



Delayed and reversible ethambutol optic neuropathy

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ABSTRACT

Purpose: To document an unusual example of ethambutol optic neuropathy developing three years from treatment start date in the absence of renal dysfunction.

Observations: The patient, an 82-year-old, 61-kg male undergoing treatment for *Mycobacterium Avium Complex*, presented with visual acuity that was significantly worse than baseline three years after beginning a treatment regimen which included ethambutol at <15 mg/kg/day. He was also found to have central and paracentral scotomas in both eyes. Ethambutol treatment was immediately halted, and the patient's visual acuity and visual fields improved in the months following.

Conclusions and Importance: It is important to have a high index of suspicion for ethambutol toxicity in any patient on this drug who presents with vision changes consistent with optic neuropathy. The development of ethambutol optic neuropathy can be delayed, and vision loss may be reversible and can continue to improve over months after cessation of therapy.

1. Introduction

Ethambutol is used in the treatment of infections caused by *Mycobacterium* species, including tuberculosis. A renowned complication of ethambutol treatment is the development of toxic optic neuropathy, which is believed to be secondary to the drug's metal chelating effects leading to mitochondrial toxicity.^{1,2} The reported incidence of this complication at various doses ranges from <1% to >35%.³⁻⁵ Due to the severe impact that this side effect has on patients' vision, monitoring for optic neuropathy through routine vision assessments and patient education is needed in all who use this medication, as is a baseline visual function assessment before starting treatment.^{2,3} Most patients who experience ethambutol optic neuropathy develop symptoms within the first nine months of treatment.^{4,5} In this study, we report a case of ethambutol optic neuropathy in a patient three years into treatment for *Mycobacterium avium* complex (MAC).

2. Case report

An 82-year-old, 61-kg man (BMI 20.29 kg/m²) undergoing treatment for MAC diagnosed in 2018 presented to the eye clinic in 2021 with rapidly progressive worsening vision in his right eye over one week. At the time, he was on a regimen of amikacin liposomal nebulizer 590 mg/

day, azithromycin 250 mg/day, rifampin 300 mg BID, and ethambutol 900 mg/day (<15 mg/kg/day, started 6/7/2018 with no intervening dose adjustment). Past medical history also included hypertension, bilateral age-related macular degeneration, and prior retinal detachment. The patient's social history was negative for past or present tobacco use and recreational drug use, and recorded alcohol intake was one drink per week. During the initial visit, corrected visual acuity (VA) with lens correction (cc) was found to be changed from 20/25 in both eyes (OU) to 20/200 in the right (OD) and 20/30 in the left (OS). Pupils were equal and reactive to light, and intraocular pressure was within normal limits OU.

A follow up exam four days later with an ophthalmologist showed a VA cc that was counting fingers (CF) at 6 feet OD and 20/40 OS. Confrontational visual fields and extraocular movements were full OU. The patient was referred to neuro-ophthalmology.

Assessment of visual function a week later by neuro-ophthalmology revealed worsening vision in his left eye as well. VA cc at this visit was CF at 1 foot OD and 20/50 OS with a right relative afferent pupillary defect (rAPD), color vision 2/14 OD and 1/14 OS, and a fundus exam showing trace nerve pallor OD > OS (Fig. 1).

Humphrey Visual Field test results were of borderline reliability but showed defects in both eyes. Optical coherence tomography (OCT, Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) showed

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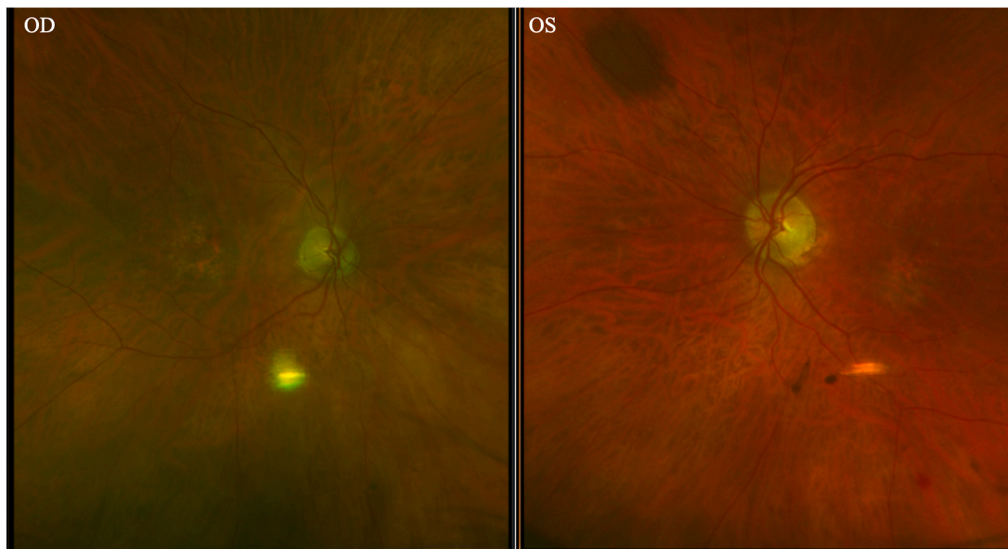


Fig. 1. Funduscopy exam OS and OD showing trace nerve pallor OD > OS in the context of worsening vision with ethambutol therapy.

borderline optic nerve thickness in the right eye (79 μm) and full thickness in the left eye (95 μm); macular ganglion cell layer (GCL) baseline measurements were also taken (Fig. 2). MRI ruled out active MAC infection intracranially. As ethambutol toxicity was suspected, the decision was made to discontinue this medication, and this was discussed with his treating internist. Medication was immediately held.

Follow-up 3 weeks later showed improved visual acuity where VA sc was 20/400 OD and 20/50 -2 OS with a persisting right rAPD. Visual field testing showed a central scotoma OD and paracentral scotoma OS. Foveal threshold in both eyes was reduced, and test reliability was borderline. OCT of the optic nerve and macular GCL thickness was largely unchanged from the previous measurement. Resulted labs at this time were negative for anemia or macrocytosis.

Follow-up exam two months later showed improved VA cc to 20/100 pinhole, 20/150 -2 OD, and 20/30 OS as well as improved visual fields from prior visits, although visual field testing had poorer reliability than previously. OCT of the optic nerve was stable compared to previous visits, although GCL OD had decreased from the previous visit (Fig. 3). Resulted labs at this time included a methylmalonic acid level of 0.25 nmol/mL (normal ≤ 0.40 nmol/mL).

Five months after cessation of therapy, the patient showed continued improvement of both acuity and visual fields with VA cc of 20/60 OD and 20/40 OS. OCT of the optic nerve was stable OS with a decrease OD to 73 μm . At the patient's most recent visit (ten months after cessation of therapy), visual fields had continued to improve; however, OCT now showed optic nerve thinning OD (67 μm) and OS (88 μm) compared to the previous exam five months prior, with continued GCL thinning OU as well (Figs. 4 and 5). The patient was advised to continue to stay off ethambutol and to follow up regularly in clinic.

3. Discussion

The painless development of decreased visual acuity with central and paracentral scotomas^{4,5} in this patient in the absence of nutritional deficiency, lifestyle risk factors, or any other known ongoing pathology (apart from hypertension, which has been noted in previous case reports without identification as a formal risk factor for ethambutol optic neuropathy⁶) and in the presence of ongoing ethambutol therapy fits the accepted characterization of ethambutol toxic optic neuropathy.¹ Other

differential diagnoses included nutritional and hereditary optic neuropathies. Regarding nutritional causes, the patient's normal-range BMI and negative lab workup for anemia and vitamin B12 deficiency suggest against a nutritional deficiency as the cause, which could explain why supplemental therapy (the mainstay of treatment for nutritional optic neuropathies, seen in vitamin B12, folate, copper, and thiamine deficiencies⁷) was not pursued. A mitochondrial DNA sequence was not available for this patient at the time of publication, though it would have been helpful in identifying whether the patient had a genetic predisposition (such as in Leber hereditary optic neuropathy) for developing optic neuropathy. This would be a helpful test to obtain in future follow-up visits or as the patient's overall health improves with ongoing treatment for his MAC infection.

Ultimately, the fact that the patient's visual acuity improved after cessation of ethambutol treatment also supports that he had developed an at least partially reversible toxic optic neuropathy because of taking this medication.^{4,5}

The patient's initial disc pallor followed by the delayed development of optic nerve and macular GCL thinning also supports the diagnosis of a toxic metabolic process. It is notable that neither outright atrophy nor retinal swelling was present at initial presentation, although it is possible that the combination of early swelling with early atrophy could have led to a falsely normal optic nerve thickness. The presence of atrophy at presentation is considered to be a poor prognostic sign,³ while swelling of the retinal layers has been observed in ethambutol optic neuropathy and attributed to ethambutol-induced damage to the nerve fiber layer of the retina.⁸ The lack of optic nerve swelling observed with sequential OCT measurements in the months following this patient's initial presentation may align with his relatively rapid recovery; however, it is impossible to state whether this or any other factors could have predicted the patient's recovery of visual function. Currently the identity of prognostic factors in the recovery course after cessation of ethambutol therapy remains largely unknown,^{4,5} although supplementation of zinc and copper have been suggested as treatment options due to ethambutol's known chelation activity.^{4,5}

The median onset of ethambutol toxic optic neuropathy is nine months.^{4,5} It is interesting that this patient developed symptoms three years after beginning treatment, especially in the absence of any dosage adjustments. One possible contributing factor in this case could have

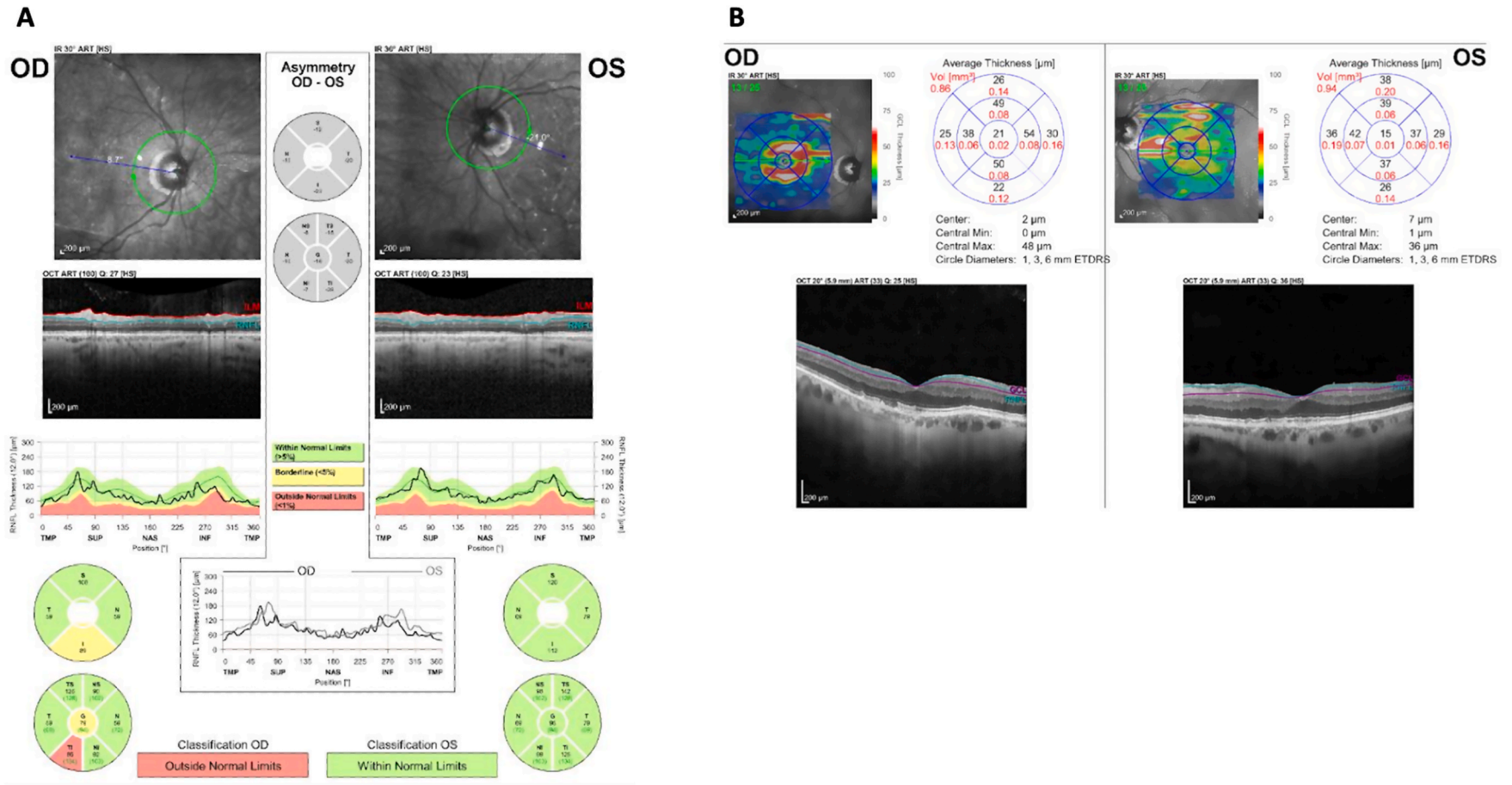


Fig. 2. (A) OCT taken for subacute worsening of visual acuity in the context of ethambutol therapy, showing borderline optic nerve thickness OD (79 µm) and full thickness OS (95 µm). (B) Macular ganglion cell layer (GCL) measurements taken during the same visit.

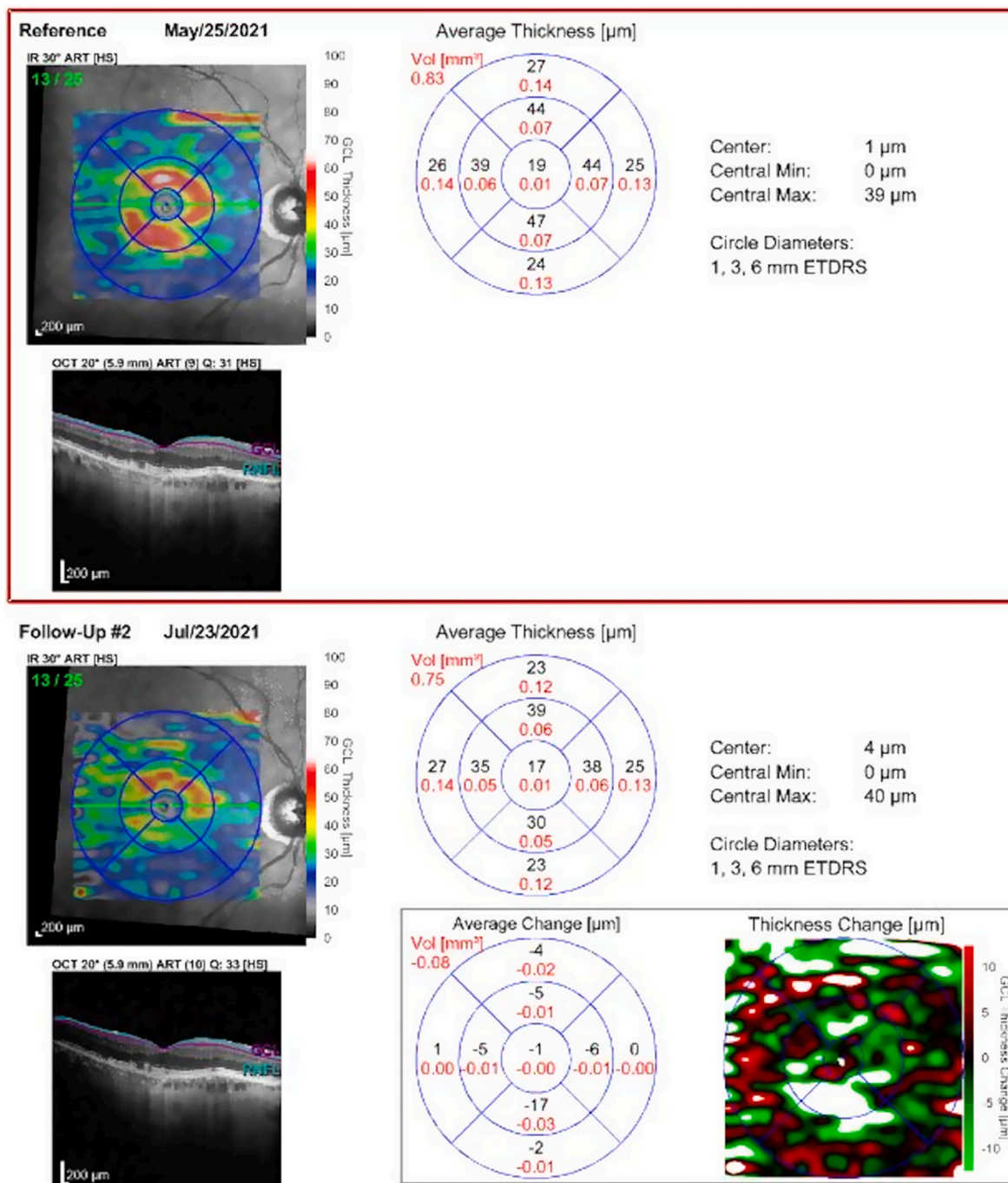


Fig. 3. Thinning of the macular GCL OD was observed from one month post-cessation of ethambutol (above) to three months post-cessation (below).

been the patient’s age, as this has been previously noted as a risk factor for the development of ocular toxicity, supposedly due to the associated decrease in renal function that comes with aging.⁶ However, this relationship has not been reported in other studies.⁴

Also of note, while the ethambutol dose may be related to the risk of optic neuropathy,^{1,5} this patient’s dose at less than 15 mg/kg/day was within one to two standard deviations below the average toxic doses noted in previous studies.^{4,5} The delayed onset of optic neuropathy on a non-exorbitant dose further serves to emphasize that there is much that remains unknown about the causative factors of ethambutol-induced optic neuropathy.

4. Conclusions

This unusual case is a reminder of the importance of having a high index of suspicion in any patient taking ethambutol who presents with symptoms that are suggestive of optic neuropathy, as well as the importance of regular follow-up and eye examination as has been previously recommended.² The development of ethambutol optic neuropathy can be delayed, and vision loss may be reversible and can continue to improve over months after cessation of therapy.

This study was approved by the Loma Linda University Health Institutional Review Board. Patient consent to publish the case report was not obtained as this report does not contain personal information that could lead to the identification of the patient.

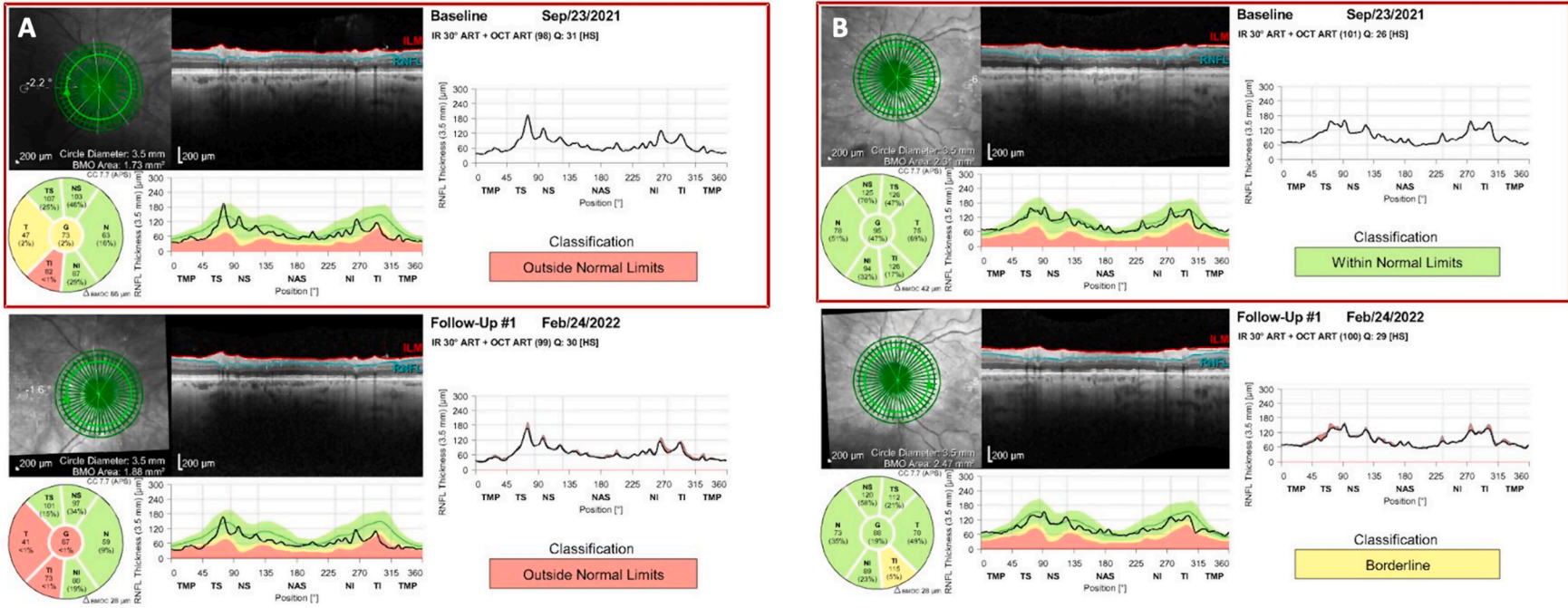


Fig. 4. Thinning of the optic nerve OD (A, from 73 µm to 67 µm) and OS (B, from 95 to 88 µm) from five months post-cessation of ethambutol to ten months post-cessation.

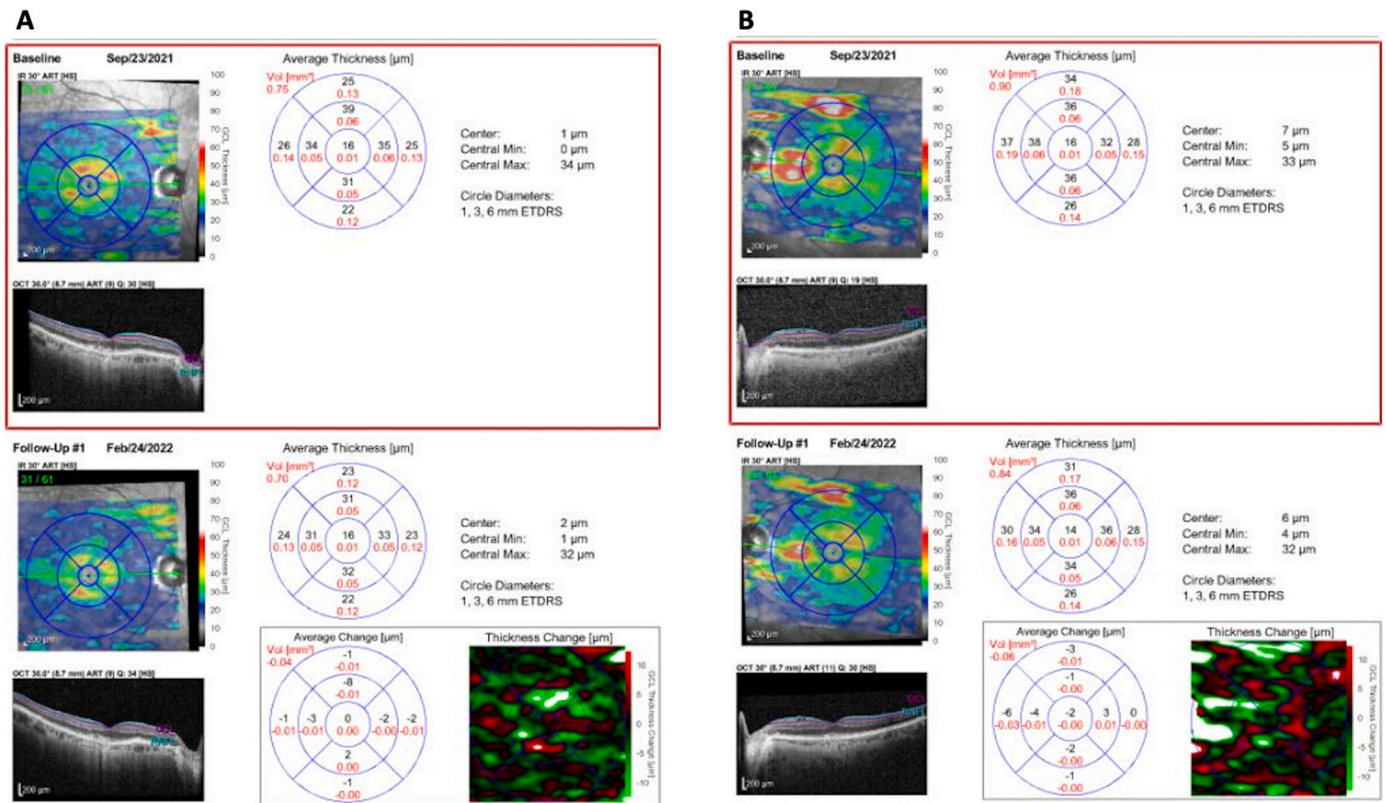


Fig. 5. Continued thinning of the macular GCL OD (A) and mild thinning of the macular GCL OS (B) from five to ten months post-cessation of ethambutol.

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