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Malignant Graves' Orbitopathy Complicated by Endophthalmitis, Vision Loss, and Antithyroid Drug-Induced Agranulocytosis: A Case Report

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Case Report

Keywords:

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11393472/v1

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Additional Declarations: No competing interests reported.

Abstract

Introduction

Severe forms of Graves' orbitopathy (GO) account for only a minority of cases, delayed diagnosis and management may result in sight-threatening complications, including orbital infection, and irreversible vision loss. Herein we report a case of a 77-year-old woman with severe GO complicated with endophtalmitis and anti-thyroid drug (ATD) induced agranulocytosis.

Case Presentation

A 77-year-old woman was referred for evaluation and management of Graves' disease associated with severe GO. Seven months before presentation, she developed progressive left-sided proptosis, conjunctival hyperemia and ocular pruritus. Initial ophthalmological management was limited to lubricating eye drops. Over the following months, her condition deteriorated with ocular pain, complete restriction of left ocular motility, and marked visual impairment. Hyperthyroidism was confirmed. Ophthalmological examination demonstrated a left corneal abscess complicated by corneal perforation sealed by iris prolapse, circumferential corneal neovascularization, ocular hypertension, and no light perception. Hyperthyroidism was initially treated with carbimazole and propranolol. One month later, the patient developed severe ATD-induced agranulocytosis with erythroderma, fever, and acute kidney injury, requiring immediate discontinuation of antithyroid therapy. Following stabilization, Lugol's iodine was administered before total thyroidectomy. Management of the orbitopathy included tarsorrhaphy, prolonged intravenous antibiotic therapy, intravenous methylprednisolone, and mycophenolate mofetil. Despite successful control of the infectious and inflammatory process, irreversible vision loss occurred, ultimately necessitating enucleation of the left eye.

Conclusion

This case highlights the devastating consequences of delayed diagnosis and treatment of Graves' orbitopathy, which may progress to irreversible blindness. It also illustrates the potential impact of antithyroid drug-induced agranulocytosis on the development of infectious complications.

Introduction

Graves’ Disease (GD) is the most common cause of hyperthyroidism, accounting for 21% of all hyperthyroidism cases according to one study [1]. GD typically manifests with a triad: Hyperthyroid symptoms with elevations in free T4 associated with a suppressed TSH value, diffuse goiter and orbitopathy [2, 3]. Graves’ Orbitopathy itself is an autoimmune disease, affecting about 30% of all GD patients, with an estimated incidence of 3.3–8/100 000/year in women and 0.9–1.6/100 000/year in men [4]. Symptoms include lacrimation, sandy sensation, photophobia, ocular pain, diplopia and decreased colour sensitivity. On ocular examination, main signs are exophthalmos with lid retraction, swelling and redness of periocular soft tissue and decreased ocular mobility [3]. The pathophysiological

mechanisms underlying acute orbital inflammation in Graves' orbitopathy are primarily driven by the overexpression and activation of thyroid-stimulating hormone receptor (TSHR) autoantibodies within orbital tissues. This autoimmune process promotes the differentiation of orbital preadipocytes into mature adipocytes, leading to expansion of the orbital adipose compartment. Simultaneously, it stimulates the recruitment and proliferation of B and T lymphocytes and activates orbital fibroblasts, which secrete a wide range of pro-inflammatory cytokines and extracellular matrix components. These events collectively contribute to orbital tissue remodeling, edema, and the inflammatory manifestations characteristic of active Graves' orbitopathy [3].

Although severe forms account for only approximately 10% of Graves' orbitopathy cases [4], delayed diagnosis and management may lead to sight-threatening complications, including exposure keratopathy, infectious keratitis, corneal abscess formation, globe subluxation, and ultimately irreversible vision loss [5].

Herein, we report the case of a 77-year-old woman with malignant Graves' orbitopathy complicated by infectious keratitis, corneal abscess, and subsequent left endophthalmitis, resulting in irreversible vision loss, in the setting of antithyroid drug-induced agranulocytosis.

Case presentation

A 77-year-old woman was referred to the Endocrinology Department for evaluation and management of Graves' disease (GD) associated with Graves' orbitopathy (GO). Her medical history was notable for a 20-year longstanding hypertension, treated with lercanidipine 10 mg once daily and moxonidine 0.4 mg once daily, and dyslipidemia under statin therapy: atorvastatin 20 mg daily. There was no prior history of passive or active smoking. Seven months prior to presentation, she had developed left-sided proptosis associated with conjunctival redness, ocular pruritus, and excessive lacrimation. She initially consulted an ophthalmologist, who prescribed lubricating eye drops. The clinical course over the following five months was characterized by progressive deterioration, including worsening conjunctival hyperemia, development of ocular pain, complete restriction of left ocular motility, and a significant reduction in visual acuity. Further evaluation by a second ophthalmologist prompted thyroid function testing, which demonstrated overt hyperthyroidism, with an FT4 concentration of 56.5 pmol/L, 3.06 times the upper normal limit and a suppressed TSH level < 0.05 mIU/L. The diagnosis of Graves' disease was established on the basis of biochemical hyperthyroidism, diffuse hypervascular goiter on cervical ultrasonography, and elevated TSH receptor antibody levels, 2.97 times the upper normal limit.

Physical examination revealed a body mass index (BMI) of 26.66 Kg/m2, normal capillary glucose level. Her heart rate was at 98 bpm. Arterial blood pressure (BP) was 110/70 mmHg. An Electrocardiogram was performed, showing sinus tachycardia at 101 bpm, with no arrhythmia or ST segment abnormalities.

Ophthalmological examination revealed, in the right eye, exophthalmos with a visual acuity of 6/10, conjunctival hyperemia, superficial punctate keratitis, ocular hypertension, and an early cataract. In the left eye, a perforated corneal abscess sealed by the iris was observed, associated with

conjunctivalization of the cornea and 360° corneal neovascularization. The anterior chamber, crystalline lens, and fundus could not be assessed. Visual acuity was reduced to no light perception (NLP). Fundus examination was not possible because of lens opacity (Figs. 1A and 1B).

b

a

Orbital magnetic resonance imaging (MRI) demonstrated bilateral grade III exophthalmos, more pronounced on the left side, as well as left preseptal cellulitis with a small subcentimetric abscess located at the medial canthus (Fig. 2).

To control hyperthyroidism, treatment with carbimazole 20 mg once daily and propranolol 20 mg three times daily was initiated after confirmation of normal liver function tests and a normal complete blood count. This regimen resulted in subsequent normalization of thyroid hormone levels. One month after treatment initiation, the patient developed an acute systemic illness characterized by erythroderma, severe generalized pruritus, extensive desquamation of both hands, nausea, intractable vomiting, and fever (39°C). Laboratory investigations revealed hyponatremia, hypokalaemia, acute kidney injury, and severe agranulocytosis, with a white blood cell count of 0.146 x 10^9/L and an absolute neutrophil count of 0.073 x 10^9/L. ALAT were 3.32 times the upper normal limit. The patient was immediately admitted to the intensive care unit. All medications were stopped, and symptomatic treatment with IV fluids, anti-emetics and correction of blood electrolyte abnormalities was administered. Significant clinical and biological improvement was subsequently noted, with a progressive decrease in white blood cell count and neutrophil count (Table 1).

Table 1
Evolution of biological parameters over time

	Day 1	Day 3	Day 6	Day 10	Day 15	Day 16	Lugol's Iodine	Day 20
WBCs (x10^9/L)	1.460	1.630	2.750	8.180	6.700	5.400		6.500
Neutrophils (x10^9/L)	0.073	0.180	0.140	2.880	3.100	1.600		2.200
ASAT (UI/L)	38	61			69			71
ALAT (UI/L)	113	168			106			105
TSH (UI/L)	< 0.05					0.02		
FT4 (pmol/L)	56.5 (UNL = 18)					15 (UNL = 14.4)		12 (UNL = 14.4)

UNL: Upper Normal Limit

One week after discontinuation of antithyroid therapy, thyroid function tests showed a free T4 level of 15.1 pmol/L, corresponding to 1.04 times the upper normal limit, while TSH remained suppressed (< 0.001 mIU/L). Preoperative preparation was achieved with Lugol's iodine solution (5%), administered at a dose of 5 drops three times daily. Propranolol was reintroduced at a dose of 40 mg three times daily to achieve adequate heart rate control. Following stabilization of the patient's clinical status, including satisfactory heart rate control, absence of electrocardiographic abnormalities, and normalization of thyroid hormone levels (FT4 at 12.1 pmol/L), total thyroidectomy was performed. The postoperative course was uneventful, and levothyroxine replacement therapy was initiated at a dose of 100 µg/day.

Following 10 days of antibiotic treatment and clinical control of the infection, systemic corticosteroid therapy was deemed necessary to manage the persistent orbital inflammation. Intravenous methylprednisolone was administered at a dose of 500 mg daily for three consecutive days, followed by weekly infusions of 500 mg. Concomitant immunosuppressive therapy with mycophenolate mofetil 1 g/day was also initiated.

Despite adequate control of the infectious and inflammatory process, the visual prognosis remained unfavorable. Given the irreversible loss of vision and the severity of the ocular damage, enucleation of the left eye was ultimately performed six months after resolution of the orbital infection and inflammation.

Discussion

GO is the most common extrathyroidal manifestation of GD [4, 6], although some forms of orbitopathy have been described in hypothyroid or euthyroid patients [7]. It is an auto-immune mediated disease where TSH-receptor auto-antibodies are positively correlated with clinical features of GO and is heavily associated with its prognosis [3, 7]. The pathophysiology of Graves' orbitopathy (GO) is initiated by autoimmune dysregulation within the orbital connective tissue, particularly involving orbital fibroblasts [7]. Activation and proliferation of these cells promote their differentiation into myofibroblasts, which secrete numerous inflammatory mediators, including prostaglandin E2, interleukin-8 (IL-8), and hyaluronan, thereby contributing to orbital inflammation and tissue remodeling [7]. In parallel, a subset of orbital fibroblasts differentiates into mature adipocytes, leading to expansion of the orbital adipose tissue and increased expression of the thyroid-stimulating hormone receptor (TSHR) [7]. Infiltration of the orbit by B and T lymphocytes also plays a central role in disease pathogenesis. Orbital fibroblasts and infiltrating immune cells overexpress insulin-like growth factor 1 receptor (IGF-1R), which functionally interacts with TSHR [3]. Autoantibody binding to TSHR triggers signaling pathways involving both TSHR and IGF-1R, resulting in crosstalk between these receptors and amplification of the autoimmune response. Consequently, fibroblast activation, adipogenesis, and lymphocytic infiltration are enhanced, leading to accumulation of fibro-adipose tissue within the orbit and extraocular muscles. The concomitant release of pro-inflammatory and pro-fibrotic cytokines promotes tissue edema, fibrosis, and

progressive expansion of the orbital contents, ultimately giving rise to the characteristic clinical manifestations of GO [3].

Non modifiable risk factors for the development and severity of GO include older age, male sex, genetic factors and elevated serum TSH-Receptor antibodies [8]. Indeed, patients under 40 years old have fat expansion, whereas patients over 60 years old have more extraocular muscle swelling [9]. Modifiable risk factors include cigarette smoking, thyroid dysfunction, and the use of radioactive iodine (RAI), whereas studies showed that statin therapy was associated with a decreased risk of GO [2]. Our patient was a 77-year-old woman, she was indeed under statin therapy, and she had high levels of TSH-Receptor antibodies. She had progressive symptoms of GO, marked soft tissue inflammatory features and impaired ocular motility. All these symptoms are associated with an increased risk of sight-threatening thyroid eye disease, according with the consensus of the American Thyroid Association and the European Thyroid Association published in 2022 [2].

Natural history of GO includes an initial phase characterized by inflammatory changes, as it is the case with our patient, then a brief static phase and finally an inactive phase developing over the course of 12–18 months after the disease onset. Improvement in signs and symptoms occur during the inactive period. However, symptoms do not tend to improve without medical intervention and they persist in 50% of patients [2]. Therefore, absence of early management and treatment can lead to dire consequences. In our patient, the clinical presentation was characterized by a rapidly progressive and markedly asymmetric course, predominantly affecting the left orbit. Studies estimated the prevalence of unilateral thyroid eye disease to be between 4.5 and 14% [6] while asymmetry had a frequency of 9–34% in other studies [10–12]. Another multi-center prospective study by Perros et al [13], including 269 newly diagnosed GO patients, found a prevalence of 30.9% for asymmetric GO and 10.7% for unilateral GO. Orbital MRI had already ruled out alternative diagnoses, including orbital tumors and lymphomas [14, 15]. Over the course of five months, our patient developed corneal abscess, orbital perforation and endophtalmia. Several studies in literature have described atypical clinical manifestations of GO. Gupta et al [16] report the case of a 34-year-old woman who had GD for over 12 years, with a gradual and slow onset of bilateral proptosis, starting three years after the diagnosis of GD. However, her eye symptoms have rapidly deteriorated over three months. A significant decrease in visual acuity was noted, dropping from 6/9 to counting finger near face. Intraocular pressure increased considerably. Proptosis increased in the left eye. Extra-ocular movements were restricted in all the gazes on examination, and there was a significant constriction of peripheral visual fields in the left eye, whereas analysis of visual field could not be performed in the right eye because of poor vision. Urgent orbital decompression was strongly advised but denied by the patient. Significant improvement was then obtained after an intravenous methylprednisolone 1 g cure for three consecutive days. Another case was reported by Macovei et al [17] about a 52-year-old male patient, a heavy smoker, with a one-month onset of severe thyroid eye disease. Six months prior to presentation, he reported being diagnosed of preseptal cellulitis and treated with antibiotics, non-steroidal anti-inflammatories, mydriatics and lubricants, with no symptom improvement. He complained or a rapid decrease in visual acuity of the left eye, bilateral marked proptosis and the onset of hyperthyroid symptoms. Ophthalmological examination demonstrated conjunctival hyperemia,

purulent discharge, chemosis, caruncular inflammation, and severe bilateral ophthalmoplegia. The right eye presented with an inferior marginal corneal ulcer, anterior uveitis, and keratic precipitates, whereas the left eye exhibited extensive corneal pannus with prominent corneal neovascularization involving two-thirds of the corneal surface. Upon being treated with intraveinous corticoids, he showed a suboptimal response, with a slight amelioration of the corneal ulceration. This case is particularly relevant to our patient, however with a more rapid onset of symptoms. Another case of corneal ulceration was reported by Wang et al [18], where a 66-year-old male patient had a 6 x 6 mm ulcer lesion in the cornea of the right eye, with central perforation and disappearance of the anterior chamber. He had a 9-month history of GO and a one-month onset aggravation of exophthalmos and rapid loss vision. Given the isolated corneal lesion and the absence of infection, the patient underwent unilateral transnasal endoscopic orbital inner wall decompression with keratoplasty under general anesthesia, after days of thyroid stabilisation, corneal protection and methylprednisolone intravenous therapy. These findings underline the unpredictable medical course of GO, and the necessity of urgent management of both hyperthyroidism and eye disease. In our patient, the severity of the inflammatory involvement, together with the corneal abscess and extensive infectious destruction of the orbital tissues, precluded this therapeutic approach. Given the poor visual and anatomical prognosis of the left eye, the ophthalmology team prioritized preservation of the contralateral eye. Tarsorrhaphy was then performed on the left eye. This simple yet crucial therapeutic intervention was evaluated by two studies in literature. In the first study [19], tarsorrhaphy was associated with significant improvement in keratitis and corneal ulceration. In the second study [20], tarsorrhaphy resulted in a significant reduction in lower eyelid retraction compared with patients who did not undergo the procedure. Furthermore, successful resolution of lagophthalmos was achieved in 91.3% of treated patients, compared with 50% in the control group ($p = 0.004$). Three consecutive days of methylprednisolone at a dose of 500 mg intravenously was initially administered in our patient, which is half the recommended dose by EUGOGO guidelines [5]. This therapeutic option is explained by the fact that corticoid treatment was risky for this patient, given the severe ongoing orbital infection. Yet, control of the inflammation was necessary, and the benefits of corticoids outweighed the risks. A lower dose was then decided by the ophthalmologists.

Our patient not only had severe, sight-threatening GO, but also had a major, rare side effect of anti-thyroid drugs. Agranulocytosis likely contributed to the deterioration of thyroid eye disease in this case, as the resulting immunosuppression may have predisposed the patient to the acute development of orbital and ocular infection. A recently published case report by Madala et al [21] may support this theory. A 68-year-old with a history of 2C uterine carcinoma status post-hysterectomy and a past GO developed a reactivation of thyroid eye disease after starting oncologic treatment with nivolumab, an immune checkpoint inhibitor. After stopping treatment and intense 2 weeks corticoid therapy, the patient's orbital symptoms significantly improved [21]. This highlights the importance of close monitoring and heightened vigilance in patients with GO who are receiving immunosuppressive therapy or who are otherwise immunocompromised.

For half a century, anti-thyroid drugs have been the first-line recommended treatment for GD [2, 22]. However, like any other drug, they may have mild to severe side effects, including skin rash, urticaria,

arthralgia, hepatotoxicity and vasculitis [22]. Agranulocytosis is the most severe side effect, although rare. It is defined by a neutrophil count < 0.5 x 10^9 cells/L and once present, definitive interruption of all molecules of anti-thyroid drugs is recommended [23]. The American Thyroid Association recommends obtaining a complete blood count with differential and liver function tests before initiating antithyroid drug therapy. Subsequent haematological monitoring is advised only in the presence of symptoms suggestive of agranulocytosis, such as fever or pharyngitis, while liver function tests are recommended in patients who develop jaundice, pruritic rash, pale stools, dark urine, arthralgia, abdominal pain, anorexia, nausea, or fatigue [2]. However, the present case highlights the potential limitations of this symptom-driven monitoring strategy, as severe agranulocytosis developed with devastating consequences, emphasizing the need for heightened clinical vigilance in high-risk patients. Indeed, some clinicians continue to regularly monitor white blood count and liver function tests during treatment [2, 24]. A survey including 730 respondents was made in 2012 and evaluated the differences in GD among international members of US based endocrine societies [24]. Routine monitoring of liver enzymes during anti-thyroid drug therapy was performed by 53.8% of physicians, and white blood count by 48.4%. The remaining respondents would not perform monitoring of either of these parameters. A few studies reported similar cases of agranulocytosis in literature. Gad et al [22] reported the case of a 47-year-old female patient who had a 17-year history of GD, with initial remission obtained after 2 years of medical therapy by carbimazole. No side effects were noted during the initial treatment. However, upon a relapse of the disease, carbimazole at a dose of 40 mg daily was restarted, and three weeks later, the patient presented with sore throat, painful swallowing and sweating. Physical examination revealed oral ulceration, pharyngeal erythema and cervical adenopathy. The patient's white blood count was 2.6 x 10^9/L and neutrophil count was 0.1 x 10^9/L. Delayed-onset agranulocytosis seems to be the most common case in the few studies described in literature, occurring after 18 months of antithyroid drug therapy in one case [25] and during treatment for a relapse of Graves' disease four years after a previous medically induced remission in another [26]. These findings underscore the unpredictability of this complication. However, several additional risk factors have been identified and may help predict which patients are at greatest risk of developing agranulocytosis. The use of PTU rather than MMI [27] was associated with a higher incidence of this complication. Moreover, dosage-dependency was incriminated in both molecules [28], with no consensual dose cutoff. Kamitani et al reported a higher risk of leukopenia with increasing doses of anti-thyroid drugs, occurring in 1.34% of patients [29].

Conclusion

Graves' orbitopathy (GO) is the most common extrathyroidal manifestation of Graves' disease (GD) and remains a potentially sight-threatening autoimmune disorder. The presence of proptosis associated with inflammatory ocular symptoms should prompt thyroid function testing to facilitate early diagnosis and timely initiation of appropriate therapy. Disease severity and progression are highly variable and influenced by both modifiable and non-modifiable factors, including age, sex, genetic susceptibility, disease activity, and high levels of TSH receptor antibodies. Management of GO relies on a

multidisciplinary approach combining ocular surface protection, corticoid therapy, and, in severe cases, surgical interventions such as tarsorrhaphy or keratoplasty.

Delayed diagnosis and inadequate management may result in devastating complications, including exposure keratopathy, corneal ulceration, orbital infection, and irreversible vision loss, as illustrated by the present case.

Optimal control of hyperthyroidism is equally essential. Although antithyroid drugs remain the recommended first-line treatment for most patients with GD, serious adverse events such as agranulocytosis and hepatotoxicity may necessitate their immediate discontinuation and the use of alternative therapeutic strategies. In our patient, antithyroid drug-induced agranulocytosis represented a major complicating factor and may have contributed to the development and progression of severe infectious ocular complications.

This case highlights the importance of maintaining a high index of suspicion for both ophthalmological and hematological complications in patients with Graves' disease. It also raises the question of whether closer laboratory surveillance may be warranted in selected high-risk patients receiving antithyroid drug therapy, particularly with severe orbitopathy.

Declarations

Disclosures

Funding:

Conflict of Interest:

The authors declare no conflict of interest.

Ethics approval

Ethics approval was not required for this case report in accordance with the applicable institutional policies.

Consent to participate

Written informed consent was obtained from the patient for participation in this case report.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Human Ethics and Consent to Participate declarations

Not applicable.

Author Contribution

M.M wrote the main manuscript and prepared the figures. All authors (A. BC, N.B, D.E, S.B, S.M, H.O and C.Z) reviewed the manuscript and added corrections to the original text written by M.M.

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Figures

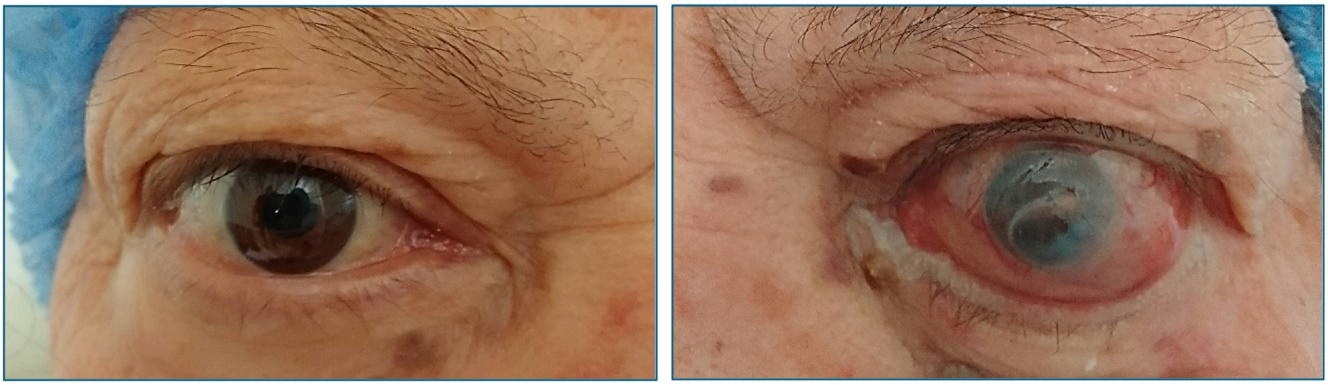


Figure 1

The patient’s appearance on admission. a: Right eye b: Left eye

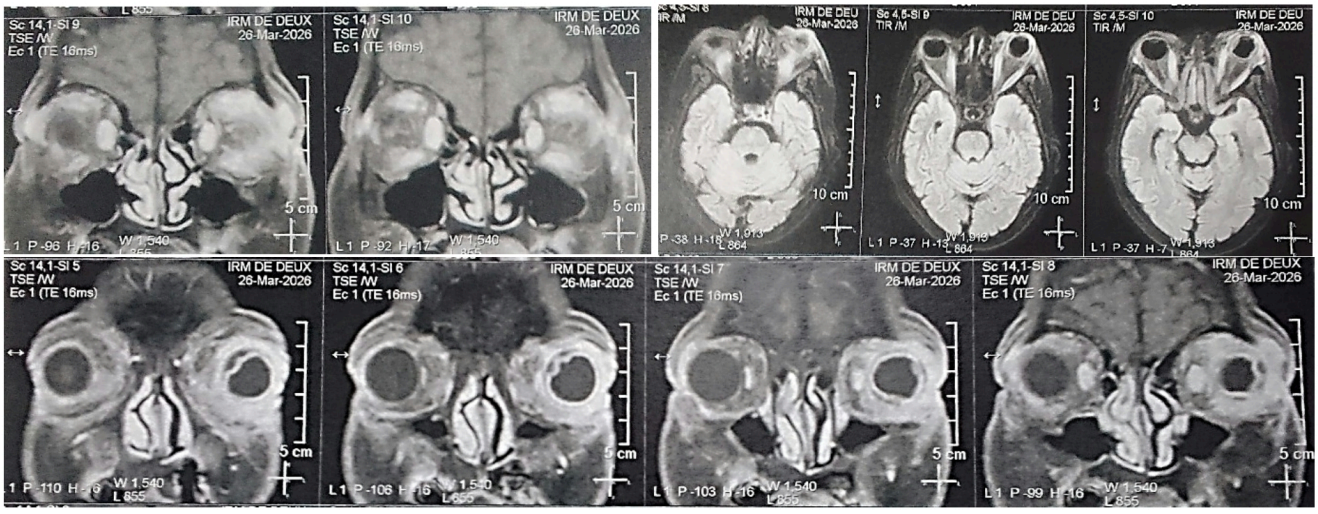


Figure 2

Orbital MRI findings: bilateral grade III exophthalmos, more pronounced on the left side, as well as left preseptal cellulitis with a small subcentimetric abscess located at the medial canthus.