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M Ali and others

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A rare case of severe bilateral Graves' orbitopathy involving an anophthalmic socket

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Summary

This is a report of a rare case of Graves' hyperthyroidism associated with severe bilateral Graves' orbitopathy, in a patient with an anophthalmic eye socket. On clinical review her prosthetic eye (left eye) was tilting upwards, along with worsening of Graves' orbitopathy (GO) in the only seeing eye. As she refused IV glucocorticoids, she was offered rituximab which only caused a transient improvement in the clinical activity score of the eye. She had persistent right upper lid retraction of 6 mm, associated with lagophthalmos. To protect her seeing eye from corneal ulceration, the patient received a botulinum toxin injection to the right upper eyelid to induce blepharoptosis as an interim measure prior to right upper eyelid blepharotomy in April 2021. This patient remains biochemically euthyroid on block and replace therapy and her TRAb level is falling over time. Treatment for active GO is ongoing and the patient required a redo blepharotomy for painful corneal exposure in the right eye.

Learning points

- Graves' orbitopathy (GO) does not actually primarily affect the eyeball itself but the orbital contents as well.
- Patients with severe GO in an only seeing-eyed patient should be referred early to a multidisciplinary Joint Thyroid Eye clinic for expert review and management.
- Patient outcomes including sight loss are likely to be improved by the extended range of medical and surgical treatment modalities available at specialist clinics treating GO, including the use of immunomodulatory drugs like rituximab or teprotumumab.

Background

Graves' disease (GD) is a common autoimmune thyroid condition in which 25–50% of patients also develop Graves' orbitopathy (GO), which is a heterogeneous disease resulting from autoimmune attack on the different structures of the orbit (1). GO can manifest as swelling of the soft tissues of the eyelids or the orbital connective tissues and fat leading to proptosis. In addition, the involvement of extra-ocular muscles can result in limited ocular motility causing significant functional visual impairment, and in the most severe cases, pressure effects on the optic nerve can cause permanent loss of sight (1, 2). GO was historically termed Graves' ophthalmopathy and is still commonly referred to as thyroid eye disease; however, the pathological processes occur in the adnexal orbital structures rather than within the globe of the eye itself (2). Illustrating this point, we report a case of severe GO in a patient affecting both the only functioning eye and the contralateral anophthalmic socket.

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Case presentation

A 54-year-old lady was referred with clinical and biochemical evidence of thyrotoxicosis and new-onset fast atrial fibrillation. She complained of excess sweating, palpitations, diarrhoea, anxiety and weight loss, and blood tests confirmed thyrotoxicosis (TSH < 0.05 mU/L (reference range: 0.3–4.5 mU/L); FT4: 30.6 pmol/L (reference range: 10–22 pmol/L)). She was an ex-smoker with past medical history of breast cancer, melanoma and hypothyroidism diagnosed 2 years beforehand. Her left eye had been enucleated 20 years previously for symptomatic relief of a painful blind eye following previous trauma. She had a left primary orbital implant and wore an artificial eye prosthesis.

Investigations

Additional investigation showed that her TSH receptor antibody (TRAb) was 33.2 IU/L (normal range: <1.0 IU/L); TSH was suppressed at 0.05 mU/L; FT4 and FT3 were 32.4 and 18.1 pmol/L (reference range: 3.1–6.8 pmol/L), respectively, and she was prescribed carbimazole 40 mg once daily. Examination showed soft tissue signs of inflammatory GO in her right eye (chemosis, conjunctival redness, discomfort on upgaze, upper lid retraction and proptosis) with a clinical activity score (CAS) of 4/10 (Fig. 1, panel B) and 3 mm lagophthalmos. Levothyroxine 100 µg once daily was added to her carbimazole therapy once her FT4 had fallen into the reference range.

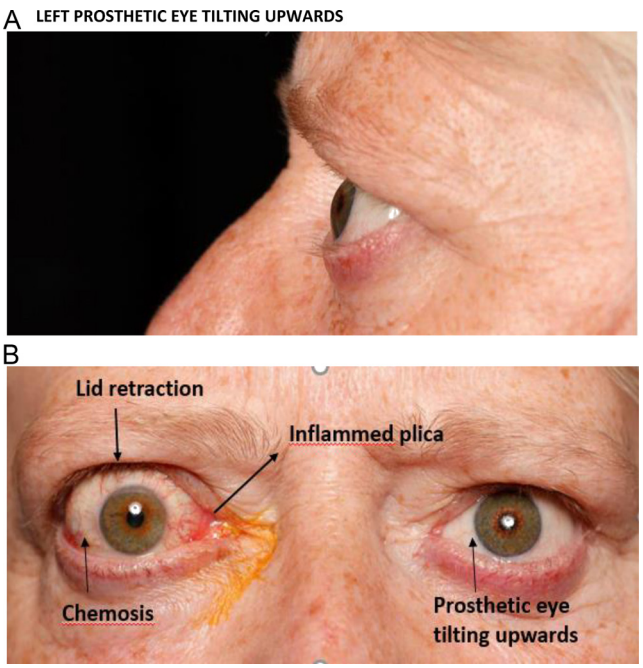

Figure 1
(A) Left prosthetic eye tilting upwards. (B) Lid retraction, chemosis and plical inflammation in the right eye and left prosthetic eye tilting upwards.

Treatment

Four weeks later in January 2020, she reported discomfort on upgaze. On reassessment, there was conjunctival and plical injection; 5 mm upper lid retraction (Fig. 1, panel B) and 2 mm lagophthalmos with no corneal exposure in the seeing right eye. Exophthalmometry showed right eye proptosis of 4 mm more than the left eye. Although the CAS remained at 4/10, she also reported a change in the appearance of her left eye prosthesis, which she described as ''tilted upwards" (Fig. 1, panel A). MRI scan of the orbits showed enlargement of the inferior and medial recti muscles (Fig. 2, panels A and B) behind her prosthesis explaining the change in prosthesis position she had reported. Due to worsening inflammatory GO in a patient with only one functioning eye, she was offered a course of pulsed methylprednisolone, which she declined citing concerns about side-effects, in particular, weight gain. As second-line therapy, the patient was offered B lymphocyte depleting therapy with rituximab (RTX), and 500 mg was administered by slow IV infusion. This resulted in a transient improvement in her right eye, with her CAS reducing from 4 to 2/10 over 6 weeks following the treatment.

In June 2020, she had persistent right upper lid retraction of 6 mm, associated with lagophthalmos, and the CAS had increased again to 4. On examination, normal visual acuity in the right eye (6/6) and full colour vision (15/15 on Ishihara plate testing) were maintained. To protect her right eye from corneal ulceration, the patient received a botulinum toxin injection to the right upper eyelid to induce blepharoptosis as an interim measure prior to right upper eyelid blepharotomy in April 2021. She was referred to the National Artificial Eye Service for a new artificial eye prosthesis which was needed as a result of the remodelling of the left orbit.

This patient remains biochemically euthyroid on block and replace therapy and her TRAb level is falling over time (6.0 IU/L by August 2021). Treatment for active GO is ongoing, and the patient recently required redo blepharotomy for painful corneal exposure in right eye.

Discussion

We describe a rare case of 54-year-old lady with an anophthalmic left socket who developed signs of bilateral GO, causing the left prosthetic eye to tilt upwards. As far as we are aware, this is the second reported case of GO

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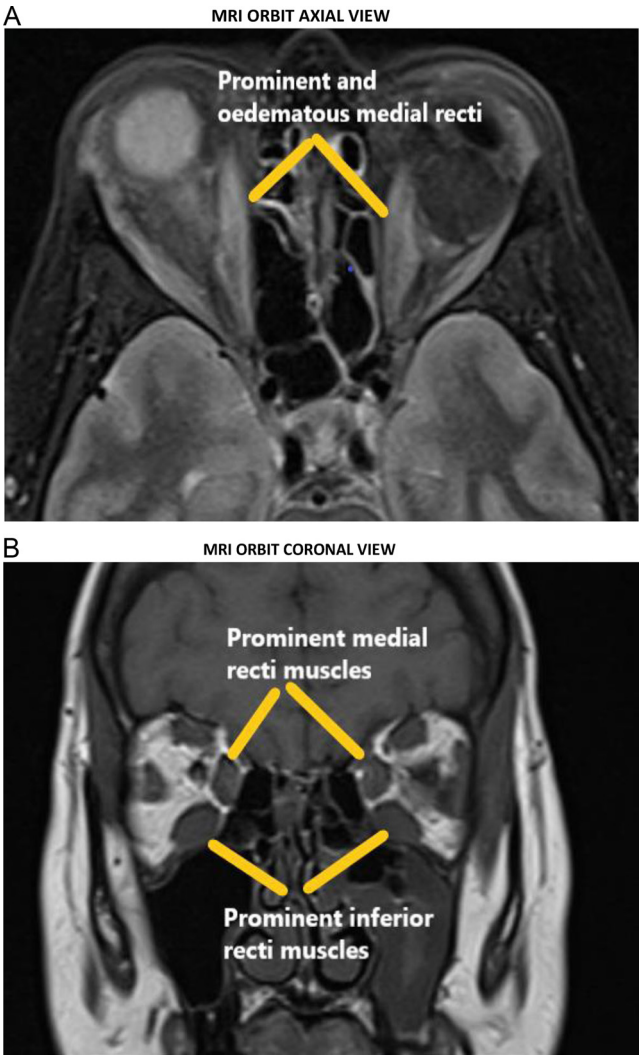

Figure 2
(A) MRI orbit axial view showing prominent and oedematous medial recti. (B) MRI orbital coronal view showing prominent medial and inferior recti muscles.

involving an anophthalmic socket and the first one was described by Salvi and colleagues (3), which documents a 63-year-old lady with anophthalmic socket (secondary to trauma) who was referred with signs of GO in the right eye and expulsion of the artificial eye from left orbit.

The occurrence of GO in an anophthalmic orbit illustrates that this is a disease of the orbital adnexal tissues, rather than of the globe of the eye itself. Potentially sight-threatening inflammatory GO in a uniocular patient also lowered the threshold for second-line treatment as substantial proptosis and lagophthalmos rendered this patient vulnerable to corneal breakdown. Treatment with pulsed methylprednisolone was refused, so B lymphocyte-depleting treatment with RTX was used instead, with some benefit. This treatment has been the subject of two small RCTs, with differing outcomes. One RCT (4), as well as several case series (5), showed that RTX was efficacious in active TED, but a second small RCT (6) showed no benefit over placebo.

In Graves' disease, oscillating thyroid function due to the presence of both stimulating and blocking TRAb is a rare but important clinical phenomenon (7). In this case, the patient had established hypothyroidism, was treated with levothyroxine and subsequently, developed hyperthyroidism which required active management. Our experience is that patients with this presentation may frequently have oscillating thyroid hormone levels, veering from hyperthyroid to hypothyroid. Block and replace treatment is an effective strategy for such patients as it prevents hypothyroidism as well as controls thyroid hormone excess.

In the anophthalmic socket of this patient, inflammation and enlargement of the extraocular muscles in the orbit resulted in a change in the position of the prosthesis and caused it to tilt upwards. This change in the appearance of the artificial eye prosthesis alerted the managing team to significant bilateral retro-orbital inflammation. The observation of extraocular muscle inflammation and enlargement in a patient with GO and an enucleated orbit illustrates that the pathogenic immune response is directed at antigens in the soft tissues (extraocular muscles, fibroblasts, adipocytes), and not primarily at the globe itself (2).

Data from a national cross-sectional study show that around 1 in 1000 people in the United Kingdom use an ocular prosthesis (8). Understanding that thyroid eye disease can occur in a prosthetic eye socket is an important lesson, as the patient's symptoms could easily have been overlooked or dismissed. Performing an orbital MRI is a key part of diagnostic workup as it gives better soft tissue differentiation, and T2-weighted images detect oedema and inflammation in extraocular muscles.

All patients with moderate to severe GO should benefit from an early assessment in a multidisciplinary expert Joint Physician-Ophthalmologist Thyroid Eye clinic, particularly, the case when there is already visual compromise in one eye, allowing therapy to be initiated early and specialist immunomodulatory treatments can be considered. In steroid-refractory disease, or in patients who are not suitable for steroids or decline steroid therapy, RTX may be used to manage active GO and prevent loss of sight due to dysthyroid optic neuropathy and corneal ulceration. Published case series have documented a significant reduction in TRAb and CAS in patients following RTX treatment (5, 9).

In this patient with bilateral GO, involving an anophthalmic socket, we have shown that treatment with RTX was successful in preventing the need for orbital surgical decompression. Another immunomodulatory drug, teprotumumab, a human monoclonal antibody against the insulin-like growth factor type I receptor, has been recently developed for the management of GO and might be an option for similar patients with moderate to severe GO where a surgical complication resulting in sight loss in the patient's only seeing eye would be catastrophic (10).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

The patient provided written informed consent for the publication of the submitted article and accompanying images.

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