Acquired Epiblepharon Alleviated With Teprotumumab Treatment in Active Thyroid Eye Disease Patient

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Abstract: **A 46-year-old Asian female patient with thyroid eye disease reported ocular irritation, eyelid swelling, diplopia, and pain with eye movement. The patient was diagnosed with active thyroid eye disease and secondary thyroid eye disease–acquired epiblepharon, which was causing bilateral punctate epithelial erosion. Treatment was started with newly U.S. Food and Drug Administration approved teprotumumab, an insulin-like growth factor-1 receptor inhibitor. Four infusion treatments later, the patient's epiblepharon was alleviated with minimal side effects. In this report, the authors present a case of thyroid eye disease–acquired epiblepharon resolving with teprotumumab treatment.**

Thyroid eye disease (TED) is an autoimmune, inflammatory disease that is associated with generalized hyperthyroidism. Approximately 40% of patients with hyperthyroidism will develop signs of TED, which can affect the orbit, eyelid, eye muscles, and optic nerve.[1] Common symptoms include eyelid retraction, dry eye, hyperemia, blurry vision, proptosis, diplopia, and infrequently epiblepharon.[1,2] Epiblepharon is a condition in which the orbicularis oculi muscle, eyelid skin, and fat override the eyelid margin.[1] This causes the eyelash cilia to orient in a vertical position, which can lead to ocular irritation and corneal damage.[1]

In January 2020, teprotumumab (Tepezza—Horizon Therapeutics, Dublin, Ireland) was approved by the U.S. Food and Drug Administration for the treatment of TED. The pathophysiology of TED lies in the overexpression of the thyrotropin receptor and the insulin-like growth factor-1 (IGF-1) receptor on orbital fibroblasts in conjunction with the production of autoantibodies by autoreactive T and B lymphocytes, resulting in the signs and symptoms associated with TED.[2,3] Teprotumumab, an IGF-1 receptor human monoclonal antibody, works by blocking the IGF-1 receptor and prevents it from forming a synergistically enhancing signaling complex with the thyrotropin receptor.[4] Thus, teprotumumab's inhibitory mechanism of action on the IGF-1 receptor attenuates the pathogenic effects of IGF-1, thyrotropin, and thyroid-stimulating autoantibodies that contribute to TED ophthalmopathy.[3,4]

In this report, the authors present a case of teprotumumab treatment successfully resolving TED-acquired epiblepharon in a patient diagnosed with active TED. The collection and evaluation of identifiable patient health information was compliant with Health Insurance Portability and Accountability Act protection guidelines and adhered to the ethical principles of the Declaration of Helsinki as amended in 2013. Written consent was obtained and archived for the use of all clinical images and patient information.

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CASE PRESENTATION

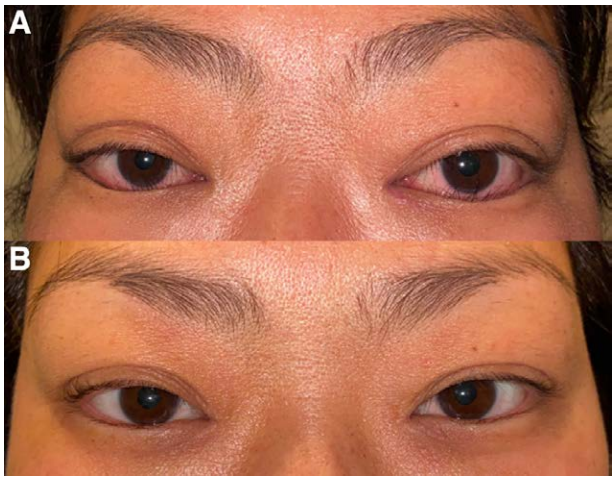
A 46-year-old Asian female diagnosed with TED in 2019 presents in June 2020 with 9 months of diplopia and bilateral ocular irritation. Physical exam demonstrates vertically oriented lower eyelashes, punctate epithelial erosion OU, chemosis, conjunctival redness, lower eyelid retraction, eyelid redness and edema, and pain with eye movement (Fig. A). She was diagnosed with active TED and presented with main clinical concerns of diplopia and secondary TED-acquired epiblepharon. Before treatment, the patient's exophthalmometry measurements were 22 mm OD and 23 mm OS. The patient had a clinical activity score of 4 before treatment due to conjunctival erythema, chemosis, pain on eye movement, and caruncular inflammation.

The decision was made to start teprotumumab therapy. Teprotumumab was administered intravenously at the standard dose of 10 mg/kg over 90 minutes on the first treatment, 20 mg/kg over 90 minutes for the second treatment, and 20 mg/kg over 60 minutes for the following 2 treatments. After 4 infusions of teprotumumab, the patient had resolution of diplopia, ocular irritation from epiblepharon, lower eyelid retraction, proptosis, edema, and redness (Fig. B). After treatment, the patient's exophthalmometry measurements were 18 mm OD and 19 mm OS with a clinical activity score of 0. The only side effect reported by the patient was muscle aches lasting 1 week after each teprotumumab infusion.

DISCUSSION

TED-acquired lower eyelid epiblepharon is a rare clinical feature of TED that is infrequently described in the literature.[5] Signs of TED-acquired epiblepharon include lash corneal-conjunctival touch, especially in downgaze and adduction in lower eyelid epiblepharon, bent or broken abnormal eyelashes, and corneal epithelial defects that stain with fluorescein.[1,2,5] Symptoms include irritation, foreign body sensation, frequent blinking or rubbing of the eyelid, tearing, and keratitis leading to corneal injury.[1,5]

The combination of orbital fat hypertrophy, extraocular muscle enlargement, eyelid retraction, increased intraorbital



Resolution of TED-acquired epiblepharon after teprotumumab treatment. Before treatment, bilateral TED-acquired lower eyelid epiblepharon is causing punctate epithelial erosion, ocular erythema, and irritation **(A)**. After 4 treatments of teprotumumab, the epiblepharon has resolved. Reduced swelling and inflammation of orbital tissues is observed **(B)**. TED, thyroid eye disease.

pressure, and proptosis all likely contribute to the etiology of TED-acquired epiblepharon, which results in overriding of the anterior lamella over the posterior lamella and subsequent eyelash malpositioning.[1,2,5–7] A 3D orbital imaging study demonstrated that teprotumumab treatment led to a significant reduction in extraocular muscle volume, orbital fat volume, and inflammation in TED patients.[8] The authors postulate the mechanism by which teprotumumab alleviates TED-acquired epiblepharon is through reducing the overall volume of inflamed and enlarged muscular and fatty tissue associated within the orbit and eyelids.[1,5,8]

Current treatments for active TED and TED-acquired epiblepharon mainly involve reducing the signs and inflammation-related symptoms through orbital radiotherapy and high-dose glucocorticoids, which can lead to spontaneous resolution of the epiblepharon.[1,4] However, these therapies are not consistently beneficial, may not modify disease outcome, and are associated with significant dose-limiting adverse effects.[4] Surgery is considered effective for TED-acquired epiblepharon but is reserved only for severe cases of epiblepharon that do not resolve with other treatment therapies.[1,5] When necessary, it is recommended that surgical management of TED-acquired lower eyelid epiblepharon proceeds sequentially in the general order of orbital decompression, lower eyelid retraction correction, and epiblepharon repair.[6] Epiblepharon-correcting surgery can be undesirable to patients, as it may involve suturing formation of an artificial eyelid crease and scar tissue.[9] Surgical intervention for correcting epiblepharon related to TED can leave patients displeased with the cosmetic results due to unfavorable alterations to the appearance of the eyelid and surrounding orbital tissue.[9] Thus, teprotumumab may prove to be an effective therapy for patients seeking nonsurgical treatment for TED-acquired epiblepharon.

The type of TED-acquired lower eyelid epiblepharon can be clinically classified as medial, central, or diffuse based on the location and extent of epiblepharon.[10] Their patient demonstrates a case of diffuse-type TED-acquired lower eyelid epiblepharon. Their patient's clinical subtype of diffuse TED-acquired epiblepharon is considered to be rarer and more severe due to an association with greater eyelid retraction, which is the most commonly reported sign of TED observed in approximately 90% of TED patients.[2,10]

Most TED-acquired epiblepharon cases reported in the literature are found in Asian patient populations, with few studies reporting epiblepharon related to TED in non-Asian patients.[1,5,7,10] The prevalence of acquired epiblepharon in Asian TED patients has been reported to be between 8% and 18%.[5,7,10] A study comparing nearly 200 TED patients of different races identified acquired lower eyelid epiblepharon exclusively in patients of Asian descent, underscoring the need for further comparative studies of TED-acquired epiblepharon patients in non-Asian populations.[5] It is thought that the anatomic uniqueness in patients of Asian ancestry predisposes them to developing TED-acquired epiblepharon.[5,10,11] It has also been postulated that orbital fat extension anterior to the orbital rim increases the tendency for higher intraorbital pressure in TED patients to cause fatty tissue prolapse and epiblepharon.[1,5,11]

New reports in the literature have demonstrated that teprotumumab treatment can resolve compressive optic neuropathy associated with TED.[12] As far as the authors are aware of, this is the first case report showing resolution of TED-acquired epiblepharon after teprotumumab therapy in a patient with active TED.

In closing, the authors report the resolution of TED-acquired epiblepharon after 4 treatments of intravenous teprotumumab administration. The authors would like to caution claiming broad efficacy of teprotumumab in alleviating TED-related epiblepharon from a single patient case. Additionally, longer term studies with more patients are needed to confirm teprotumumab's sustained safety, efficacy, and recurrence rate in resolving TED-related epiblepharon.

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