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Bilateral Retinal Nerve Fiber Layer Loss and Recovery with Teprotumumab in Thyroid Eye Disease

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Abstract

Background: Thyroid Eye Disease (TED) is known to alter tissues of the orbital cavity, including the optic nerve. However, its effect on measured global Retinal Nerve Fiber Layer (gRNFL) is not well elucidated. This case evaluates the effect of teprotumumab on gRNFL in a patient with moderate TED. *Observations*: A 60-year-old female with controlled ocular hypertension and moderate TED received 8 standard IV teprotumumab infusions. Comprehensive ocular evaluations were performed pre-, during-, and post-treatment. Bilateral gRNFL thickness decreased (−10 μm OD; −12 μm OS) at 4 months post-treatment start, persisting at 8 months, but recovered at 20 months. *Conclusions and Importance*: Teprotumumab treatment in patients with TED led to a transient bilateral decrease in gRNFL thickness, which was restored to baseline levels with no adverse events reported. Monitoring gRNFL changes in teprotumumab-treated patients is crucial as gRNFL thinning indicates retinal ganglion cell damage. Teprotumumab's ability to dampen the IGF-IR inflammatory cascade may have reduced retinal inflammation, leading to recovery.

Keywords

Teprotumumab, Thyroid Eye Disease, RNFL, Clinical Activity Score, Ocular Hypertension

1. Introduction

Thyroid eye disease (TED) is a self-limited autoimmune disorder that presents most commonly with Grave's Disease. The disease manifests with an active phase, characterized by inflammation involving the orbit, surrounding muscles

and periorbital fat resulting in tissue remodeling which transitions to a predominantly fibrotic, inactive phase [1] [2]. The most common symptoms reported with TED include eyelid retraction, exophthalmos, and dry eyes. However, the most feared complication is vision loss secondary to optic nerve compression [1] [3]. The pathogenesis of TED has been demonstrated to involve cross-talk between the Thyroid-stimulating hormone receptor (TSHR) and the Insulin Growth Factor I receptor (IGF-IR).

Teprotumumab is an IGF-IR antagonist that has been demonstrated to inhibit the activation of orbital fibroblasts (OF) through inhibition of this cross-talk [4] [5]. TED patients treated with Teprotumumab had a reduction in proptosis, improved quality of life as well as reduced clinical activity scores (CAS). Adverse events reported with Teprotumumab include muscle spasms, nausea, diarrhea, hyperglycemia, hearing impairment, dry skin and dysgeusia [1] [3]. The effects of Teprotumumab on the global Retinal Nerve Fiber Layer (gRNFL) during the active phase, infusion treatment phase, and post treatment phase are currently unclear. In this report, we present a case of bilateral gRNFL nerve thinning after teprotumumab initiation with subsequent bilateral gRNFL recovery in a patient with controlled ocular hypertension.

2. Case Report

A 60-year-old caucasian female, non-smoker, with a history of ocular hypertension, no family history of glaucoma, active moderate to severe TED, treated one year prior with IV methylprednisolone, presented with increasing ocular pain and proptosis. On this day of presentation, CAS was 5: spontaneous orbital pain, gaze evoked orbital pain, eyelid swelling, and left eye proptosis increase >2 mm (**Figure 1**). Hertel exophthalmometry was 22 mm in the right eye and 23 mm in

Figure 1. Patient clinical photos throughout teprotumumab.

the left eye at a base of 92 mm. Visual acuity was 20/20 bilaterally and intraocular pressure (IOP) by goldmann applanation was 21 mmHg in the right eye and 18 mmHg in the left eye, with full Ishihara color plates bilaterally, no relative afferent pupillary defects, and 0.1 cup: disc, pink and sharp nerves bilaterally. Her ocular hypertension was well controlled on timolol and latanoprost, with three years of stability on gRNFLs. She had average pachymetery. Global ONH RNFL was 83 microns in the right eye and 91 microns in the left eye. At this time her diagnosis was consistent with stable ocular hypertension.

After her sixth infusion (four months after treatment initiation, Figure 2), she had a 10 micron and 12 micron decrease in gRNFL in the right eye and left eye respectively, despite medication adherence (Figure 2). IOP was 17 mmHg in the right eye and 15 mmHg in the left eye, with medication adherence. CAS was 2: conjunctival injection and gaze evoked pain. Hertel exophthalmometry was 21

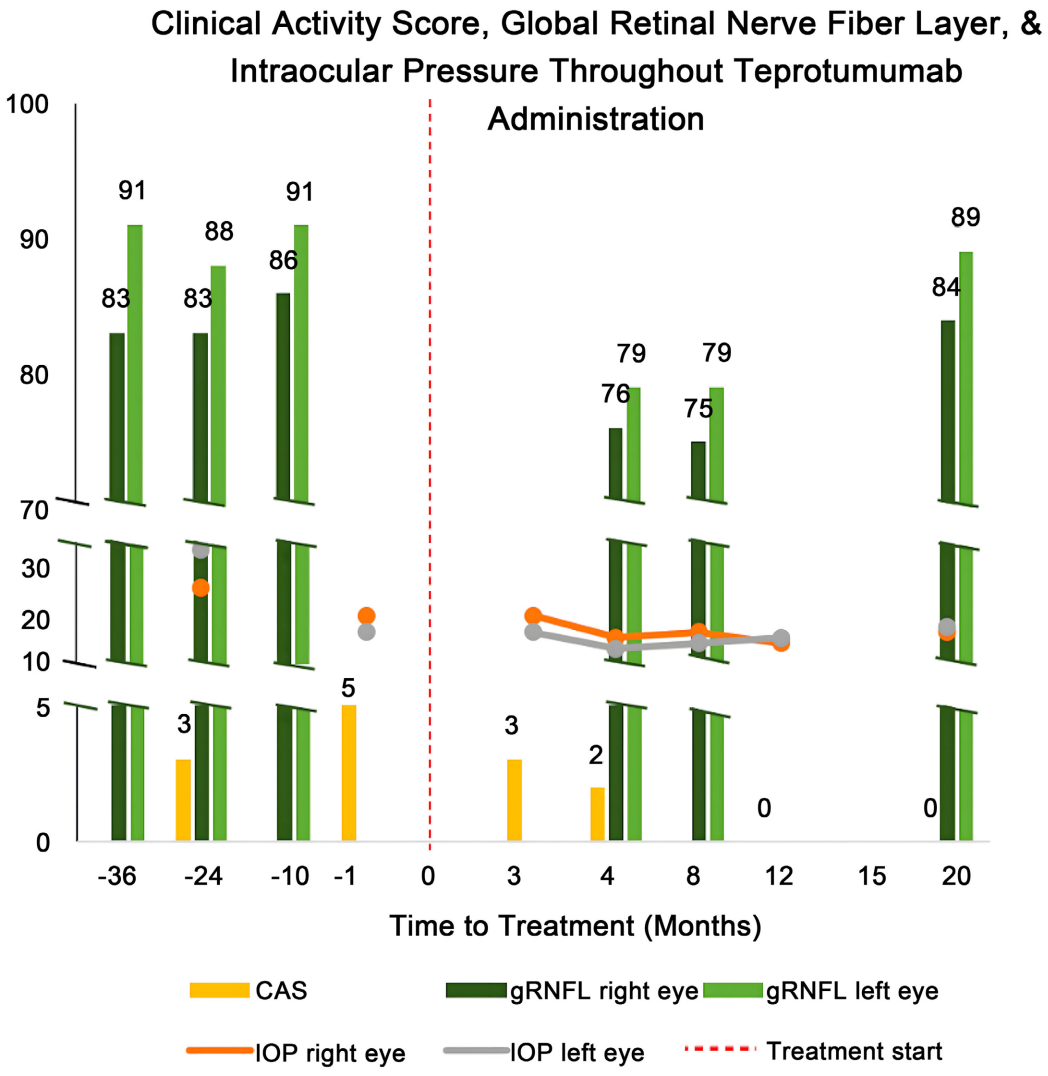

Figure 2. Clinical activity score, global retinal nerve fiber layer, & intraocular pressure before and after teprotumumab administration. Patient received the standard protocol of eight teprotumumab infusions without pause.

mm in the right eye and 22 mm in the left eye at a base of 92 mm. Vision, color plates, and nerve appearance remained stable. Her intraocular pressures at this time were at goal on timolol and latanoprost. Timolol was switched to dorzolamide due to pharmacy backorder of the medication. The decrease in RNFL was suspected to be due to an orbital process related to TED, such as a compressive or inflammatory optic neuropathy versus a reduction in nerve swelling reflective of reduced orbital inflammation, rather than a glaucomatous process. Therefore, no additional glaucoma agent was introduced and it was recommended to continue observation on the teprotumumab treatment at this time.

Eight months after teprotumumab initiation (or two weeks after completion), gRNFL measurements were repeated and found to be persistently decreased (**Figure 2**). Intraocular pressures remained stable on dorzolamide and latanoprost. 20 months after teprotumumab treatment initiation, gRNFLs recovered bilaterally to baseline measurements of 84 μm in the right eye and 89 μm in the left eye. CAS was 0. Hertel exophthalmometry was 20 mm in the right eye and 20.5 mm in the left eye and left eye at a base of 92 mm.

Throughout treatment, thyroid panels were within normal limits and Humphrey 24-2 visual fields were full bilaterally.

3. Discussion

There have been significant advancements in understanding the pathogenesis of TED. In vitro studies have demonstrated that OFs, the primary effector cells in TED, as well as microglia in the retina, are able to create a favorable environment for inflammation in the orbit and retina, respectively [5] [6]. OFs in TED have been shown to express increased levels of IGF-IR and actively interact with T and B lymphocytes to produce chemokines and cytokines such as IL-6, macrophage chemoattractant protein-1 (MCP-1) and TGF-β [7] [8]. Teprotumumab, an IGF-IR antagonist, is the most recent FDA approved therapy for TED.

The pathogenesis of gRNFL changes in the setting of active TED and teprotumumab treatment remains to be fully elucidated. One mechanism that has been observed in TED is the widespread orbital inflammation that can involve the retina and optic nerve head. We suspect the mechanism in the gRNFL change, seen in our patient, occurred secondary to the ability of teprotumumab to shut off the inflammatory cascade involving the IGF-IR leading to decreased inflammation surrounding the retina during the treatment phase, which manifested as a decrease in gRNFL. Following the completion of treatment, the recurrence of inflammation within the optic nerve head may have been captured by an increase in gRNFL, suggesting that the underlying TED persists despite the cessation of teprotumumab therapy. It is possible that this reflects asymptomatic TED disease activity that is not captured in the typical CAS score.

Within the retinal environment of post-teprotumumab TED patients, changes have been identified in inflammatory cell density and retinal vasculature. Microglia, myeloid cells found in the central nervous system and retina, express IGF-IR

and MHC molecules. Microglia are capable of presenting antigens to T cells and secreting cytokines, thus playing a significant role in retinal pathology by perpetuating or downregulating the inflammatory response [6]. Teprotumumab has been found to alter the retina's cellular environment and inflammatory contributors, as well as cause vascular changes. Otero-Marquez *et al.* described a case of TED where post-teprotumumab treatment, there was an observed decrease in retinal surface macrophage density and a significant decrease in optic nerve head edema reflected on optical coherence tomography (OCT) RNFL thickness. Before treatment with teprotumumab, RNFL thickness was 209 μm in the right eye and 137 μm in the left eye and after treatment completion, RNFL thickness decreased to 107 μm in the right eye and 109 μm in the left eye [9]. This case, in conjunction with ours, reveals teprotumumab's ability to alter retinal cell physiology and change in optic nerve head edema during treatment.

Another mechanism for alterations in gRNFL, involves the pathogenesis of dysthyroid optic neuropathy (DON) in which the optic nerve is compressed by inflammatory orbital tissues, resulting in apical crowding and subsequent ischemia of nerve tissue [10]. Though there is no gold standard for the diagnosis of DON, clinical suspicion arises when the appearance and function of the optic nerve are impacted (optic nerve edema, visual field deficits, afferent pupillary defect, color plates, visual acuity). The optic nerve appearance when DON is suspected may be edematous or atrophied. The utility of teprotumumab during active TED, can further cloud the diagnosis of DON as the orbital fibroblasts and retinal inflammatory mediators are also altered by this medication and consequently change the gRNFL. Though in this reported case the clinical picture, with preserved optic nerve function, does not follow a classic DON picture, it is important for clinicians to consider whether the changes in optic nerve are reflective of a teprotumumab response or of increasing TED activity.

Other mechanisms for gRNFL change may be related to teprotumumab's neuropathic mechanisms and effects on vascular morphological changes. Shah *et al.* demonstrated in a multicenter trial, that 82% (107) of patients treated with teprotumumab for TED experienced at least one adverse event, with only 8.4% of these being severe. Hearing impairment was seen in 13.7% (18) of patients with only 50.0% of them recovering after discontinuation of teprotumumab [11]. The hearing impairment is thought to be multifactorial, however is most likely due to the neurotrophic effects of IGF-I on cochlear hair cells and synaptic support, suggesting that teprotumumab's inhibition of IGF-I activity could lead to similar neuropathic mechanisms in other neural tissues [12]. Given the role of IGF-I in neuronal health, another possibility is that the prolonged blockade of IGF-I by teprotumumab could similarly affect the retinal nerve fiber layer (RNFL) in patients with TED, a concept not explored in existing literature. Other possibilities to consider are effects of teprotumumab on plasma endothelin dysregulation and vascular morphological changes as hypothesized by Chu *et al.* and Sen *et al.* or on astrocytic glial tissue as one case report demonstrated rapidly progressive cognitive decline in a patient treated with teprotumumab which

was reversed with plasmapheresis [13] [14] [15] [16].

In conclusion, we observed decreased gRNFL in a patient after six infusions of teprotumumab therapy, with a subsequent return back to baseline gRNFL almost one year after treatment completion. Potential mechanisms for this decrease in gRNFL during teprotumumab treatment and subsequent increase in gRNFL in the absence of teprotumumab may involve the drug's ability to downregulate the inflammatory cascade, change the density of microglia, alter the retina's cellular environment and inflammatory contributors, induce vascular morphological changes, as well as exhibit neuropathic effects on retinal tissue. It is important to note that when monitoring optic nerve changes in TED, dysthyroid optic neuropathy must be considered as it may cause both optic nerve edema and ischemia and result in permanent vision loss. Further studies are warranted to explore the mechanisms by which teprotumumab alters the retinal nerve fiber layer in active TED.

4. Conclusion

We present a unique case of bilateral gRNFL nerve thinning after teprotumumab initiation with subsequent bilateral gRNFL recovery in a patient with controlled ocular hypertension.

Patient Consent

The patient has given written informed consent for the reporting and publication of examination and imaging findings, including images, for purposes of diagnosis, education, and research.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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