

Sight-Threatening Condition in Severe Thyroid Eye Disease: How We Should Manage

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ABSTRACT

Thyroid eye disease (TED) is an autoimmune disorder that is associated with thyroid gland dysfunction which causes muscle and orbital fat enlargement. This case report is aimed to present a case of sight-threatening TED and how we should manage this condition. We present a case of patient with chief complaint of vision loss and prominent eyes for 5 months prior to the visit to our eye hospital. Patient had sought advice from an ophthalmologist and internist. TED was eventually diagnosed 2 months after consulted with an ophthalmologist in the rural area. According to EUGOGO guidelines, TED with sight-threatening condition should be treated with glucocorticoid IV 500-1000 mg for 3 days consecutively. Although the patient was already given steroid injection for the initial treatment, the dosage was inadequate. After the inflammation process was reduced, the patient was reluctant to have an orbital decompression that was suggested. Hence, TED progressed continuously besides sight-threatening complications arising. He indeed underwent fat decompression and tarsorrhaphy as eyelid surgery to prevent corneal exposure. In follow-up, both visual acuity and corneal improvement were finally achieved. In the management of TED, collaboration between ophthalmologist and internist, who may be specialized in endocrinology, is imperative. They should be able to manage TED promptly and correctly, hence sight-threatening and other complications can be prevented and satisfactory results are achieved. Fat decompression should be considered as a good help to improve visual acuity nevertheless orbital decompression cannot be done.

Keywords: *grave's disease, thyroid eye disease, dysthyroid optic neuropathy, orbital decompression, fat decompression.*

INTRODUCTION

Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (hyperthyroidism). It is the most common cause of hyperthyroidism in the United States. Generally occurring in patients with hyperthyroidism, sometimes thyroid-associated ophthalmopathy or thyroid eye disease (TED) occurs in patients with euthyroid or hypothyroid chronic autoimmune thyroiditis. The condition has an annual adjusted incidence rate of 16 women and 3 men per 100,000 population.¹

TED is an autoimmune disorder that is associated with thyroid gland dysfunction which causes muscle and orbital fat enlargement. TED generally accompanies Graves hyperthyroidism where the course of eye disease does not always parallel with the activity of thyroid gland. The onset of TED can precede, together, or after the onset of hyperthyroidism.²⁻⁵

TED pathophysiology is complex and the treatment has not fully focused on the pathogenesis of the disease. Although the majority of TED cases are mild, around 3-7% of patients develop vision-threatening complications such as corneal damage or dysthyroid optic neuropathy (DON). The strategy for handling this disease consists of various methods such as medical therapy, surgery, and radiotherapy.⁴⁻⁶

The ability of ophthalmologists and internists to diagnose and assess the activity and severity of this disease correctly is expected to help determine the right treatment for patients. In an active TED, proper handling can improve vision, appearance, and quality of life. Therefore, TED is a challenge for ophthalmologists and internists both in diagnosis and appropriate management.⁴⁻⁶ This case report discussed severe TED with corneal damage and DON. Eventually, TED was diagnosed, yet the treatment given was not according to guidelines, so the patient was deteriorating and in high risk of losing his sight.

CASE ILLUSTRATION

A 64-year-old male was referred to our eye hospital presented with complaint of vision loss, protrusion and soreness on both eyes. Five months

prior, he complained of redness, swelling, and blurred vision. There was no other sign of systemic infection, previous illness, and family illness. All of these conditions lead his first-seen-ophthalmologist to diagnose his red eyes with an eye infection. Two months later, he went to an internist with a complaint of trembling, sweating, weight loss, heart palpitations, and sleep deprivation. There was no data about physical examination because he was seeking the internist in another hospital in rural area. The laboratory tests supported the diagnosis of hyperthyroidism and type two diabetes mellitus because he has high level of Total T3 (5.15 ng/mL), high level of Total T4 (20,7 µg/dL) and low level of TSHs (<0,02 µIU/mL). There was no data on blood glucose level. He was a heavy-smoker although he had already been advised to quit smoking. The patient was given Thiamazole 3x10 mg, Glimpiride 1x2 mg, and Univoxy® 1x1 tablet per day from the internist.

One month later, both of his eyes became protruded. Right eye (RE) was blind and left eye (LE) was otherwise normal. Clinically suspected with pseudotumors, the doctor evaluated him with orbital Computed Tomography (CT) Scan, but neither retrobulbar nor pseudotumor was found. This patient was then referred to ophthalmologist at another hospital in urban area.

One month later, he felt his LE vision began to be blurred. Orbital CT-scan depicted an orbital muscle enlargement with a coke-bottle sign and proptosis in both eyes, hence the patient was eventually diagnosed with TED and received steroid injections twelve times for three days (divided doses of steroid) of hospitalization consecutively from the first ophthalmologist. **(Figure 1)** The patient did not remember the dosage of steroid injection that was given by the ophthalmologist. In spite of the inflammation process that was subsided, one week later, swelling of both eyes became recurrent and the visual acuity of his LE got worsened until he lost his vision. The laboratory tests revealed a hypothyroid condition with low FT4 (0.28 ng/dL), high TSHs (28.834 µIU/mL) and low Total T3 (0.46 ng/mL). Hence, the internist in the second hospital reduced the dosage of Thiamazole to 1x10 mg. This patient did not have a regular schedule of follow up for thyroid and diabetes mellitus.



Figure 1. Axial, sagittal, and coronal CT-scan showed proptosis and extraocular muscles enlargement (coke-bottle sign).

The patient came to our eye hospital. On examination, there was no light perception (NLP) for the RE and light perception (LP) for the LE. He has 30° exotropia. Both eye movements were -4 in all directions (fixed eyeball). There were proptosis, edema on upper and lower eyelids, retraction of upper and lower eyelids, lagophthalmos, severe chemosis, and caruncular edema in both eyes. Corneal ulceration in the RE and corneal infiltrate in the LE were also recognized. Pupillary light reflexes were reduced for both eyes, so relative afferent pupillary defect (RAPD) was difficult to be assessed. Cataract could also be identified in both eyes. The result of Hertel exophthalmometers on each eye was 25 mm. Diabetes mellitus was again confirmed by laboratory tests with high level of HbA1c (NGSP 6.4% and IFCC 46 mmol/mol). At the same time, his hypothyroidism condition was supported by laboratory tests such as low FT3 (1.55 pg/mL), low FT4 (0.68 ng/dL), high TSHs (0.375 μ IU/ml), low Total T3 (0,51 ng/mL), low Total T4 (4,49 μ g/dL), high TRAb (15,74 IU/L), and low Anti-TPO (<0.5 IU/mL).

Based on all manifestations and work-up studies, this patient had complex problems due to the complications of Grave's disease, such as bilateral proptosis, RE corneal ulcer, LE exposure keratitis, bilateral dysthyroid optic neuropathy (DON), and bilateral immature cataracts. He was hospitalized and treated with Methylprednisolone intravenous (IV) 500 mg for three consecutive days, Chloramphenicol eye ointment 3 times/day, Citicoline 2x500 mg, Mecobalamin 2x500 μ g, Gatifloxacin eye drops every 3 hours, and Solcoseryl® eye gel every hour. After the methylprednisolone IV administration,

patient's blood glucose level increased to 355 mg/dL indeed. He was given insulin (Lantus 1x14 unit and Novorapid 3x10 unit) and Thiamazole 1x10 mg from the internist.

His LE vision was improved to 2/60 on his fourth day of hospitalization. However, he still had DON and at high risk for corneal perforations on both eyes, hence he was suggested to undergo an orbital decompression. As he was being reluctant to proceed, he underwent fat decompression and blepharorrhaphy. The procedures included chemosis incision, eyelid fat removal, upper and lower blepharotomy, amniotic membrane transplant, bandage contact lenses, and blepharorrhaphy. Two consecutive days after the surgery, he was given an infusion of 250 mg MP per day. The blepharorrhaphy was then released after 3 days. Central corneas were healed but left scars at the inferior corneas of both eyes.

During hospitalization, intraocular pressures (IOP) were high (20.7 mmHg for RE and 34.3 mmHg for LE). He was given Latanoprost-Timolol Maleate eye drops 2 times/day, Acetazolamide 3 x 250 mg, Potassium L-Aspartate 3 times/day, Calcium-Vitamin D₃ 2 x/day, Acetylsalicylic Acid 2 x 160 mg, Tobramycin-Dexamethasone eye drops 1 x/day, Gatifloxacin 4 x/day, Solcoseryl® 4 x/day, Selenium 1 tablet/day, Vitamin C 500 mg IV, Ciprofloxacin 2 x 500 mg and Mefenamic Acid 2 x 500 mg.

On the 11th day of hospitalization, his eye movements improved to -3 in all directions for both eyes and his dosage of Methylprednisolone was increased to 500 mg. He was finally allowed to go home on the 12th day of hospitalization. (**Figure 2, Figure 3**)



Figure 2. a) before surgery, there were eyelid retraction on the RE and chemosis on both eyes; b) eye condition after fat decompression and blepharorrhaphy was released. Chemosis was gradually diminished but caruncular oedema was still recognized. On the LE, eyelid oedema was slowly subsided.

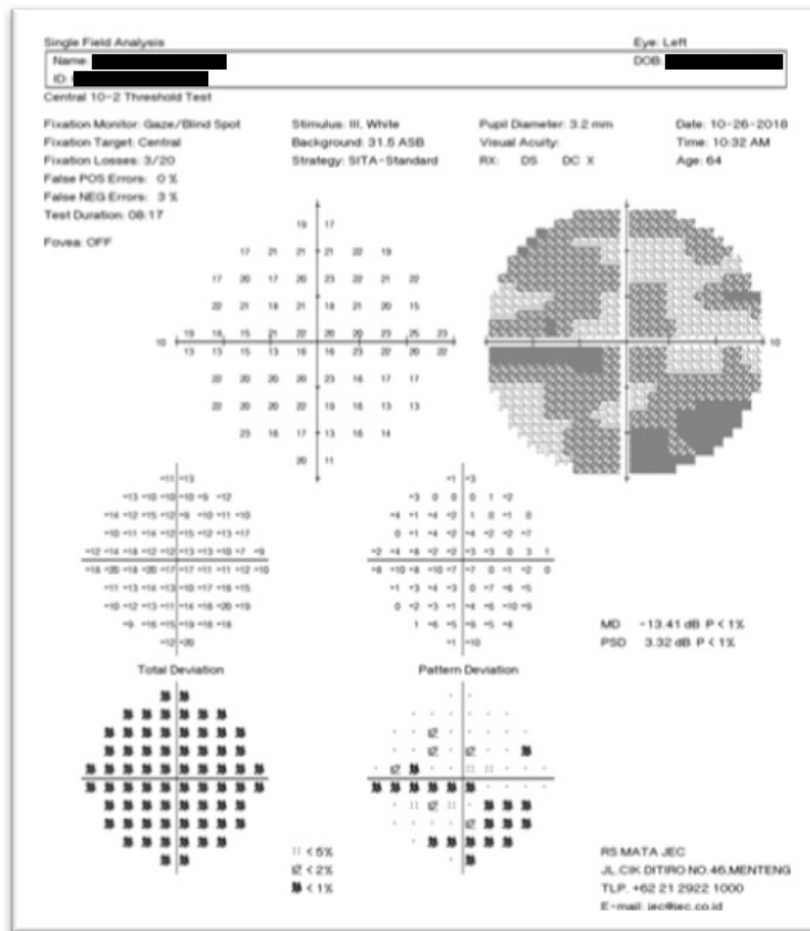


Figure 3. Perimetry of the LE demonstrated a visual field defect.

On the last visit, his eye pain was alleviated, vision of the RE remained NLP and vision of the LE improved to 0.1. Exotropia improved to 15° and both eye movements were improved in all directions as well. In spite of eyelid oedema, caruncular oedema and conjunctival chemosis that were still found, his eyes were generally improved compared to the initial condition. RAPD was positive in the RE. Ishihara test for the LE showed total colour blindness. **(Figure 4)**

DISCUSSION

The assessment recommended by The 2018 European Thyroid Association (ETA) guidelines for suspected Grave’s hyperthyroidism is Thyroid-Stimulating Hormone (TSH), free T3 (fT3), free T4 (fT4), TSH Receptor Antibodies (TRAb), and thyroid gland ultrasound examination. TSHs should be used as an initial screening test because it has the highest sensitivity and specificity for evaluating suspected Grave’s hyperthyroidism.

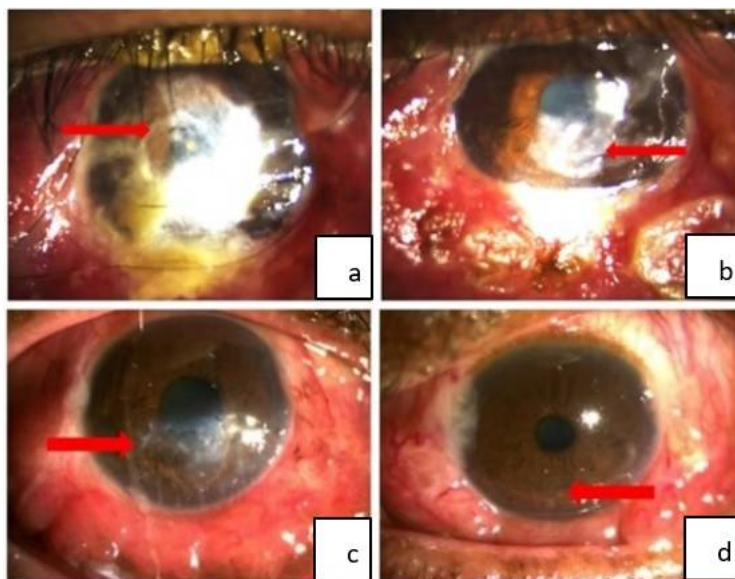


Figure 4. a) corneal ulcer on the RE; b) corneal infiltrate was seen on the LE; c) corneal leucoma (improvement on the RE); d) corneal nebula (improvement on the LE).

Serum TSH levels are more sensitive than thyroid hormone (T3, T4) tests for assessing thyroid hormone excess. Diagnostic accuracy improves when both serum TSHs and fT4 are assessed at the initial evaluation. TRAb measurements are also sensitive and specific in evaluating suspected Grave's hyperthyroidism. TRAb is a specific biomarker for the extrathyroidal manifestations of Grave's disease and correlates with TED activity and severity.⁷⁻¹⁰ In Grave's hyperthyroidism, 30-50% of patients will have ocular involvement. In one-third of TED cases, symptoms and signs appear altogether with hyperthyroidism.

Diagnosis of TED is made when 2 of the following 3 signs are present: (1) typical orbital signs (1 or more of the following): unilateral/bilateral eyelid retraction with typical temporal flares (with/without lagophthalmos), unilateral/bilateral proptosis, restrictive strabismus, compressive optic neuropathy, eyelid oedema/erythema, or caruncular oedema/chemosis; (2) immune-related thyroid dysfunction (1 or more of the following): Grave's hyperthyroidism, Hashimoto thyroiditis, or presence of thyroid antibodies without a coexisting dysthyroid state (TSH-receptor antibodies, thyroid-binding inhibitory immunoglobulins/TBII, thyroid-stimulating immunoglobulins/TSI,

anti microsomal antibody); (3) radiographic evidence of TED (enlargement of 1 or more of the following): inferior/medial/superior/lateral rectus muscle or levator palpebral muscle.¹⁻³

In this patient, the diagnosis of TED was made based on ophthalmology examination, laboratory tests, and orbital CT-scan findings. Orbital CT-scan of this patient demonstrated an extraocular muscle enlargement with tendon sparing and optic nerve compression at the orbital apex.^{11,12} Prior ophthalmologists were unable to recognize the disease despite all orbital signs, laboratory findings and CT-scan that supported the diagnosis of TED. As a result, the patient did not get the proper treatment immediately. Even after the patient was eventually diagnosed with TED, he was not given an appropriate treatment according to The European Group on Grave's Orbitopathy (EUGOGO) guidelines.

This patient had a poor prognosis because of several risk factors of TED including old age, smoking habits, and diabetes mellitus. Furthermore, the patient came to us when he already had DON. Therefore, these conditions deteriorated and lead his eyes to a severe sight-threatening TED consequently. In the age of 64 years old, he was considered as in the peak incidence of TED (age 45-49 years old and at 65-69 years old in men). DON generally

occurs at older ages (over age 60 years old).^{2,13} Hyperthyroid patient who smokes is five times higher to suffer from TED and will suffer more severe form than non-smokers. The risk of TED in an active smoker is related to the number of cigarettes smoked per day which causes the progression of TED. Smokers have a poor response to immunosuppressant therapy, hence, the patient should be advised to taper and stop smoking.^{2,5,6} Diabetes mellitus (DM) is also an important risk factor for the occurrence of DON. The incidence of DON in patient with DM is greater (15-35%) than without DM (3-4%) due to vasculopathy. Visual improvement is not significant in DON, smoker and diabetic patients.^{4,5,14}

In accordance to EUGOGO guidelines and Italian consensus, the priorities in TED cases are prompt correction of thyroid dysfunction and stable maintenance of euthyroidism, smoking cessation, conservative therapy for eyes, and assessing the activity and severity of TED. Based on 7/7 Clinical Activity Score (CAS), the patient was indicated as an active TED.^{2,4,6,15} It is imperative to determine TED activity because high-dose glucocorticoid is only effective in an active phase. Severity assessment is also important to decide whether it is worth running the risk of high-dose glucocorticoid or it is preferable to limit the therapeutic intervention to local and preventive measures.^{3,6,7} According to EUGOGO guidelines, the severity of TED in this case is categorized as sight-threatening (very severe) TED due to corneal damage and DON in both eyes. Both of these conditions are emergencies that must be treated immediately.^{4,6,7}

Until the third day of hospitalization, even though the patient already received an infusion of methylprednisolone 500 mg/day for 3 consecutive days, both eyes were still protruded, eyelids were still retracted, and lagophthalmos were still present. Thus, the risk for corneal perforation in both eyes was still inevitable. We decided to do chemosis incision and fat decompression, blepharotomy, amniotic membrane transplant for corneal ulceration, bandage contact lenses, and partial blepharorrhaphy in both eyes. This appears in line with EUGOGO recommendations that

stated severe corneal exposure should be treated immediately, medically or with surgery, to avoid corneal perforation. After blepharorrhaphy was released, both corneas were healed and the vision of the LE could finally improve.

In this case, methylprednisolone IV was continued until the second week with total of 3 grams. Vision of the RE did not improve but vision of the LE improved from LP to 2/60. The pupillary light reflexes of both eyes were still decreased, so DON has not been resolved. Therefore, it was required to do orbital decompression surgery for the LE. Instead, the patient was reluctant to undergo such surgery. We decided to continue giving Methylprednisolone IV, corresponding to EUGOGO guidelines for severe TED treatment (infusion of Methylprednisolone 500 mg/week for 6 weeks, followed by infusion of Methylprednisolone 250 mg/week for 6 weeks, with the total limit should not exceed 8 grams).⁶ On the last day of treatment, RE vision remained NLP and LE vision improved to 0.1.

Surgery for TED is not advised until a euthyroid state is maintained and it has been in the stable phase for at least 6-9 months. Exceptions include DON or corneal damage, in which cases urgent surgical intervention is warranted.^{18,19} Studies from Kahaly *et al* and Vaphiades *et al* revealed case series of 3 patients who had DON with NLP vision and onset of 5 days to 3 months, showed a return of vision following orbital decompression surgery suggesting that axonal death may be delayed by months after total nerve function loss. Orbital decompression surgery may still be effective in reversing compressive optic neuropathy in patients with NLP vision of up to 3 months.^{7,20}

The TED course is conceptualized by the Rundle's Curve. TED consists of 2 phases, the inflammatory/active phase which lasts for 6-24 months, followed by the inactive phase where fibrotic changes occur.⁴⁻⁶ TED treatment during the active phase aims to reduce the immune and inflammatory reactions and to limit destructive consequences. In our case, the active phase had occurred 5 months before the patient was treated with methylprednisolone infusion. Referring to Rundle's Curve, it was more difficult to shift this

disease to be inactive. Therefore, TED is indeed a challenge for ophthalmologists and internists, both in the diagnosis and management. It is crucial to be able to diagnose TED immediately because early initiation of therapy lead to a better prognosis.^{4,5,6}

CONCLUSION

The ability to diagnose TED promptly and manage this disease correctly is importantly needed to prevent sight-threatening complications and to achieve satisfying results. A collaboration between internist, who may be subspecialized in endocrinology, and ophthalmologist should be established to control and treat the associated systemic disease.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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