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K Okolie and others | Thyroid eye disease in multinodular goitre

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Exophthalmos and multinodular goitre, an unusual combination

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Summary

Multinodular goitre is not associated with eye disease, unless in a rare case of Marine–Lenhart syndrome where it coexists with Grave's disease. Therefore, other causes of exophthalmos need to be ruled out when the eye disease is seen in a patient with multinodular goitre. Confusion can arise in patients with features suggestive of Graves' ophthalmopathy in the absence of thyroid-stimulating hormone receptor autoantibodies and no evidence of other causes of exophthalmos. We present a case of multinodular goitre in a patient with exophthalmos which flared up after iodine contrast-based study. A 61-year-old Australian presented with a pre-syncopal attack and was diagnosed with toxic multinodular goitre. At the same time of investigations, to diagnose the possible cause of the pre-syncopal attack, computerised tomographic (CT) coronary artery angiogram was requested by a cardiologist. A few days after the iodine contrast-based imaging test was performed, he developed severe eye symptoms, with signs suggestive of Graves' orbitopathy. MRI of the orbit revealed features of the disease. Although he had pre-existing eye symptoms, they were not classical of thyroid eye disease. He eventually had orbital decompressive surgery. This case poses a diagnostic dilemma of a possible Graves' orbitopathy in a patient with multinodular goitre.

Learning points:

- Graves' orbitopathy can occur in a patient with normal autothyroid antibodies. The absence of the thyroid antibodies does not rule out the disease in all cases.
- Graves' orbitopathy can coexist with multinodular goitre.
- Iodine-based compounds, in any form, can trigger severe symptoms, on the background of Graves' eye disease.

Background

MNG, unlike Graves' disease, is not an autoimmune disease and shares no direct aetiopathogenic linkage with GO, which is believed to be an autoimmune disease, possibly arising from the interaction of the TRAb and the receptors found on the fibroblasts and the pre-adipocytes in the orbital tissues, with consequent inflammation and swelling of the extraocular connective and muscular tissues. The expansion of the extraocular orbital tissues, within the fixed orbital volume, lead to the symptoms and signs of the disease. Hence, TRAb may be the initiator of the disease and at the centre of its diagnosis.

However, some cases of GO in the absence of hyperthyroidism and TRAB have cast doubt on TRAb as the initiator of the disease (1, 2). Factors other than TRAb have been noted to play some roles in the pathogenesis of the thyroid eye disease. These include insulin-like growth factor-1 (IGF1) (3) and antibodies targeting other orbital connective tissues, including calcium binding protein calsequestrin (CASQ1), as well as the orbital fibroblast membrane antigen collagen XIII (4). These other factors may explain rare cases of Graves' orbitopathy with negative TRAb. Some authors have also linked IGF-1 with

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thyroid nodules (5), and since this same factor has been linked with GO, one may ask if the two disorders can actually be linked in some patients. Ours is an interesting case of a man with unexplainably high levels of IGF-1 and exophthalmos on the background of MNG, a possible case of Marine–Lenhart syndrome.

Case presentation

A 61-year-old male Caucasian presented in 2016, with an episode of near-syncope, and was found to have suppressed TSH, slightly high free T3 and high-normal free T4; further history revealed heat intolerance and severe fatigue, but he denied other classical thyrotoxic symptoms; in particular, he denied palpitations, tremor, flushing, increased appetite, weight loss or diarrhoea. He reported no headaches, nausea, vomiting, double vision or painful red eyes, but reported blurring of vision that warranted a visit to an optometrist in the same month.

A repeated thyroid function test, without therapy, revealed high-normal free T3 and free T4, but persistently suppressed TSH (Table 1).

He had a prior history of recurrent corneal ulcers of unknown cause, which started in 1990; the last episode was in 2013.

He has an underlying haemochromatosis and undergoes regular venesection. His other medical conditions included occasional gastro-oesophageal reflux disease (GORD) and allergic rhinitis, managed with rabeprozole 20 mg and fluticasone/azelastine 50 mg, 125 µg respectively, as required. He was using multifocal lenses.

He was not a smoker and rarely drinks alcohol.

No family history of thyroid disease.

A cardiologist was involved in his work-up to rule out cardiac disease, as a possible cause of his presenting symptom of pre-syncope, and CT coronary angiogram was requested, among other tests. A few days after the imaging test he developed red, painful and weepy eyes, with proptosis, more on the left than the right. He reported diplopia, blurring of vision and photophobia. There was no prior history of orbital trauma and he did not complain of tinnitus, which may suggest carotid cavernous fistula; he reported no headaches or fever. He also had no symptoms suggestive of myasthenia gravis or IgG disease.

Examination revealed his height to be 177 cm and weight was 88 kg, with BMI of 28.3 kg/m^2. His blood pressure was 110/80 mmHg, with no postural drop; he was afebrile, did not appear sweaty and had no tremor. There were no signs suggestive of acromegaly.

He had weepy eyes with obvious proptosis, more on the left; the conjunctivae were markedly injected and oedematous; the eyelids were oedematous and retracted; no corneal ulcers noted. His ocular movement was severely restricted, with failure of upward gaze. He had no ocular bruit. The Clinical Activity Score (CAS) of his eye disease was 4 with pain, conjunctival injections, chemosis and lid oedema. He had a corrected visual acuity of 6/9 in both eyes.

His neck and cardio-respiratory examinations were unremarkable.

Investigations

Table 1 shows the result of his thyroid function tests and autothyroid antibodies over time. Table 2 depicts other hormonal and non-hormonal assays performed.

Liver and renal function tests, full blood counts, calcium levels and iron studies revealed no abnormalities.

Initial IGF-1 was two times the upper limit of normal at 52 nmol/L (7–27), but growth hormone was normal at <0.1–<3.1 mIU/L. The IGF-1 decreased in subsequent tests but remained elevated.

Ultrasound of the neck revealed a small multi-nodular goitre. The largest nodule was situated within the

Table 1 Thyroid function test and autothyroid antibodies, over time.

	TSH (IU/L)	**Free T3** (pmol/L)	**Free T4** (pmol/L)	**TRAb**	**Anti-TG** (U/mL)	**Anti-TPO** (U/mL)
Reference range	0.5-4	3.5-6	10-20	<1.08	<41	<60
06/2016	<0.02	6.8	19	0.9	<20	<28
11/2016	0.03	5.5	15	0.9	<20	<28
12/2016	0.06	5.4	16			
Carbimazole started						
01/2017	0.56	4.6	15	0.9		
04/2017	2.9	5.0	15	0.9	<20	<28
01/2018	3.1	5.4	18	0.9		
Carbimazole ceased						
03/2018	1.7	5.5	16			

Table 2 Other hormones and non-hormonal assays performed.

	01/2017	03/2017	07/2017	Ranges
Growth hormone	<0.1	<0.1	1.3	<3.1 mIU/L
IGF-1	52	41	31	7–27 nmol/L
Prolactin	359	305		40–450 mIU/L
FSH	11	10	9	<14 IU/L
LH	5.9	7.5	5.2	<11 IU/L
Oestrogen	113			<150 pmol/L
Testosterone	9.1	8.0	12	8.3–29 nmol/L
ACTH		4.1		<11 pmol/L
Cortisol (am)			174	100–535 nmol/L
Alpha TSH subunit	0.38			0–0.7 IU/L
PTH	7.8			1.5–9.9 pmol/L
Vitamin D	42			>51 nmol/L
Selenium	1.57			0.8–1.9 µmol/L
CRP	<4.0			<6 mg/L
Acetylcholine receptor antibody	<0.20			0–0.5 nmol/L
IgG	11.42			6.5–16 g/L
IgG4	0.04			0.04–0.86 g/L

posterior inferior aspect of the right lobe and exhibited features most consistent with colloid changes. One atypical nodule measuring 12 mm in its widest diameter, with irregular borders and posterior shadowing was noted on the right.

Thyroid nuclear scan revealed a heterogeneous distribution of tracer throughout the two lobes, but with relatively increased uptake on the right when compared to the left. There was an area of more focally increased uptake involving the superior portion of the right lobe, not clearly associated with a discrete nodule. Overall T uptake value was 1.2% (1.0–3.0%). The atypical nodule seen on ultrasound was said to be possibly cold and fine-needle aspiration was advised.

Fine-needle aspiration cytology revealed a haemorrhagic colloid nodule.

MRI of the orbit performed in December 2016 revealed bilateral exophthalmos, more prominent on the left than right. This was associated with increased T2 signal involving the inferior rectus on the left and lesser change on the right, and with minor thickening of the superior and medial rectus on each side, consistent with thyroid ophthalmopathy. Within the cranium, no significant abnormality was found, and there was however mucoperiosteal disease in the right sphenoid sinus (Fig. 1A and B).

Treatment

In December 2016, he was started on prednisolone 50 mg daily and referred to an orbital surgeon. He was also started on latanoprost eye drops in the left eye every night and single vision lens was recommended.

In January 2017, he was started on carbimazole 5 mg daily. Although the redness of the conjunctivae and the swollen lids improved, with decrease in his CAS from 4 to 2; he still had pain and mild injection of the conjunctivae, but chemosis and swollen lids had virtually disappeared; his proptosis and diplopia, however, worsened.

The prednisone was tapered off, with no change in his symptoms.

On April 2017, he underwent left orbital decompression surgery. His proptosis improved, but the diplopia persisted. He continued to use the single vision lenses.

Follow-up

A few weeks after surgery, he developed swelling of the right eye lids with proptosis, and mild redness of the right eye. There was no blurring of vision.

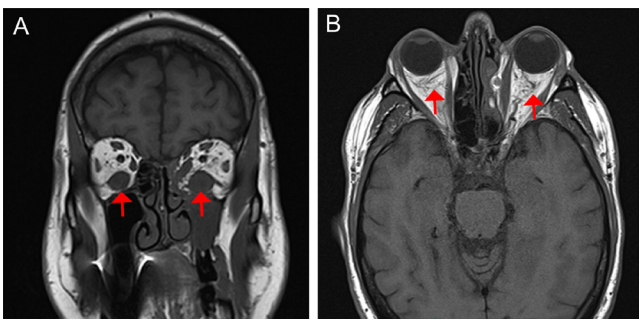

Figure 1
(A) MRI performed in 2016, showing the prominently thickened inferior rectus muscles in both sides (red arrows). (B) Showed MRI of the same patient with bilateral proptosis and increased post-septal vascularity (red arrows).

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In May 2017, MRI of the orbits and brain was repeated and compared with the one performed in December 2016. It showed gross thickening of the inferior rectus bilaterally, but very less prominent on the left; more prominent on the right when compared with previous images. There was mild thickening of the lateral rectus bilaterally.

The team considered radiotherapy, but later settled for decompression surgery on the right, to be followed up with strabismus surgery.

Discussion

MNG with exophthalmos is an unusual clinical presentation and raises the possibility of non-thyroidal causes of exophthalmos. Further confusion arises when TRAb are negative. The current belief is that Graves' orbitopathy is autoimmune mediated, with TRAb playing a central role, rather than being a direct consequence of altered thyroid function (6); hence, GO has a link with and seen in about 25–50% of patients with Graves' disease (7). Therefore, if seen in a case of MNG, possible reasons for the coexistence should be explored.

This patient has bilateral eye disease, which when combined with MRI findings, ruled out some causes of proptosis, such as lymphoproliferative disorder, pseudotumor cerebri, meningioma, cavernous carotid fistula, sarcoidosis, orbital cellulitis, intraorbital tumours and haematoma. The patient has no clinical features of myasthenia gravis and his acetylcholinesterase antibodies were normal; he also had no features suggestive of IgG4 disease and his IgG4 levels were also normal. In patients with GO, MRI will not only show the characteristic features such as enlargement of extraocular muscles and expansion of adipose tissues, as seen in this patient, it can also show the sight threatening complication of dysthyroid optic neuropathy (DON), and at the same time, rule out most of the diseases listed above (1). With most common and uncommon cases of exophthalmos ruled out, this can still be a case of idiopathic inflammation of the extraocular muscles, except that the flare up of symptoms following iodine-based contrast study makes the GO more likely (8).

Apart from the ocular symptoms and findings and persistent subclinical hyperthyroidism, this patient has no other clinical, biochemical or radiological features of Graves' disease. His TSH receptor antibodies were not raised, his thyroid ultrasound and nuclear scan did not show features suggestive of Graves' disease; rather, they were in support of multinodular goitre. But the absence of the clinical features or TSH receptor antibodies, at the time of presentation, does not rule out GO.

Some cases of isolated GO, without hyperthyroidism and raised TRAb, have been reported (1, 2) but none of the reported cases was found to coexist with a non-Graves' thyroid disorder, such as multinodular goitre. The temptation is to dismiss the eye disease as non-thyroid. Our case and other reported cases of GO with normal TRAb support the argument that other endogenous mediators, aside TRAb, play significant role in the pathogenesis of GO (3, 4).

One of the mediators implicated in the pathogenesis of GO is IGF-1 (3). The recent clinical trial which demonstrated the efficacy of teprotumumab, an IGF-1 receptor inhibiting antibody, in GO laid credence to the proposed role of IGF-1 in the pathogenesis of the disease (9). This patient has persistently raised levels of IGF-1, with no clinical or laboratory evidence of acromegaly; the cause remains unclear, and we have wondered the significance of this finding. IGF-1 has also been linked to thyroid nodules (5), so we are not sure if this factor is the missing link between the patient's two conditions – GO and multinodular goitre.

The coexistence of the two conditions can also be explained by Marine–Lenhart syndrome, a situation where multinodular goitre coexists with Graves' disease (10). If that is the case, we expect that this patient's TRAb may rise, over time (1).

Radiotherapy is a known treatment modality we did not utilise in this patient, while up to 60% response rate has been reported, successful outcome depends on the selection of patients – those with recent active opthalmopathy do better than those with long standing, inactive disease. Proptosis and long-lasting extraocular muscle dysfunctions do not respond very well to radiotherapy, compared to those with active inflammatory disease, recent muscle dysfunction and optic neuropathy (11).

Although we used a high-dose oral steroid therapy, with some improvement in the patient's acute inflammation, intravenous steroid is known to have a superior efficacy (12). Targeted biological therapies, such as the use of rituximab has also been shown to be effective, not only in the management of the GO, but also in the management of Graves' disease itself (13). The latest targeted biological therapy shown to be effective in GO was teprotumumab (8).

Declaration of interest
Daniel Chen is a Senior Editor of Endocrinology, Diabetes and Metabolism Case Reports. Daniel Chen was not involved in the review or editorial process for this paper, on which he is listed as an author. The other authors have nothing to disclose.

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Patient consent
A written informed consent has been obtained from the patient.

Author contribution statement
K O performed literature search and drafted the initial manuscript; R S, D C and R G edited the manuscript.

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