disc swelling on optical coherence tomography (OCT). At approximately 4 months acuity was 6/6 in both eyes, with mild temporal disc pallor and reduced macular thickness. The Naranjo score was 6 (probable adverse drug reaction). **Conclusion:** Optic neuropathy followed a period of elevated lithium exposure and continued to progress after serum lithium had returned to the therapeutic range, improving only after lithium was withdrawn. Clinicians should evaluate visual symptoms promptly in patients taking lithium, including those whose serum levels are within the target range.

Keywords: serum lithium, toxic optic neuropathy, optic disc swelling, adverse drug reaction, visual evoked potential, bipolar disorder.

Introduction

Lithium is an established and effective long-term treatment for bipolar disorder and reduces the risk of relapse [1,2]. It has a narrow therapeutic index, and its adverse effects on the kidney, thyroid and nervous system are well described [2,3]. Ocular adverse effects, particularly those involving the optic nerve, are rare. Toxic optic neuropathies are most often associated with drugs such as ethambutol, amiodarone and linezolid [4], whereas the reported optic nerve effects of lithium consist mainly of optic disc swelling in the setting of lithium-associated intracranial hypertension [5-7]. Separately, lithium neurotoxicity is recognized at serum concentrations within or below the therapeutic range, and may persist after serum levels have fallen [8-10].

We report a patient who developed bilateral optic neuropathy with optic disc swelling after an increase in lithium dose that was accompanied by an elevated serum concentration. Her vision continued to deteriorate after the serum level had returned to the therapeutic range and improved only after lithium was withdrawn. This report follows the CARE guidelines [11].

Case Description

Patient information: A 37-year-old woman with a 10-year history of bipolar affective disorder had been treated with lithium carbonate 400 mg/day for three years, together with diazepam 5 mg at night. Historical serum lithium levels had consistently been below 0.9 mmol/L. She took no other regular or over-the-counter medications, including non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors or diuretics. Approximately two months before presentation, her lithium dose was increased to 600 mg/day because of a psychiatric relapse. Bilateral blurring of vision and headaches began approximately five weeks before presentation, that is, about three to four weeks after the dose increased, and progressed steadily thereafter. The full clinical timeline is summarised in Table 1.

Initial assessment at a general hospital: She was admitted to a general hospital, where a 12-hour trough serum lithium level was 1.5 mmol/L. There were no systemic features of lithium toxicity (no tremor, ataxia, confusion or gastrointestinal symptoms) and no history of dehydration, vomiting or diarrhoea. Renal function, serum sodium and thyroid function were normal. Blood pressure and body mass index were within normal limits. Computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) of the brain and orbits, together with magnetic resonance venography (MRV), were normal, with no optic nerve enhancement and no imaging signs of raised intracranial pressure. A lumbar puncture performed in the sitting position recorded an opening pressure of 22 cm H2O; because the pressure was not measured in the lateral decubitus position, this value cannot be interpreted as raised intracranial pressure. Cerebrospinal fluid (CSF) protein, glucose and cell count were normal. Lithium was reduced to 200 mg/day on hospital day 2, and the trough level was 0.5 mmol/L on day 3. An ophthalmology review was reported as unremarkable. In view of her recent relapse and the normalized serum level, she was discharged on 400 mg/day by the treating team.

Clinical findings at presentation: Three days after discharge her vision deteriorated further and she was referred to the Royal Victoria Eye and Ear Hospital (day 0), where visual acuity was hand movements in both eyes. Intraocular pressure was normal bilaterally. The pupils were mid-dilated with sluggish light reactions and no relative afferent pupillary defect (RAPD). Fundoscopy showed bilateral Frisén grade 2 optic disc swelling12 without hemorrhages or cotton-wool spots (Figure 1). Fundus autofluorescence (AF) showed no optic disc drusen, and fundus fluorescein angiography (FFA) showed no disc leakage. She reported no pulsatile tinnitus, diplopia, transient visual obscurations or pain on eye movement, and there was no sixth nerve palsy. Color vision and perimetry could not be performed because of the reduced acuity. Optical coherence tomography (OCT) confirmed marked peripapillary retinal nerve fiber layer (RNFL) thickening (average 201 μm right, 175 μm left; Table 2).

Diagnostic assessment and therapeutic intervention: She was admitted for urgent evaluation. Serum lithium on admission was 0.5 mmol/L, and lithium was discontinued on the day of

presentation in view of suspected drug-induced optic neuropathy. Pattern-reversal visual evoked potentials (VEP), recorded on day 2, showed grossly delayed P100 latencies in both eyes; the numerical latency and amplitude values were not retrievable from the archived report. The pattern electroretinogram (PERG) and flash VEP were reported as within normal limits. The infectious and autoimmune screen including ANA, ANCA, ACE, syphilis serology, ESR/CRP, vitamin B12 was negative, apart from a weakly positive myelin oligodendrocyte glycoprotein antibody (MOG-IgG) on a live cell-based assay; the test was not repeated, and aquaporin-4 antibodies were not tested. Her psychiatrist started olanzapine 10 mg on day 2. No corticosteroids were given at any stage.

Follow-up and outcomes: Vision improved progressively after lithium was stopped. On day 3, visual acuity was 3/36 in the right eye and 2/60 in the left, Ishihara color vision was 7/15 and 8/15 respectively, and she was discharged. At review on day 22 she reported substantial subjective improvement. Visual acuity was 6/6 right and 6/7.5 left, color vision was 15/15 in both eyes, the pupils reacted normally, and Humphrey visual field (HVF) 30-2 testing was normal. OCT showed resolution of disc swelling, with average RNFL thickness of 104 μm right and 101 μm left, within normal limits. At approximately 4 months after presentation (day 134), left visual acuity had improved further to 6/6, so that acuity was 6/6 in both eyes. Mild bilateral temporal disc pallor was noted (Figure 2), and average macular thickness had fallen to 261 μm right and 253 μm left, with the left outer macular ring below the first percentile of the normative database, consistent with inner retinal thinning (Table 2, Figure 3). Optic nerve function remained clinically preserved. She continues to be followed in ophthalmology and psychiatry clinics.

Patient perspective: From the patient's perspective, the loss of vision was frightening and frustrating, and the steady improvement after lithium was stopped was a great relief.



Figure 1: Ultra-widefield fundus images (Optos) of the right (RE) and left (LE) eyes on the day of presentation (day 0), showing bilateral optic disc swelling with blurred disc margins. The corresponding peripapillary RNFL thickening measured by OCT is shown in Figure 3 and Table 2.

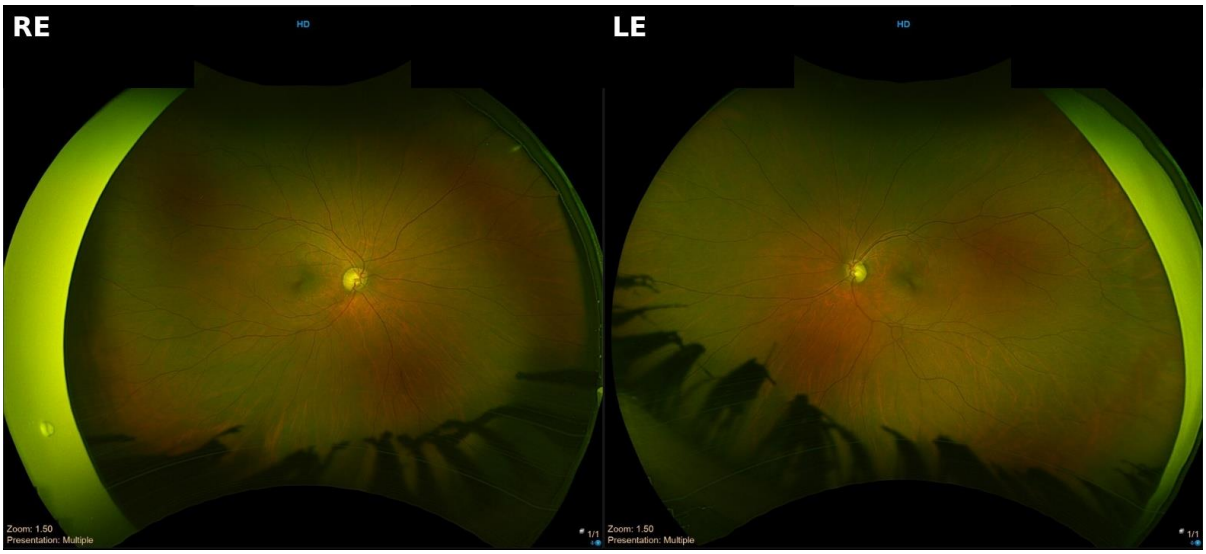


Figure 2: Ultra-widefield fundus images (Optos) at the final follow-up visit (day 134), showing resolution of optic disc swelling with flat discs and sharply defined margins. Mild temporal pallor is present bilaterally, indicating residual optic nerve damage. OCT measurements are shown separately in Figure 3 and Table 2.

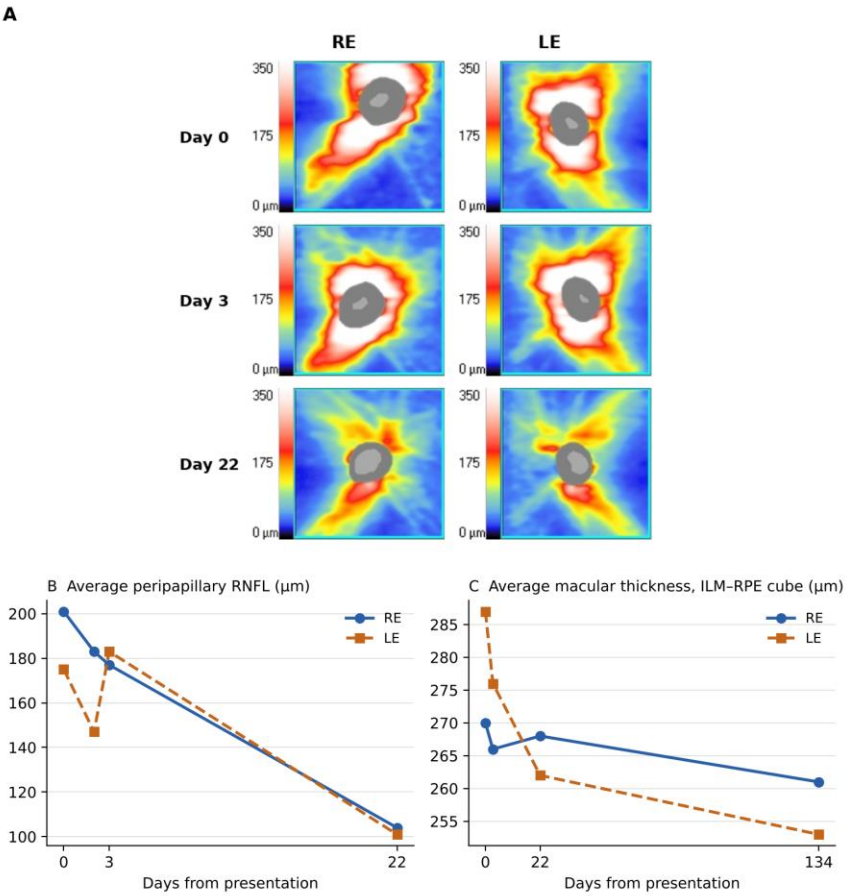


Figure 3: Serial OCT. (A) Peripapillary RNFL thickness maps of the right (RE) and left (LE) eyes on days 0, 3 and 22, showing resolution of nerve fiber layer swelling. (B) Average peripapillary RNFL thickness. (C) Average macular thickness, measured from the internal limiting membrane to the retinal pigment epithelium (ILM-RPE), showing a progressive decline in the left eye. Day 2 macular values are omitted because the scan was decentered (fovea not detected).

Table 1: Clinical timeline (CARE format): lithium dosing, serum levels, investigations, visual function and management. Days are counted from presentation to the Royal Victoria Eye and Ear Hospital (day 0).

Time point	Lithium dose	Serum lithium (12-h trough)	Visual acuity RE / LE	Optic disc / OCT (avg RNFL, µm, RE / LE)	Investigations and management
Previous 3 years	400 mg/day	< 0.9 mmol/L	—	—	Diazepam 5 mg nocte; no interacting drugs

Time point	Lithium dose	Serum lithium (12-h trough)	Visual acuity RE / LE	Optic disc / OCT (avg RNFL, µm, RE / LE)	Investigations and management
~2 months before presentation	Increased to 600 mg/day	—	—	—	Psychiatric relapse
~5 weeks before presentation	600 mg/day	—	—	—	Onset of bilateral blurred vision and headache (≈3–4 weeks after dose increase), progressive thereafter
General hospital, day 1 (≈ day −5)	600 mg/day	1.5 mmol/L	6/36 / 6/36	Ophthalmology review reported unremarkable	No systemic toxicity; renal function, Na^+, TFTs normal; BP/BMI normal; CT, MRI/MRV normal; LP (sitting) OP 22 cm H_2O, CSF normal
General hospital, day 2 (≈ day −4)	Reduced to 200 mg/day	—	—	—	Dose reduced
General hospital, day 3 (≈ day −3)	Discharged on 400 mg/day	0.5 mmol/L	—	—	Discharged (recent relapse; level normalized)
Day 0 (3 days after discharge)	Stopped	0.5 mmol/L	HM / HM	Frisén grade 2 swelling OU; 201 / 175	Admitted; no RAPD; AF no drusen; FFA no leakage; infectious/autoimmune screen
Day 2	Nil	—	—	183 / 147	Pattern-reversal VEP: delayed P100 OU; PERG and flash VEP normal. Olanzapine 10 mg started; no corticosteroids
Day 3	Nil	—	3/36 / 2/60	177 / 183	Ishihara 7/15 / 8/15; discharged
Day 22	Nil	—	6/6 / 6/7.5	Swelling resolved; 104 / 101	Ishihara 15/15 OU; HVF 30-2 normal
Day 134	Nil	—	6/6 / 6/6	Mild temporal pallor OU	Macular thinning on OCT (LE > RE); ongoing follow-up

Table 2: Serial OCT measurements (Cirrus HD-OCT). Peripapillary RNFL values from the Optic Disc Cube 200×200; macular values from the Macular Cube 512×128 (ILM-RPE).

	Day 0	Day 2	Day 3	Day 22	Day 134
Average RNFL, RE (µm)	201	183	177	104	n/a
Average RNFL, LE (µm)	175	147	183	101	n/a
RNFL quadrants RE, S / N / I / T (µm)	321 / 132 / 183 / 168	216 / 175 / 222 / 118	202 / 170 / 212 / 125	125 / 95 / 127 / 69	n/a
RNFL quadrants LE, S / N / I / T (µm)	223 / 155 / 211 / 113	216 / 144 / 176 / 54	211 / 177 / 230 / 115	118 / 87 / 119 / 78	n/a
Central subfield thickness RE / LE (µm)	259 / 311*	—†	249 / 250	250 / 248	252 / 247
Average macular cube thickness RE / LE (µm)	270 / 287*	—†	266 / 276	268 / 262	261 / 253
Signal strength RE / LE (disc scan)	6 / 7	9 / 8	7 / 9	10 / 8	—

Table 3: Naranjo adverse drug reaction probability scale.

Question	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes	+1
2. Did the adverse event appear after the suspected drug was administered?	Yes	+2
3. Did the adverse reaction improve when the drug was discontinued?	Yes	+1
4. Did the adverse reaction reappear when the drug was readministered?	Not done	0
5. Are there alternative causes that could on their own have caused the reaction?	Do not know (weakly positive MOG-IgG)	0
6. Did the reaction reappear when a placebo was given?	Not done	0
7. Was the drug detected in the blood in concentrations known to be toxic?	Yes (1.5 mmol/L)	+1
8. Was the reaction more severe when the dose was increased, or less severe when decreased?	No (worsened after dose reduction)	0

Question	Answer	Score
9. Did the patient have a similar reaction to the same or similar drugs previously?	No	0
10. Was the adverse event confirmed by any objective evidence?	Yes (OCT, VEP)	+1
Total score		**6 (probable)**

Discussion

Lithium-associated optic neuropathy is rare and not widely recognized. In this patient, optic neuropathy developed after a dose increase accompanied by an elevated trough concentration of 1.5 mmol/L. The defining feature of the case is that vision continued to deteriorate after the dose had been reduced and the serum level had returned to 0.5 mmol/L, and improved only after lithium was discontinued. Neurotoxicity that develops or persists despite therapeutic or falling serum levels is well described in the lithium literature and has been attributed to the slower movement of lithium into and out of the central nervous system, so that tissue concentrations need not parallel serum levels.2,8-10 This case is consistent with that pattern, but it does not establish the mechanism.

Differential diagnosis: Several alternative causes of bilateral optic disc swelling were considered. Papilledema from intracranial hypertension is an important consideration, particularly because lithium itself has been associated with raised intracranial pressure.5-7 The lumbar puncture opening pressure of 22 cm H2O was obtained in the sitting position and therefore cannot be used to diagnose or exclude raised intracranial pressure.13 However, the patient's body mass index was normal, she had none of the symptoms of raised intracranial pressure, MRI and MRV were normal with no indirect signs of intracranial hypertension, and the marked central visual loss with delayed VEP latencies is atypical for papilledema of this grade. Lithium-associated intracranial hypertension contributing to the disc swelling cannot be fully excluded, and either mechanism would still implicate lithium.

Optic neuritis, including MOG antibody-associated disease (MOGAD), was considered because of the bilateral disc swelling and the weakly positive MOG-IgG. Against this, there was no pain on eye movement, no optic nerve enhancement on MRI, and visual recovery followed lithium withdrawal without corticosteroids. Low-titer MOG-IgG results have a low positive predictive value, and current diagnostic criteria require supporting clinical or MRI features in patients with low-titer antibodies.14,15 Because the test was not repeated and aquaporin-4 antibodies were not measured, an inflammatory cause cannot be completely excluded, and we have listed this as a limitation.

Non-arteritic ischemic optic neuropathy was considered unlikely given her age, the absence of vascular risk factors, normal blood pressure and the simultaneous bilateral involvement with

rapid recovery. Pseudopapilloedema was excluded by the absence of drusen on autofluorescence and the documented resolution of swelling on serial OCT. Compressive and infiltrative causes were excluded by neuroimaging.

Electrophysiology: The combination of delayed pattern-reversal VEPs with a normal PERG localizes the dysfunction to the optic nerve rather than the retina. The normal flash VEP is not contradictory: flash VEPs have wide inter-individual variability and are relatively insensitive to conduction delay, whereas pattern-reversal VEPs are the standard test for detecting optic nerve conduction abnormalities.16 Because the pattern-reversal VEP was recorded on day 2, when acuity was still severely reduced, the latency delay should be interpreted with some caution, although the normal PERG argues against a purely retinal or optical cause.

Risk factors: Recognized risk factors for lithium toxicity include dehydration, renal impairment, sodium depletion, intercurrent illness, older age and interacting drugs such as non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and thiazide diuretics.2,3 None of these were present in our patient. Renal function, serum sodium and thyroid function were normal, she was not dehydrated, and her only other medication was diazepam, which has no clinically significant interaction with lithium. The rise in serum lithium is therefore best explained by the 50% dose increase alone.

Causality: Using the Naranjo adverse drug reaction probability scale,17 the score was 6, indicating a probable adverse drug reaction (Table 3). Points were given for previous reports of lithium-associated optic disc swelling, the temporal relationship with the dose increase, improvement after withdrawal (positive dechallenge), a documented supratherapeutic serum concentration and objective evidence from OCT and VEP. No points were given for the absence of alternative causes, because of the weakly positive MOG-IgG. No points were given for dose-response either, because vision worsened after the dose was reduced. Lithium was not reintroduced. Clinical improvement after withdrawal supports a probable association but does not prove causation or a specific mechanism.

Possible mechanisms: The mechanism of lithium-associated optic nerve injury is unknown. Mechanisms proposed for drug-associated toxic optic neuropathies include mitochondrial dysfunction, oxidative stress and impaired axoplasmic transport, which preferentially affect the metabolically demanding papillomacular bundle.4 These mechanisms remain speculative for lithium, and our observations cannot distinguish between them.

Limitations: This is a single case. The lumbar puncture opening pressure was measured in the sitting position, the weakly positive MOG-IgG was not repeated, aquaporin-4 antibodies were not tested, numerical VEP values were not retrievable, and VEPs were not repeated after recovery.

Conclusion: In this patient, bilateral optic neuropathy with disc swelling followed a period of elevated lithium exposure, continued to progress after the serum level had returned to the therapeutic range, and improved after lithium was withdrawn, leaving mild residual optic atrophy. Visual symptoms in patients taking lithium warrant prompt ophthalmic assessment, and

a serum level within the target range should not be taken as reassurance that lithium is not responsible. Early recognition and withdrawal of lithium may limit permanent visual loss.

List of Abbreviations

AF: Fundus autofluorescence.
ACE: Angiotensin-Converting Enzyme
ANA: Antinuclear Antibodies
ANCA: Antineutrophil Cytoplasmic Antibodies
BMI: Body mass index.
BP: Blood pressure.
CARE: Case Report guidelines.
CSF: Cerebrospinal fluid.
CT: Computed tomography.
CRP: C-Reactive Protein
ESR: Erythrocyte Sedimentation Rate
FFA: Fundus fluorescein angiography.
HM: Hand movements (visual acuity).
HVF: Humphrey visual field.
ILM-RPE: Internal limiting membrane to retinal pigment epithelium.
LE: Left eye.
LP: Lumbar puncture.
MOG-IgG: Myelin oligodendrocyte glycoprotein immunoglobulin G antibody.
MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease.
MRI: Magnetic resonance imaging.
MRV: Magnetic resonance venography.
Na+: Serum sodium.
OCT: Optical Coherence Tomography.
OP: Opening pressure.
OU: Both eyes.
P100: Major positive peak, at approximately 100 ms, of the pattern-reversal visual evoked potential.
PERG: Pattern electroretinogram.
RAPD: Relative afferent pupillary defect.
RE: Right eye.
RNFL: Retinal nerve fiber layer.
TFTs: Thyroid function tests.
VEP: Visual evoked potential (pattern-reversal VEP and flash VEP).

Author Contributions

S. Ahmed was responsible for the case report, patient follow-up and drafting of the manuscript. C. Hartnett supervised the case review and critically revised the manuscript for important intellectual content.

Ethical Commetti Approval and Consent to Participate

Formal Research Ethics Committee approval was not required for this single-patient case report, in accordance with the policy of the Royal Victoria Eye and Ear Hospital, Dublin, Ireland. This was confirmed in a signed and stamped letter from the hospital's Education Centre on 15/10/2026. The patient was informed about the details of this case report, and written informed consent was obtained from her for publication of this case report and the accompanying clinical images

Human Rights

This case has been reported in accordance with the principles of the Declaration of Helsinki.

Consent for Publication

All images have been anonymized.

Availability of Data and Material

All the clinical data (timeline, OCT values, test results) are already available in Tables 1-3 and Figures 1-3. There is no dataset, no code and no materials to share, and the patient’s records are confidential.

Figures/Images

All images included in this manuscript are original and were taken by the department of ophthalmic photography at the Royal Victoria Eye and Ear Hospital. Figure 3 was prepared by the authors from the patient's own OCT data. No figure has been reproduced or adapted from previously published material. All patient-identifying information has been removed from the images.

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Conflicts of Interest

The authors declare no conflict of interest.

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with the CARE guidelines for case reports.11 A completed CARE checklist is provided as a supplementary file.

AI-declaration

Grammarly was used for language editing and restructuring of the manuscript. The author reviewed and verified all clinical data and references and take full responsibility for the content of this manuscript.

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