# Severe Graves Orbitopathy in a Euthyroid, Thyroid Stimulating Hormone Receptor Antibody-Negative, 64-Year-Old Male: A Case Report

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**Introduction.** Graves orbitopathy (GO) is an autoimmune disease affecting the orbits and the periorbital tissues with an annual incidence of 16 per 100,000 population in women and 2.9 in men. While GO occurs in the spectrum of hyperthyroidism or Graves disease, 7.9% of these patients have a normal thyroid function and only a few are negative for thyroid antibodies. When left untreated, GO may become debilitating and threaten vision.

**Case description.** A 64-year-old male presented with gross bilateral proptosis and chemosis, which developed over a period of 10 years. Palpitations, hand tremors, heat intolerance, weight loss, and insomnia were notably absent, and the thyroid gland was normal. The bilateral proptosis was left unattended for 10 years until extreme lagophthalmos and chemosis with corneal and mucosal exposure leading to dryness, foreign body sensation, excruciating eye pain, and blurred vision resulted. Thyroid-stimulating hormone (TSH), T3, and T4, were normal. TSH-receptor antibody (TRAb) and thyroid peroxidase antibody were negative. The computed tomography scan with contrast of the orbits showed bilateral proptosis and extraocular muscle enlargement typical for thyroid eye disease. The patient was diagnosed with TRAb-negative euthyroid GO with a European Group on Graves' Orbitopathy (EUGOGO) clinical score of 7/7, indicating a severe, active disease. Screening prior to administration of GO immunosuppressive therapy revealed chronic hepatitis B infection. The patient was started with tenofovir for 2 weeks before treatment for GO. The patient was given intravenous methylprednisolone with cumulative dose of 4.5 g for 12 weeks, with daily mycophenolate sodium 0.72 g for 12 weeks. Upon completing the 12-week treatment regimen and undergoing an adjunctive lateral canthotomy and partial tarsorrhaphy, the GO signs and symptoms dramatically resolved, and visual acuity markedly improved.

**Conclusion.** This case report presents an unusual condition of a euthyroid, TRAb-negative Graves orbitopathy. It provides insights on the diagnosis and treatment of patients with such atypical presentation. Despite the chronicity and severity of this patient's GO, excellent results were achieved with appropriate and guideline-directed treatment.

**Keywords.** *Graves orbitopathy, Euthyroid, Proptosis, Methylprednisolone pulse therapy, Mycophenolate sodium*

## Introduction

Graves orbitopathy (GO), also known as thyroid eye disease or Graves ophthalmopathy, is an autoimmune disorder primarily affecting the orbit and its surrounding tissues.[1] Its annual incidence is 16 per 100,000 population in women and 2.9 in men.[2] The prevalence of patients with GO in euthyroid state varies between 0.9% and 15.4%. The frequency of GO in Asians with hyperthyroidism ranges from 35% to 60%.[3] In the Philippines, the prevalence of GO is 48%, with individuals aged 30 to 49 years being the most affected.[4]

Eighty to ninety percent of patients with ophthalmopathy have hyperthyroidism.[2] In contrast, only 10% of GO patients present with minimal to absent signs and symptoms of thyroid hormone abnormalities. This type of

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isolated ophthalmopathy is classified as euthyroid Graves ophthalmopathy (EGO).[5] Individuals with EGO have milder ophthalmic symptoms of eyelid retraction, proptosis, restrictive strabismus, and dysthyroid optic neuropathy.

EGO remains a unique presentation of Graves disease, rendering the diagnosis difficult to make. Thyroid-stimulating hormone (TSH)-receptor antibody (TRAb)-negative orbitopathy is an even rarer condition, which makes the diagnosis even more challenging.[6] This may lead to delayed diagnosis or even misdiagnosis, inappropriate management, subsequent disfigurement, and vision impairment.

We present a case of a euthyroid adult male with gross proptosis and overt mucosal protrusion in both orbits, which progressed over a period of 10 years. This report serves to improve recognition and management of EGO.

## Case Presentation

A 64-year-old male presented with gross protrusion of both orbits, with severe periorbital swelling and conjunctival eversion in both eyes. Ten years prior to consultation, the patient started to have bilateral proptosis, which gradually progressed to the present condition. There were no associated tremors, fever, heat intolerance, skin lesions, nervousness, or significant unintentional weight loss, dyspnea, chest pain, or changes in eating habits.

In the interim, there was worsening bilateral periorbital swelling, gradually increasing in intensity, associated with lacrimation, redness, and pain. He occasionally self-medicated with oral prednisone 10 mg/tablet, which offered temporary relief. The patient did not seek any medical consultation, so no diagnostic work-up was done.

Six months prior to consultation, the patient developed eversion and exposure of the conjunctiva of the both eyes, resulting in lagophthalmos, dryness, excruciating eye pain, and blurring of vision, prompting the initial medical consultation.

The patient had no comorbidities, and he was not on any maintenance medications. He had a 26 pack-year smoking history and consumed alcoholic beverages occasionally. He denied illicit drug use, and he had no known food or drug allergies. There were no known hereditary familial diseases. Specifically, he had no family history of thyroid disorders or relatives with proptosis. There was no known direct exposure to active tuberculosis.

On examination, he was awake and alert with stable vital signs. The neck had neither visible enlargement nor masses. The thyroid gland was normal in size, soft, smooth, symmetrical, non-tender, and rose slightly with swallowing. Focused examination of both eyes done by the ophthalmology service is presented in Table 1.


**Figure 1**: The patient's eye findings before initiation of intravenous methylprednisolone and mycophenolate sodium. Physical examination revealed bilateral marked proptosis with associated lower lid eversion and chemosis affecting mostly the left eye and could not fully cover the exposed left conjunctiva.

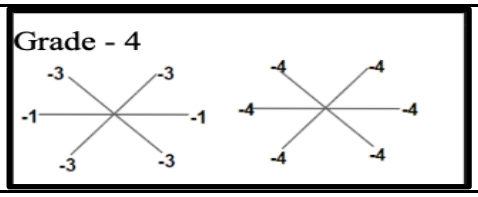
| | |
|---|---|
| Physical examination | (+) Marked proptosis, bilateral<br>(+) Lid inversion, left eye<br>(+) Exposed conjunctiva, left<br>(+) Cannot close left eyelids, thus unable to fully cover the exposed conjunctiva, left |
| Visual acuity | OD: 8/200<br>OS: Hand motions with good light perception |
| Pupils | OD: 2–3 mm BRTL<br>OS: 3 mm NRTL |
| Intraocular pressure | OD: 18<br>OS: 22 |
| Extraocular muscle mobility |  |
| Slit lamp | (+) Periorbital swelling<br>(+) Exposure keratopathy<br>(+) Corneal thinning |

**Table 1**. Complete ophthalmological physical examination of the patient prior to initiating treatment

Taking the patient's clinical history and physical examination, the differential diagnoses revolved around diseases that presented primarily with proptosis associated with other eye symptoms. These were orbital lymphoma, cranial space-occupying lesions, cavernous malformations, thyroid eye disease (TED), and Graves ophthalmopathy. These conditions similarly present with gradual proptosis. GO and TED typically present bilaterally, whereas the other conditions more frequently affect one eye. Imaging studies ruled out the presence of lymphoma, masses, and cavernous malformations.

Thyroid function tests T3, T4, and TSH were all within normal range. TRAb, thyroid peroxidase antibody, and thyroglobulin antibodies were also normal. Paradoxically, the absence of abnormal results among these tests would likely rule out pathologies related to a thyroid disease. However, the axial orbital computed tomography (CT) scan revealed the characteristic finding of symmetric extraocular muscles typically found in cases of GO, clinching the diagnosis.

| | **Actual value** | **Normal value** |
|---|---|---|
| Free thyroxine | 10.24 pmol/L | 7.90–14.000 |
| TSH | 0.56 µIU/mL | 0.38–5.33 |
| TRAb | <0.800 IU/L | <1.75 |
| Thyroglobulin antibody | 0.0 IU/mL | <4.00 |
| Thyroglobulin | 10.1 ng/ml | 1.59–50.03 |
| Thyroid peroxidase antibody | 0.6 IU/mL | <9.00 |

**Table 2**. Thyroid profile and thyroid autoantibody results

A cranial CT scan with contrast revealed proptosis of both globes, with the distance of the anterior surface of the globe from the interzygomatic line measuring 3.2 cm in the right and 3.4 cm in the left. The orbital septum was enlarged and bulging anteriorly. No masses were found. There was fat stranding in the bilateral periorbital regions, with soft tissue density measuring 2.0 x 4.1 x 1.1 cm in the left orbit. There was also increased orbital fat and symmetric extraocular muscle enlargement on both sides with the following measurements:

| | Right | Left |
|---|---|---|
| **Inferior rectus:** | 0.7 cm | 0.8 cm |
| **Medial rectus:** | 0.8 cm | 0.9 cm |
| **Superior group:** | 1.1 cm | 1.0 cm |
| **Lateral rectus:** | 0.9 cm | 0.9 cm |

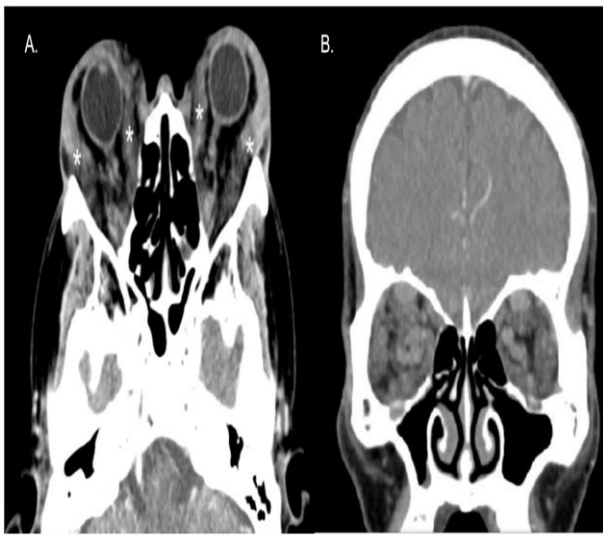



**Figure 2.** Axial orbital CT scan (A) shows an increase in orbital fat and enlargement of the extraocular muscles marked by {*}. Coronal orbital CT scan (B) shows bilateral enlargement of extraocular muscles.

The patient was diagnosed with TRAb-negative Euthyroid GO with a clinical activity score 7/7 (presence of spontaneous retrobulbar pain, pain on upward or downward gaze, redness of conjunctiva, swelling of caruncle, swelling of eyelids, and swelling of conjunctiva), indicating severe active GO.

The primary treatment plan was based on the European Group on Graves' Orbitopathy (EUGOGO) 2021 Clinical Practice Guidelines using a course of methylprednisolone 0.5 grams intravenous once weekly for 6 weeks, followed by 0.25 grams/week for 6 weeks in combination with mycophenolate sodium 0.72 g daily for 24 weeks.

Routine screening prior to treatment initiation revealed seropositive hepatitis B surface antigen, hepatitis B virus DNA, and antibody to hepatitis B core, indicating chronic hepatitis B infection. The patient was started with tenofovir 300 mg/tablet, one tablet once a day for 2 weeks prior to GO treatment. The patient underwent lateral canthotomy with partial tarsorrhaphy on his third week of intravenous methylprednisolone with mycophenolate sodium, to further reduce the proptosis and avoid further complications caused by lagophthalmos.

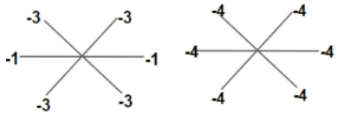
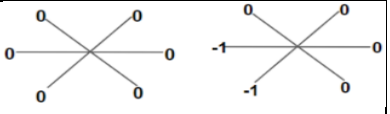

**Figure 3**. The patient after tarsorrhaphy and three cycles of methylprednisolone pulse therapy + mycophenolate sodium. There is a noticeable reduction of chemosis (*) and proptosis, with noted improvement in visual acuity after ophthalmologic exam.

Throughout the treatment, alanine aminotransferase levels were consistently monitored and remained below the upper normal limit, to detect any potential hepatitis B flare.

After 12 weeks of intravenous methylprednisolone with a cumulative dose of 4.5 grams in combination with mycophenolate sodium 360 mg/tab, one tablet twice daily, there was marked reduction of proptosis, chemosis, and lagophthalmos, as well as resolution of eye pain and foreign body sensation and improvement in vision.

**Figure 4.** The patient prior to initiating EGO treatment (A). After 12 cycles of intravenous methylprednisolone and mycophenolate sodium (B, C), the proptosis on the right eye has been resolved (B), while on the left eye there was a great reduction of the bulging palpebral conjunctivae (C).

Table 3 shows the comparison of the physical examination of the bilateral eyes before and after 12 weeks of weekly intravenous methylprednisolone and daily mycophenolate sodium regimen for the patient.

| **Table 3.** Comparison of ophthalmologic findings before and after 12 weeks of intravenous methylprednisolone with mycophenolate sodium**Parameters** | **Baseline findings** | **After 12 cycles of intravenous methylprednisolone + mycophenolate sodium** |
|---|---|---|
| Signs and symptoms | (+) Periorbital swelling<br>(+) Difficulty of sleeping<br>(+) Foreign body sensation<br>(+) Blurring of vision, left eye<br>(+) Lagophthalmos<br>(+) Throbbing pain<br>(+) Left-sided headache<br>(+) Epiphora<br>(+) Eye redness, bilateral<br>(+) Swelling of the conjunctivae | (↓) Periorbital swelling<br>(-) Foreign body sensation<br>(-) Blurring of vision, left eye<br>(-) Lagophthalmos<br>(-) Throbbing pain<br>(+) Swelling of the conjunctivae |
| Physical examination | (+) Marked proptosis, bilateral<br>(+) Lid inversion, left eye<br>(+) Exposed conjunctiva, left<br>(+) Cannot close left eyelids, thus unable to fully cover the<br>(↓) Exposed conjunctiva, left | (↓) Proptosis, bilateral<br>(↓) Lid inversion, left eye<br>(+) Able to close the left eye, thus able to fully cover the |
| Visual acuity | OD: 8/200<br>OS: HMGLP<br>OS HP: NO IMPROVEMENT | OD: 20/100<br>OS HP: 20/50 |
| Pupils | OD: 2–3mm BRTL<br>OS: 3 mm NRTL | OD: 2–3 mm BRTL<br>OS: 3 mm NRTL |
| IOP | OD: 18<br>OS: 22 | OD: 18<br>OS: Hypotonic |
| EOM mobility |  **Grade -4** |  **Grade 1** |
| Slit lamp | (+) Periorbital swelling<br>(+) Exposure keratopathy<br>(+) Corneal thinning | (-) Periorbital swelling |

## Discussion

The hallmark of Graves disease is the low TSH and elevated thyroid hormones and the TRAb, which is almost always present in patients with the condition.[7] GO, on the other hand, may occur with normal thyroid function and with either positive or negative TRAb. In this case, the patient was euthyroid and was negative for thyroid autoantibodies, including the TRAb. Therefore, the diagnosis of GO in our case was made based on clinical parameters and imaging characteristics on CT scan of the orbits. The typical imaging characteristics of GO, such as bilateral proptosis, extra-ocular muscle enlargement and periorbital fat deposition, were all seen in the patient and solidified the diagnosis.

These are the plausible reasons for the negative thyroid autoantibodies in the setting of GO. First, is the duration

of the disease. The longer the duration of the disease, fewer or no antibodies can be detected.[7] Second is that the presence of intrathyroidal TRAbs on affected cells are not exposed to the circulation and therefore are undetectable by available assays.[8] Lastly, current tests may have inadequate sensitivity to detect low antibody activity. Again, our patient had the condition for more than 10 years already, thus possibly affecting the detection of the TRAb.

The pathogenesis of GO involves the stimulation of the orbital fibroblasts to produce insulin-like growth factor-1 by the TSH receptor antibodies and T cells.[8] This results in the production of glycosaminoglycans, specifically hyaluronic acid that accumulates in the extraocular muscles. The orbital fibroblasts are also stimulated to differentiate into adipocytes and myofibroblasts that result in orbital adipose tissue expansion, orbital inflammation, and tissue remodeling, causing increased extraocular muscle volume with excess retro-ocular fat. These result in proptosis, diplopia, congestion, and periorbital edema.[9]

Smoking is one frequently associated factor that increases the risk of developing GO.[10] Accentuation of fibroblast human leukocyte antigen–DR expression and hypoxia contribute to the disease severity. Time and length of smoking exposure affect the management of the disease.[9] The patient had a 26 pack-year smoking history which could have contributed to the development and progression of the disease.

The clinical activity score (CAS) is a standardized 7-point scoring system to assess the activity and severity of GO. It consists of the following: spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of caruncle or plica, swelling of eyelids, and swelling of conjunctiva (chemosis). CAS <3 indicates inactive GO, while CAS $\geq$3 indicates active disease.[11] The patient had a CAS of 7, classifying the condition as active and severe GO.

Moderate-to-severe (MTS) GO requires immunosuppression in active disease and/or surgical interventions in inactive disease.[11] Two large randomized clinical trials established the first-line treatment for MTS GO as a dual therapy of glucocorticoid and mycophenolate. In a 2017 single-center trial, dual therapy with intravenous glucocorticoid and mycophenolate mofetil exhibited an overall superior response rate (71% vs 51 at week 12) and disease inactivation rate (94% vs 69% at week 24) when compared with a pure glucocorticoid combination regimen.[12] Treatment with intravenous glucocorticoid, namely methylprednisolone, provided an 83% vs 11% response rate in GO when compared with placebo, with the route preferred in terms of efficacy and tolerance over the oral route (77-88% vs 51-63%).[12,13]

Before initiating the intravenous methylprednisolone regimen, the patient was revealed to have chronic hepatitis B infection, which raised a treatment dilemma since based on EUGOGO guidelines, patients having an infection like hepatitis B may be disqualified from initiation of the therapy since it may result in a flare. However, studies showed that patients treated with antiviral prophylaxis showed reduced hepatitis flare, especially with steroid therapy for more than 4 weeks.[14] Prior to starting therapy, the patient had a 2-week course of tenofovir 300 mg/tab, 1 tablet once a day, and was subsequently kept on it throughout the GO treatment regimen.

According to the current EUGOGO guidelines, the duration of the disease may negatively affect treatment response. Immunosuppressive medications have less effect on patients having the disease for more than 18 months.[14] However, our case showed a very good treatment response to the regimen despite the 10-year chronicity and severity of his GO.

A lateral canthotomy with partial tarsorrhaphy was done to the patient, mainly to reduce chemosis, with a goal of decreasing spontaneous eyeball perforation, maintenance of vision, and preventing irreversible damage such as scarring. Surgical intervention is adjunctive in the prevention of effects caused by severe chemosis in GO patients.[15]

## Conclusion

Euthyroid TRAb-negative GO is a rare condition that presents significant challenges in both diagnosis and treatment. A timely diagnosis is crucial in preventing disease progression and optimizing patient outcomes. In this case, a thorough medical history and physical examination, supplemented by appropriate laboratory tests and imaging, led to the diagnosis of the patient's decade-long orbitopathy. Management decisions were guided by the disease's clinical activity and duration. This case highlights that even in patients with severe, active, and long-standing GO, substantial resolution can still be achieved through the recommended cornerstone therapy of intravenous methylprednisolone and mycophenolate sodium.

## Conflict of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010 Feb 25;362(8):726-738.

2. Hiromatsu Y, et al. Graves' ophthalmopathy: epidemiology and natural history. Intern Med. 2014;53(5):353-360.

3. Macovei ML, et al. A systematic review of euthyroid Graves' disease (Review). Exp Ther Med. 2021 Nov;22(5):1346

4. Lat, AM, et al. Risk factors associated with the activity and severity of Graves' ophthalmopathy among patients at the University of the Philippines Manila–Philippine General Hospital. J ASEAN Fed Endocr Soc. 2017;32(2):151-157.

5. Şahlı E and Gündüz K. Thyroid-associated ophthalmopathy. Türk Oftalmoloji Dergisi. 2017;47(2):94-105.

6. Moeen Z, et al. An interesting case of euthyroid Graves' ophthalmopathy, with negative thyroid-stimulating hormone receptor antibodies. Cureus. 2021;13(10):e19015.

7. Tabasum A, et al. Thyroid antibody-negative euthyroid Graves' ophthalmopathy. Endocrinol Diabetes Metab Case Rep. 2016;2016:160008.

8. Kamath C, et al. The role of thyrotrophin receptor antibody assays in graves' disease. J Thyroid Res. 2012;2012:525936.

9. Khoo TK and Bahn RS. Pathogenesis of Graves' ophthalmopathy: the role of autoantibodies. Thyroid. 2007;17(10):1013-1018.

10. Muñoz-Ortiz J, et al. Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: a systematic review of the literature. Syst Rev. 2020;9(1):201.

11. Bartalena L, et al; EUGOGO. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021;185(4):G43-G67.

12. Kahaly GJ, et al; European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. Lancet Diabetes Endocrinol. 2018;6(4):287-298.

13. Ye X, et al. Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy. Clin Endocrinol (Oxf). 2017 Feb;86(2):247-255.

14. Lin YC, et al. The prevalence and risk factors of hepatitis B flares in chronic hepatitis B patients receiving glucocorticoid pulse therapy. Int J Clin Pharm. 2018 Feb;40(1):169-174.

15. Baldeschi L. Rehabilitative surgery. In: Graves' Orbitopathy A Multidisciplinary Approach – Questions and Answers, 3rd ed. Basel, Switzerland: Karger; 2017.