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# A 46-Year-Old Woman with a 4-Year History of Graves Disease, with Severe Corticosteroid-Unresponsive Thyroid Eye Disease, Successfully Treated with Tocilizumab

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Patient:** Female, 46-year-old
**Final Diagnosis:** Graves' disease
**Symptoms:** Progressive exophthalmos • decreased vision • red and painful eyes • restriction of eye movements bilaterally
**Medication:** Intravenous tocilizumab
**Clinical Procedure:** —
**Specialty:** Ophthalmology

**Objective:** Unusual or unexpected effect of treatment

**Background:** Tocilizumab is a therapeutic biologic antagonist of the interleukin-6 (IL-6) receptor that has been approved to treat some autoimmune and chronic inflammatory diseases. This report is of a patient with a history of Graves disease and severe corticosteroid-unresponsive thyroid eye disease that included edema of the optic nerve and choroid, which was successfully treated with tocilizumab.

**Case Report:** A 46-year-old woman with a 4-year history of Graves disease presented with acutely progressive bilateral severe optic nerve compression, severe bilateral optic nerve edema, bilateral restriction of eye movement, and bilateral choroidal folds. The patient was managed with an initial high dose of systemic steroid without any success. She then underwent bilateral orbital wall decompression without any noticeable amelioration. She subsequently received 4 doses of a tocilizumab (8 mg/kg) infusion. This resulted in a considerable decrease in inflammatory signs and improvement in optic nerve function, thereby improving her quality of life. The patient did not have any adverse reactions to the tocilizumab.

**Conclusions:** The findings from this case support recent case reports and clinical trials indicating that tocilizumab may be effective in corticosteroid-resistant thyroid eye disease associated with autoimmune hyperthyroidism.

**Keywords:** Exophthalmos • Hyperthyroidism • Optic Nerve Diseases • Tocilizumab

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## Background

Thyroid eye disease (TED) is an autoimmune-mediated disease with variable presentations ranging from mild to moderate to severe [1]. Optic nerve compression, also known as dysthyroid optic neuropathy (DON) is a rare but devastating condition that accounts for about 4% to 8% of TED cases [2-4]. It may present as blurry vision, loss of vision, abnormal color vision, visual field loss, or a combination of these symptoms [5,6].

It is hypothesized that more than 90% of DON cases are caused by compression of the nerve by the enlarged extraocular muscles, while the remainder of DON cases are caused by stretching of the nerve without direct compression or raised intra-orbital pressure from the orbital inflammation [3]. Traditionally, the first choice of treatment for DON has been intravenous administration of steroids, with or without radiotherapy [7]. In the unfortunate event of unresponsiveness to systemic steroids, development of complications due to systemic steroids, and/or contraindication to systemic steroids, surgical decompression would be the next step in the treatment ladder [7].

Inflammatory manifestations of TED respond well to orbital radiotherapy (ie, extraocular motility dysfunction, and optic neuropathy); however, proptosis and chronic motility dysfunction respond poorly [8], and in our patient, we aimed for the treatment of both proptosis and chronic motility dysfunction. Biologics are being used with increasing frequency for different stages of TED. One of the breakthrough therapies is teprotumumab. Teprotumumab is a monoclonal antibody that blocks insulin-like growth factor 1 receptor [9]. Clinical trials with teprotumumab have shown very promising results in the treatment of TED [10,11], and it has been approved by the United States Food and Drug Administration (FDA) for TED [12]. Another agent that is being increasingly used is tocilizumab which is a humanized monoclonal antibody directed against the interleukin 6 (IL-6) receptor [13-18]. Tocilizumab is FDA approved for giant cell arteritis, adult rheumatoid arthritis, and systemic juvenile idiopathic arthritis [13-18]. It was first introduced as a treatment for severe steroid-resistant TED in 2009, with the first results published in a case series by Pérez-Moreiras et al [13].

The following case demonstrates the successful use of tocilizumab infusion after both intravenous steroid and surgical decompression have failed to alleviate signs and symptoms of optic nerve compression.

## Case Report

A 46-year-old East Asian woman was transferred to our hospital as a case of newly diagnosed steroid-resistant TED associated with Graves disease. She reported a 1-month history of progressive exophthalmos, decreased vision, red, painful eyes, and restriction of eye movements bilaterally.

On presentation to our facility, her ocular examination revealed visual acuity of 6/120 bilaterally. The pupillary reaction was sluggish in both eyes. There was a bilateral limitation of extraocular movements in all directions. External examination revealed fullness and redness of both upper and lower eyelids and moderate injection of conjunctiva. Both corneas showed superficial punctate epitheliopathy with minimal nuclear cataract bilaterally. Intraocular pressure was normal in the primary position and in the up-gaze. The Hertel exophthalmometry measurements were 21 mm in the right eye and 24 mm in the left eye at the base of 120. Fundus examination revealed bilateral choroidal folds and bilateral optic nerve edema grade 4 according to the modified Frisen scale (**Figure 1**). Color vision was 0/17 in both eyes. The visual field test showed a total visual field defect for the right eye and a subtotal defect for the left eye (**Figure 2**). Computerized tomography and magnetic resonance imaging showed bilateral exophthalmos with bilateral symmetrical enlargement of the extraocular recti muscles extending to the orbital apex leading to compressive optic neuropathy. The patient was admitted and managed with a multidisciplinary approach by ophthalmology, otolaryngology, and endocrinology teams. She received another course of IV methylprednisolone (1 g/day) for 3 days. Her visual evoked potential showed an absence of P100 distal latency in the right optic nerve while being severely prolonged in the left optic nerve. An emergency bilateral orbital wall decompression was offered, but the patient refused the surgery and opted for further medical management. She was discharged on a course of oral steroids. Approximately 1 month later, she presented again to our facility with a worsening of her condition. Her visual acuity had further reduced to counting fingers in both eyes. The patient agreed to undergo bilateral lateral, and bilateral endoscopic medial and inferior orbital wall decompression. During that admission, she was started on another 3-day course of 1 g/day IV methylprednisolone. A standard lateral orbital wall decompression was performed by the oculoplastic surgeon and an endoscopic medial orbital wall decompression was performed by the otolaryngology team. Two weeks after the surgery, her best corrected visual acuity, optic disc swelling, and choroidal folds had not improved. A repeat postoperative computed tomography (CT) scan showed further potential to decompress the orbit medially; hence the patient underwent a further endoscopic right medial wall decompression. She also had a total thyroidectomy and started on replacement thyroxin tablets thereafter. Eight weeks later, her condition remained unchanged, and our team decided to proceed with tocilizumab injection. This decision was based on the team's previous experience with tocilizumab for DON. Appropriate insurance approvals and consent were obtained,





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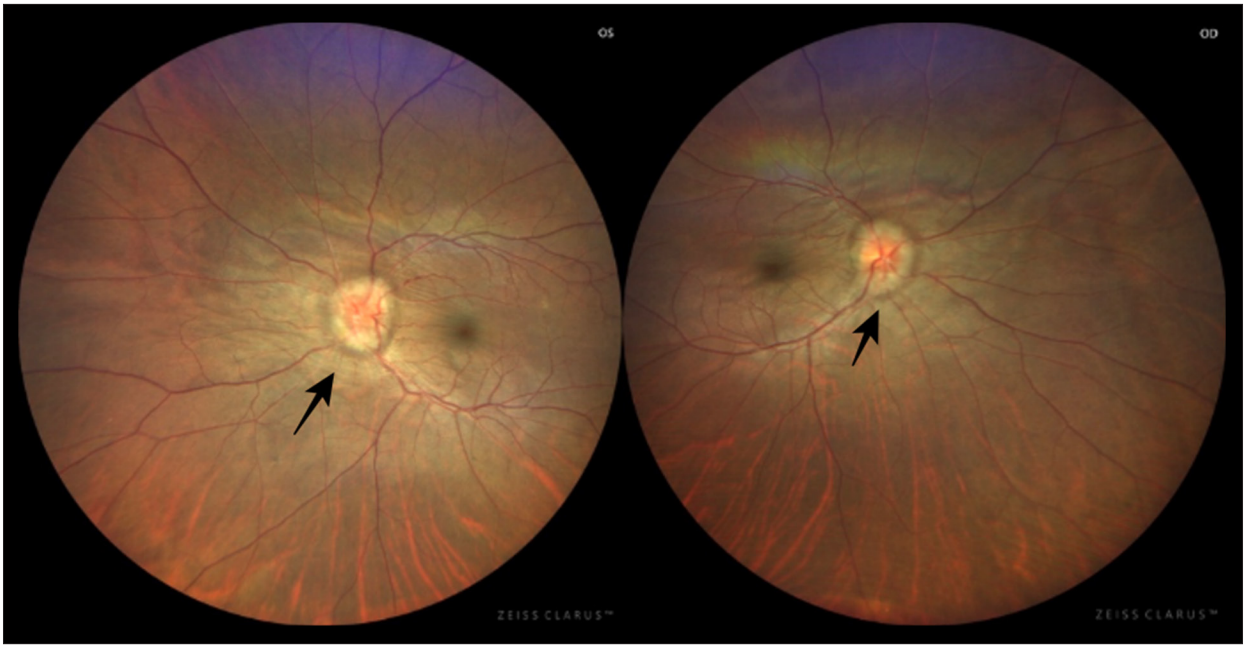


**Figure 1.** Fundus photo showing bilateral choroidal folds with bilateral optic nerve edema grade 4.

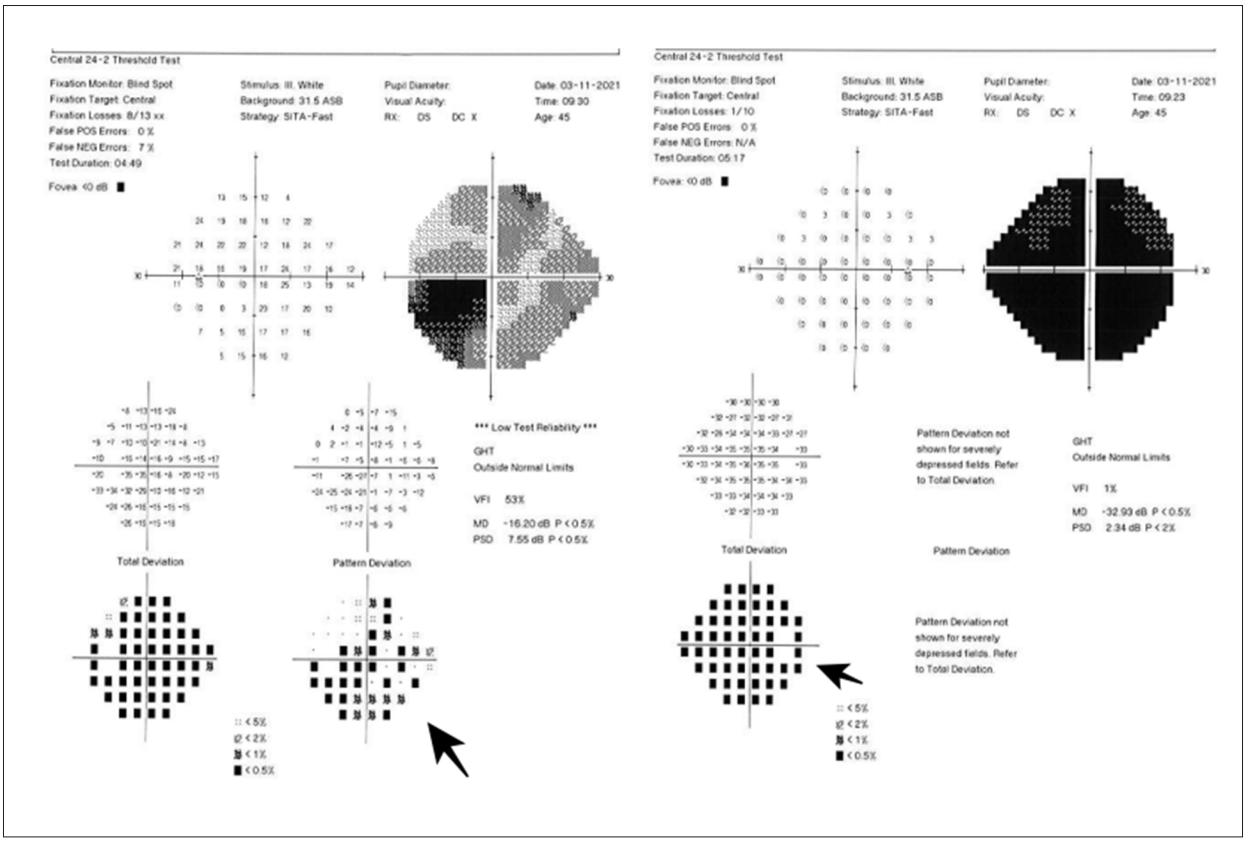


**Figure 2.** 24-2 Humphrey visual field test on presentation showing total visual field defect for right eye and subtotal defect for left eye.





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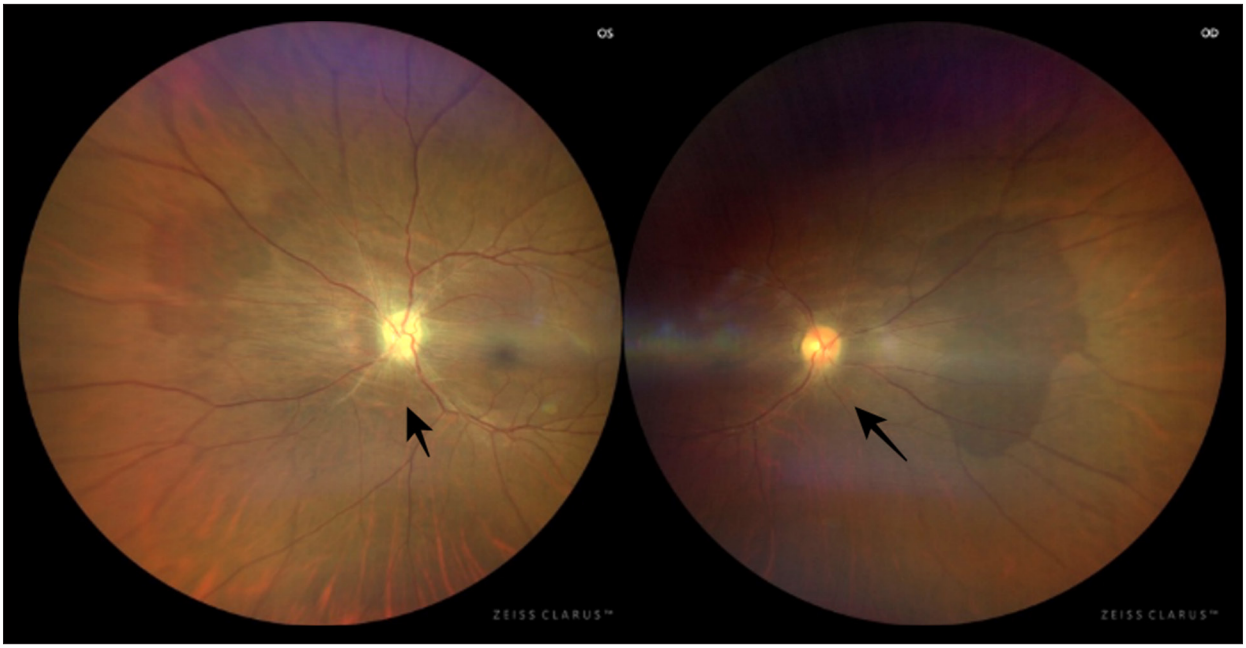


**Figure 3.** Fundus photo, 4 weeks after 4th tocilizumab injection showing resolving bilateral disc edema.

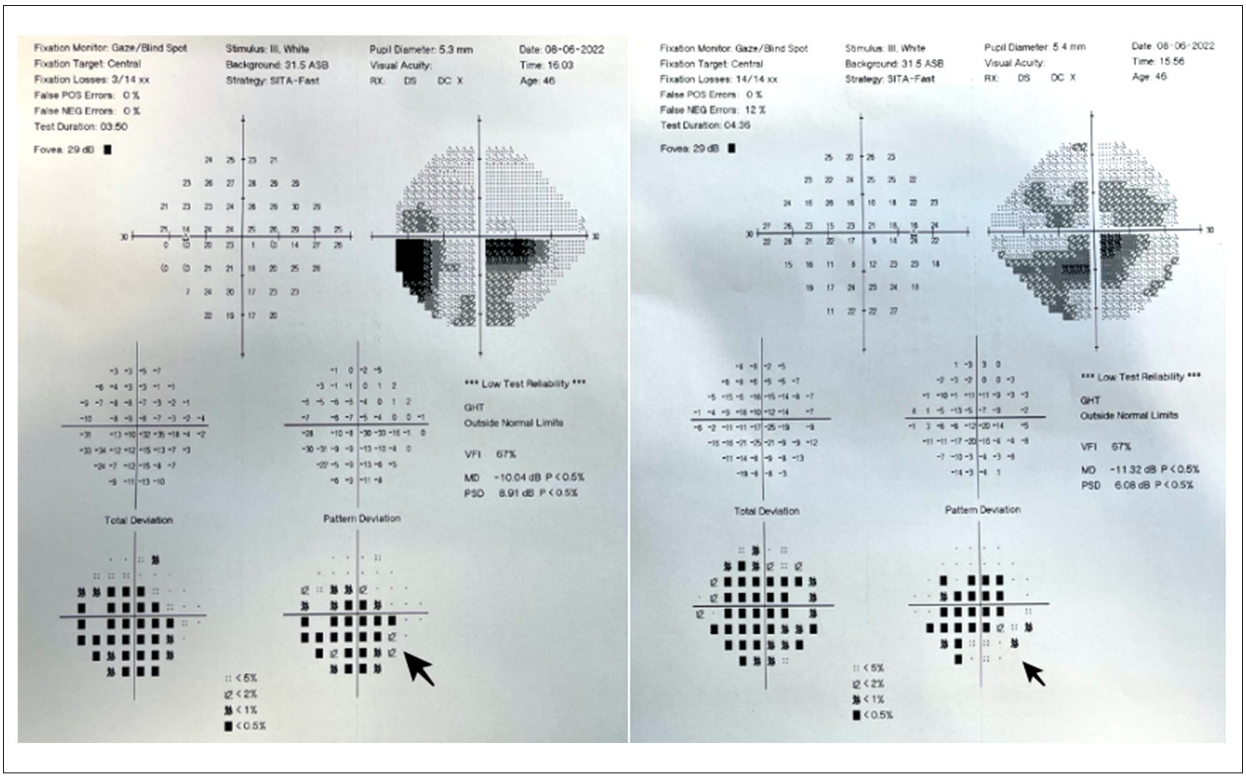


**Figure 4.** 24-2 Humphrey visual field test, 4 weeks after fourth dose of tocilizumab injection.

and the patient received 4 doses of 8 mg/kg tocilizumab infusion, each infusion 4 weeks apart. The patient started to show progressive improvement in her symptoms. The optic nerve edema subsided and there was an improvement in the visual field defect. Her final visual acuity following the fourth injection was 6/18 in the right eye and 6/9 in the left eye. Color vision was 11/17 in the right eye and 13/17 in the left eye. Bilateral disc edema had resolved fully but both discs were moderately pale (**Figure 3**). There were residual choroidal folds and her visual field examination also improved (**Figure 4**). The patient





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did not have any adverse reaction to tocilizumab. Due to this dramatic improvement in her condition, the patient was able to return to her full-time job, thereby improving her quality of life.

## Discussion

This case illustrates the successful use of tocilizumab in a patient with Graves TED. Moreover, our patient presented with acute onset bilateral optic nerve compression, bilateral severe optic nerve head edema, and choroidal folds. This resulted in severely reduced optic nerve functions [19]. Our patient responded to tocilizumab infusion after exhausting all available medical and surgical treatment options. Improvement in optic nerve function can be immediate or it may take up to 2 weeks following the decompression surgery [14-15]. The consensus in the literature is that the earlier the decompression, the better the outcome [19]. In our case, the condition did not improve, even 8 weeks following the surgery. When we did see improvement, it was most probably attributable to the addition of the tocilizumab or the tocilizumab treatment may have acted as a catalyst to potentiate the effect of surgical and/or medical decompression. Tocilizumab is a recombinant humanized antihuman monoclonal antibody of the immunoglobulin G1 subclass directed against the IL6 receptor, produced by recombinant DNA technology [13]. IL6 is overproduced in people with TED and overexpressed by adipocytes, macrophages, and fibroblasts and, further, acts as a proinflammatory cytokine involved in the pathogenesis of TED [20].

Tocilizumab has been used in different stages of TED. In a multicenter study where tocilizumab was used in the treatment of moderate to severe corticosteroid-refractory TED, 48 patients (95 eyes) were involved with moderate disease (n=29) or severe disease (n=19) and DON (n=7) [21]. Another article investigated the effect of tocilizumab vs placebo in 32 patients with moderate to severe TED that was resistant to corticosteroid therapy. Results showed improvement in clinical activity score (CAS) by at least 2 points in 93% of treated patients with tocilizumab at week 16 vs 59% in the placebo group [22]. The largest retrospective case series for tocilizumab was conducted by Perez et al. Over the course of 9 years, 114 patients were treated with tocilizumab in our hospital. Of these, 54 patients were included in the study, and these 54 were followed, with a median followup of 22 months after the first injection. The absolute CAS response (CAS=0 or 1) was achieved in 74% after the fourth dose of tocilizumab, while a relative CAS response (reduction ≥2 points) was reached in 90.9% of patients after the first dose of tocilizumab with significant reduction of proptosis, eyelid retraction, and diplopia noticed after the fourth dose [23]. Eatamadi et al reported the first case of using tocilizumab in treating progressive pediatric TED [24]. Other authors have reported cases in which tocilizumab was used for the treatment of TED. Similarly to our case, Mehmet et al reported a case of severe TED associated with DON that was unresponsive to intravenous steroids and orbital radiotherapy but responded to tocilizumab [25]. Due to this, more studies need to be conducted to investigate the possibility of tocilizumab being a treatment option for TED, as according to Hamed Azzam et al, there are currently no data from randomized controlled trials evaluating the efficacy and adverse effects of tocilizumab for TED [19].

Tocilizumab has proven to be a very safe medication for adult and pediatric age groups. Conventional modalities of treatment such as steroids have their adverse effects inducing myopathy, osteopathy, skin atrophy, and metabolic and endocrine adverse effects [26]. Orbital decompression carries its own risks in an inflamed and tense orbit, potentially causing loss of vision, double vision, and squint [27].

To our knowledge, this is one of the few reported cases of TED with optic nerve edema and choroidal folds that was successfully managed with tocilizumab when all other options have failed.

## Conclusions

This is a very complex and intriguing case of TED that adds to the ambiguity of the disease process, response to different treatment modalities, and outcomes. In the pursuit of success, all available modalities need to be considered. We believe that this promising targeted medical treatment should be studied more and opted for before resorting to surgical options. Time and a higher number of patients are needed to certify the efficacy of these treatment modalities.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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