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International Journal of Clinical Case Reports and Reviews
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Case Report

Keeping an Eye on Graves' Ophthalmopathy: Case Series

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Received Date: June 20, 2025 | **Accepted Date:** July 02, 2025 | **Published Date:** July 28, 2025

Citation: Emanuelle L Ferreira, Heloisa Moreira de Lima, Caio Hayashi, Isadora Bulati, Aline Maciel, et al, (2025), Keeping an Eye on Graves' Ophthalmopathy: Case Series, *International Journal of Clinical Case Reports and Reviews*, 28(2); **DOI:10.31579/2690-4861/893**

Abstract:

Graves' orbitopathy (GO) is the most common extrathyroidal manifestation of Graves' disease (GD) and manifests itself in symptoms and signs of involvement of the orbits and neighboring tissues. Approximately 15% of patients with GD who do not present clinical signs of GO at the onset of the disease will develop it in the first 3 to 6 months. TSH receptors are also expressed in several extrathyroidal tissues, especially in the retroorbital tissues. For this reason, complaints such as strabismus, diplopia, proptosis (exophthalmos) and eyelid retraction are common in this ophthalmopathy.

Its incidence is higher in women, as it is an autoimmune disease, but it is still considered relatively rare, with 5-6% of cases classified as moderate to severe. Therefore, as it is a less frequent condition, this case series aims to report the diagnosis and management of Graves' orbitopathies in two male patients with moderate activity of severe disease in a large endocrinology service. By considering and expanding the dissemination around this diagnosis, it may be possible to improve the prognosis of these patients, preventing fibrosis and sequelae such as changes in appearance, proptosis and dysfunction of the extrinsic ocular muscles.

The objective of this study is to highlight possible errors in the diagnosis and treatment of Graves' disease and ophthalmopathy that may lead to future consequences.

Key words: graves' disease; graves' ophthalmopathy; ocular findings; clinical evaluation

Introduction

Graves' orbitopathy (GO) is the most common extrathyroidal manifestation of Graves' disease (GD) and manifests itself in symptoms and signs of involvement of the orbits and neighboring tissues [1]. It consists of an initial phase of gradual deterioration (lasting 6 to 12 months) followed by a phase of slow improvement (lasting 2 to 3 years) [1].

The incidence is higher in women, as it is an autoimmune disease, and other risk factors include certain genetic factors (however, specific genes or mutations remain unidentified in having a direct causal relationship) and exposure to radioiodine as a treatment modality for Graves' disease [2,3]. It is still considered relatively rare and often misdiagnosed as conjunctivitis or allergy [4]. Just 2 to 6% of cases are classified as moderate to severe [5]. And GO is a major therapeutic challenge in these forms, often incompletely responsive to available medical treatments [6].

The onset of the disease is usually interconnected with the hyperthyroid state in 80 to 90% of cases, however, there may be situations in which GO precedes or appears after the resolution of hyperthyroidism.

The underlying cause is molecular mimicry with the TSH receptor in ocular fibroblasts, leading to an immuno-mediated pathogenesis [7]. The pathophysiology occurs through the production of autoantibodies, especially TRAb, which binds to the TSH receptor and generates hyperproduction of thyroid hormones. This receptor is expressed in thyroid cells, but also in adipocytes, fibroblasts, among others. The production of these autoantibodies activates T lymphocytes and IGF-1 receptors, which mediate the pathophysiology of orbitopathy through inflammation and cell expansion [8].

Since this condition is still considered rare, this case series aims to report the diagnosis and management of Graves' orbitopathies in a large endocrinology service. In this article, there are peculiarities that are important to be highlighted, such as the possible differential diagnoses of

asymmetric ophthalmopathy and the treatment of Graves' disease in these patients.

Case description:

Case 1:

Patient B.C., male, 65 years old. Hypertensive, non-smoker, diagnosed with Graves' disease in 2023, using tapazol 10 mg/day since diagnosis.

He began his follow-up at the endocrinology service of Mackenzie University Hospital in June/2024, with complaints of ocular irritation, proptosis, paralysis of movement in the left eye, eyelid retraction and diplopia (Figure 1). He denied previous treatment, other than the antithyroid drug.

Among the initial evaluation exams, laboratory tests were performed, which showed:

TSH 8.28 mIU/ml (VR 0.38-5.33 mIU/ml), T4L 0.81 ng/dL (VR 0.61-1.12 ng/dL), T3L 3.43 pg/mL (VR 1.81-4.59 pg/mL), TRAb 4.02 UI/L (VR < 1.75 UI/L). Patient reported to medical team that, at the end of 2023, he noticed worsening of ocular symptoms and sought an ophthalmology service, which performed a magnetic resonance imaging exam with imaging criteria for inflammatory pseudotumor of the orbits (Figure 2) and description, in the examination report, of volumetric asymmetries between the optic nerves, with a volumetric reduction observed in the cross section of the right optic nerve in percentages of approximately 50%, when correlated with the contralateral optic nerve. At the time, his drug treatment was maintained.

About the severity of the disease the patient had: reduced eyelid opening, proptosis, and constant diplopia. There was no corneal involvement.

The degree of activity was assessed using the clinical activity score (CAS score), shown in Table 1.

The patient was then hospitalized for additional exams and to begin treatment for the ophthalmopathy.

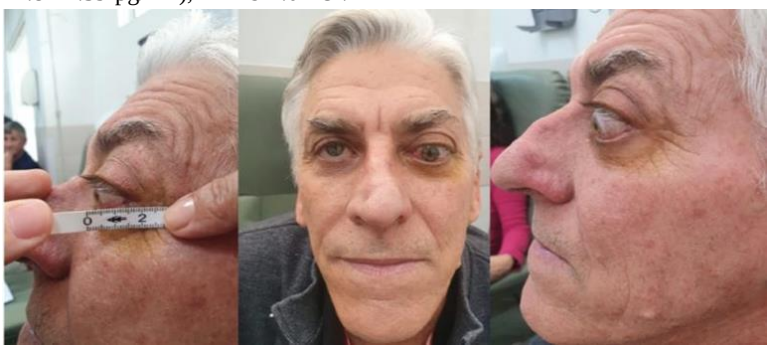

Figure 1: Ectoscopy of B.C. patient demonstrating: proptosis, eyelid retraction and dysfunction of the extrinsic ocular muscles.

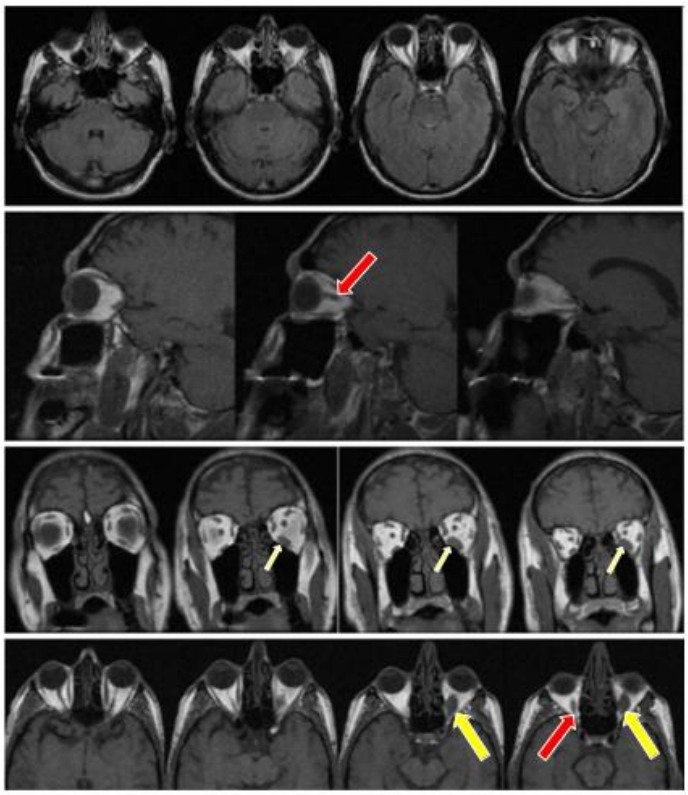

Figure 2: Magnetic resonance imaging (MRI) - Line 1: axial section in the Flair sequenc

Line 2: sagittal section, in T1 sequence. Line 3: coronal section, in T1 sequence. Line 4: axial section, in T1 sequence. Showing typical findings of Graves' orbitopathy with marked fusiform thickening in the fascicles of the bellies of the extrinsic muscles of the right and left orbits (red arrow), severely in the belly of the inferior rectus muscle on the left (yellow arrow).

Case 2:

Patient C.C.O., male, 67 years old. Previously dyslipidemic and with a history of ischemic stroke in 2023, in addition to being an active smoker of approximately 50 pack-years. He began his follow-up at the Mackenzie University Hospital in May/2024, when he was referred from Marialva, his city of residence, for an ophthalmological evaluation.

The patient reports a history of hyperthyroidism since 2020, using tapazol since diagnosis- at the time, he presented unquantified weight loss and ocular proptosis, but denies tremors, palpitation or goiter. He was using tapazol 10 mg from Monday to Thursday, and 20 mg from Friday to Sunday. In July/2023, the patient noticed worsening of proptosis with the appearance of hyperemia and ocular pain, denying specific treatments for the condition until the time of his admission.

At the initial evaluation by the ophthalmologist, the patient presented ocular proptosis, pain when moving the eyes, hyperemia and edema of the conjunctiva, eyelids and caruncle (Figure 3) - the degree of activity was assessed using the CAS score, shown in Table 1. He was admitted for evaluation by the hospital's ophthalmology service, where a computed tomography scan of the orbits was performed, which detected hypertrophy of the inferior and superior medial rectus muscles, bilaterally, in addition to bilateral ocular proptosis, more significant on the right (Figure 4). He opted for hospitalization to perform additional tests and begin treatment for the ophthalmopathy.

Among the initial evaluation exams, laboratory tests were performed, which showed TSH 7.54 mIU/ml (VR 0.38-5.33 mIU/ml), T4L 0.79 ng/dL (VR 0.61-1.12 ng/dL), T3L 2.83 pg/mL ((VR 1.81-4.59 pg/mL), TRAb 5.01 UI/L (VR <1.75 UI/L). These findings were compatible with methimazole overdose - treatment that was adjusted during hospitalization. Imaging exams for cardiological evaluation were also performed, such as transthoracic echocardiogram and carotid and vertebral Doppler, both exams being within normal limits - with no signs of tachycardiomyopathy due to hyperthyroidism and without significant stenosis in the carotid and vertebrobasilar territory.

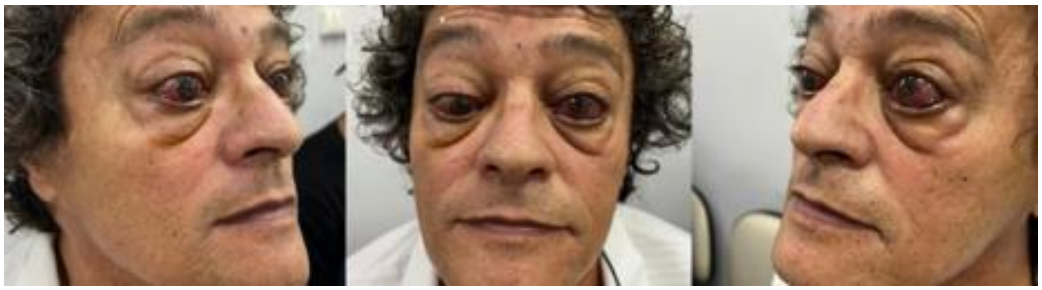

Figure 2: Magnetic resonance imaging (MRI) - Line 1: axial section in the Flair sequence.

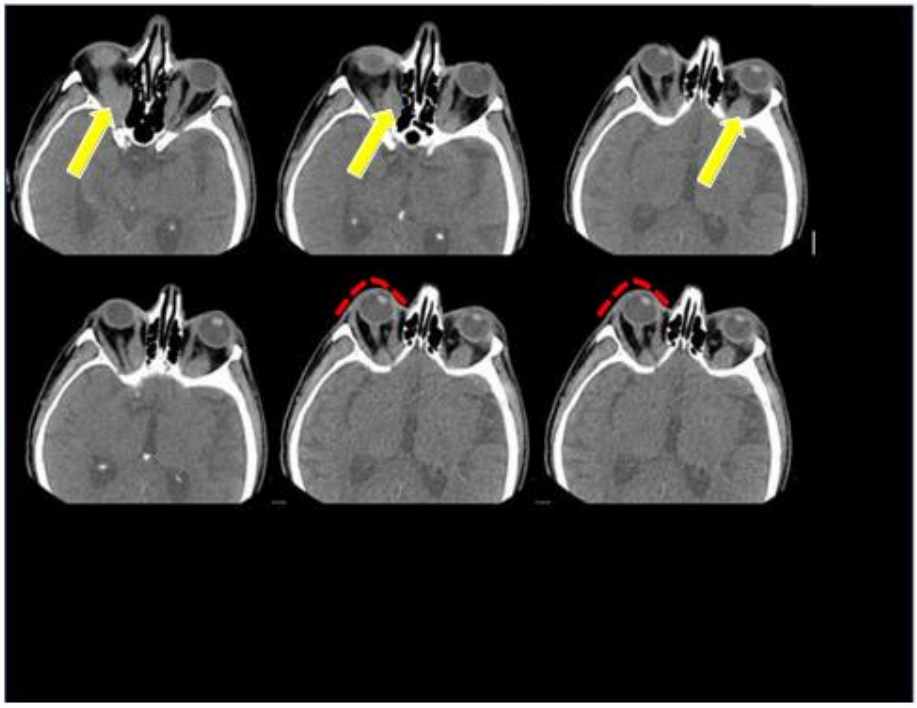

Figure 4: Computed tomography (CT) images of the orbits of C.C.O patient. In lines 1 and2, in the transverse plane, and in line 3 in the sagittal plane. It demonstrates hypertrophy of the inferior and superior rectomedial muscles (yellow arrow), bilaterally, in addition to bilateral ocular proptosis, more evident on the right (red dashed). Findings compatible with Graves' ophthalmopathy.

CAS parameters [9]	Criteria present in the patient 1	Criteria present in the patient 2
• Spontaneous retrobulbar pain		
• Pain when moving the eye up or down	X	X
• Eyelid erythema		
• Conjunctival erythema		X
• Eyelid edema	X	X
• Inflammation of the caruncle and/or plica	X	X
• Conjunctival edema		X

Table 1: Comparison of the classification of the degree of ophthalmopathy activity (CAS) in the two reported patients.

	Classification of severity of ophthalmopathy:		
	Mild	**Moderate to severe**	**Very severe**
Impact on daily activities:	Minor	Present, however, without threat to vision.	Present, with threat to vision.
Number of factors present:	One or more factors below:	Two or more factors below:	At least one below:
Factors evaluated according to each severity	*Eyelid retraction < 2mm *Mild soft tissue involvement *Exophthalmos < 3mm above the upper limit of normal for sex and race *Absence or intermittent diplopia/corneal exposure	*Eyelid retraction > 2 mm *Moderate to severe soft tissue involvement *Exophthalmos >= 3 mm above the upper limit for sex and race *Constant or intermittent diplopia	*Dysthyroid optic neuropathy (DON) and/or *corneal breakdown.

Table 2: Comparison of the classification of the severity of ophthalmopathy in the two reported patients.

Mild disease comprises one or more of the following: minor lid retraction < 2 mm, mild soft-tissue involvement, exophthalmos < 3 mm above normal for sex and race, and transient or no diplopia. Moderate-to-severe disease comprises one or more of the following: lid retraction > 2 mm, moderate-to-severe soft-tissue involvement, exophthalmos > 3 mm above normal for sex and race, and inconstant or constant diplopia. Finally, sight threatening disease includes DON, or corneal breakdown [6].

Moderate to severe		
Factors:	**Pacient 1**	**Pacient 2**
Eyelid retraction > 2 mm		
Moderate to severe soft tissue involvement	X	X
Exophthalmos >= 3 mm above the upper limit for race and gender	X	X
Constant or intermittent diplopia	X	X

Table 2.1: Classification according to factors present in each patient. The authors highlight the factors present in both patients.

Management:

The objective of this case series is to report the diagnostic and treatment difficulties in these patients, which will have an impact on the prognosis.

The first example is of the patient in Report 1, whose asymmetric symptoms suggested an inflammatory pseudotumor on magnetic resonance imaging. This was initially a onspecific finding, but when we gathered the clinical, laboratory and imaging data, we validated the diagnosis of Graves' ophthalmopathy. This shows that this diagnostic possibility should be considered, so that there is no delay in detection and initiation of treatment.

The second example is to emphasize the importance of treating Graves' disease to control hyperthyroidism. It is important to note that iatrogenic hypothyroidism is as harmful as uncontrolled hyperthyroidism in these patients. In both reports, the patients presented iatrogenic hypothyroidism, requiring a reduction in the dose of methimazole used. In the case of the patient in Report 2, guidance was given on the importance of quitting smoking – considered one of the main risk factors for the onset and progression of the disease.

In general terms of treatment, due to the inability to close the eyes completely, there is a greater risk of developing keratopathy due to exposure in this patient profile.

Therefore, both patients were advised on the use of lubricating eye drops and to bring their eyelids together when lying down.

For specific treatment of ophthalmopathy, both patients received the same approach: due to the degree of activity and classification of the disease as moderate to severe (as evident in table 2), intravenous corticosteroid

therapy was performed at the dose recommended by EUGOGO – intravenous methylprednisolone 500mg weekly for 6 weeks, followed by intravenous methylprednisolone 250mg weekly for another 6 weeks, totaling 12 weeks of treatment and a total dose of 4.5 grams of corticosteroid.

The patients were linked to the endocrinology service at Hospital Evangélico Mackenzie for follow-up and, in the future, depending on the clinical response, discussion about administering teprotumumab.

Discussion:

Approximately 15% of patients with GD who do not present clinical signs of GO at the onset of the disease will develop it within the first 3 to 6 months. The progression of ophthalmopathy usually begins with the acute phase of the disease, followed by a plateau and then remission until inactive disease, with the total duration of approximately 18-24 months in most patients [6]. receptors are also expressed in several extrathyroidal tissues, especially in the retroorbital tissues; therefore, complaints such as strabismus, diplopia and proptosis (exophthalmos), and eyelid retraction are common in this ophthalmopathy. TRAB is useful not only for diagnosis, but also as a measure of severity and response to the proposed treatment [3].

In the evaluation, the use of imaging, particularly magnetic resonance imaging (MRI) of the orbits, aims to identify patients with active disease, in order to better select those who would respond adequately to immunosuppressive therapy [4]. MRI can also be useful in the evaluation of atypical cases and unilateral proptosis, such as the patient in report 1, when the differential diagnosis with other diseases is crucial (e.g., retroorbital tumor or cyst) as well as in cases of suspected optic nerve compression causing optic neuropathy.

Treatment of the disease should be based on the degree of activity, classification of severity and duration of ophthalmopathy symptoms – this is because immunosuppression is less effective after 18 weeks of disease [6].

To classify disease activity, the CAS score, previously shown in Table 1, is used. This classification is based on the classical signs of inflammation-pain, redness, swelling, and impaired function. After two consecutive clinical examinations an 'activity score' can be determined, ranging from 0 to 10 points [9]. Ophthalmopathy is considered active if the score is equal to or greater than 3 points [6,9].

The EUGOGO (European Group of Graves' Orbitopathy) severity grading system assesses clinical activity and severity with mild, moderate-to-severe, and very severe (sight-threatening) categories, based on the impairment of the patient's daily activities (Table 2) [6].

Treatment of Graves' ophthalmopathy is divided into general recommendations and drug therapy. Regarding recommendations, treatment of hyperthyroidism itself with antithyroid drugs is essential, with caution to avoid iatrogenic hypothyroidism in these patients.

Treatment of hyperthyroidism with radioiodine can cause progression and even recurrence of ophthalmopathy, which can be avoided by performing a cycle of prednisone before treatment, at a dose of 0.1-0.2 mg/kg/day for 6 weeks [6,10]. In addition, guidance regarding smoking cessation is of utmost importance – one of the main risk factors for the disease, as was the case of the second patient reported.

Furthermore, topical measures for ocular hydration are important, since there is a higher risk of keratopathy due to exposure in this patient profile – including artificial tears and ophthalmic gels [6,7].

Ophthalmopathy classified as mild may present spontaneous remission of symptoms. Therefore, expectant treatment may be considered. In addition to topical treatment, these patients may also benefit from selenium replacement when they live in areas considered deficient – replacement may be done with sodium selenite at 200 mcg/day for 6 months [6].

For active ophthalmopathy classified as moderate to severe, the goal of treatment is symptomatic improvement and reduction of the active phase of the disease, and starting treatment in the first year of manifestation usually yields better results. Intravenous glucocorticoid is indicated as first-line therapy [6.7]. Treatment is preferably with methylprednisolone in a total dose of 4.5 grams – divided into 6 cycles of 500 mg once a week, followed by another 6 cycles of 250 mg once a week. Both patients reported received the initial dose in-hospital and were instructed to continue treatment on an outpatient basis, at the above doses, completing the 12 weeks of treatment. There are reports in the literature of higher doses, up to 7.5 grams in total for patients with diplopia, but care should be taken not to exceed 8 g due to the potential for toxicity. The use of corticosteroids by other routes of administration, such as oral and topical, has not demonstrated similar efficacy to intravenous administration in these patients; however, the topical route may be considered when there is a contraindication to the intravenous route [1,4]. Before treatment, it is important to rule out infection and perform follow-up with liver enzyme testing [6,7].

Another first-line option is the use of mycophenolate sodium, an immunosuppressant generally used in transplant patients. Because it acts by inhibiting T and B lymphocytes, with lower production of immunoglobulins, it appears to be beneficial in patients with ophthalmopathy. A Chinese study demonstrated the benefit of the medication, used at a dose of 0.72g/day for a total of 24 weeks. The 2021 EUGOGO guideline recommends the use of mycophenolate in combination with intravenous glucocorticoids as the first line of treatment in patients with moderate to severe ophthalmopathy [6].

As a second line of treatment, corticosteroids may be used via oral in association with immunosuppressants, such as cyclosporine or azathioprine. Another option is orbital radiotherapy, which can be associated with the use of intravenous corticosteroids. The use of rituximab, contraindicated in patients at risk of dysthyroid optic neuropathy, hasalso been studied in resistant patients. Furthermore, teprotumumab has been gaining ground in the treatment of ophthalmopathy, with significant results in patients refractory to intravenous glucocorticoids [6]. A summary of the approach is presented in Table 3.

Classification of severity of ophthalmopathy:	Mild	Moderate to severe	Very severe
Conduct:	In general, immunomodulatory drugs or surgical treatment are not indicated.	Surgical indication (if inactive disease) or use of immunosuppression (if active disease).	Aggressive treatment with immunosuppression.

Table 3: Suggested management based on classification of severity of ophthalmopathy [6].

Beside this, it is worth noting that, despite treatment, the risk of recurrence is 5-10% [6,7]. This is another reason that highlights the importance of regular follow-up with an endocrinologist.

Conclusion:

Despite progress in understanding the pathophysiology, there are still doubts and controversies regarding clinical management. For this reason, assessing the activity and severity of the disease is extremely important

for the correct therapeutic approach. In addition, remembering the differential diagnosis in cases of unilateral or asymmetric changes is of

utmost importance. Furthermore, it is worth highlighting the importance of controlling Graves' disease, since both uncontrolled hyperthyroidism and iatrogenic hypothyroidism are harmful in these patients.

By recognizing and increasing awareness of this diagnosis, the prognosis of these patients can be improved, preventing fibrosis and sequelae such as changes in appearance, proptosis, and dysfunction of the extrinsic ocular muscles.

There are still therapeutic challenges, such as the fact that the ideal treatment is not always immediately available, and that, because there are multiple factors involved, combined treatment may be necessary. Screening for Graves' orbitopathy (GO) should be performed in all patients with GD at each medical appointment, so that a cautious eye should always be kept on these patients.

Conflict of Interest

The authors of this study have no conflict of interest.

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DOI:10.31579/2690-4861/893