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Thyroid eye disease in patients with multiple sclerosis who have been exposed to immune reconstitution therapies

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Abstract

Background: Immune reconstitution therapy for multiple sclerosis (MS) is associated with thyroid eye disease (TED), although this has not been described with autologous haematopoietic stem cell transplantation (AHSCT).

Methods: A retrospective review of all patients with TED and MS attending a tertiary thyroid eye multidisciplinary clinic.

Results: Eight women (age at MS diagnosis 23–43 years; median peak Expanded Disability Status Scale 5.75; 50% non-Caucasian) were identified between January 2015 and 2026. All received immune reconstitution therapy (alemtuzumab n=6, AHSCT n=3; one patient received both). All were previously euthyroid, and 3 had prior optic neuritis; Graves' hyperthyroidism (GH) developed a median of 34.5 (12–49) months post-IRT and TED a median of 12 (2–35) months after GH. Presenting CAS was ≤2 in seven patients and very high TRAb levels (>30 IU/L in five patients). All developed EUGOGO moderate-to-severe TED at final review. Orbital MRI revealed marked heterogeneity of fat and extraocular muscle involvement. TED treatment included intravenous methylprednisolone (n=4), local triamcinolone (n=3), orbital decompression (n=2), strabismus surgery (n=1), and eyelid surgery (n=2). GO-QoL appearance and visual function scores were low (<75) at baseline and final visits.

Conclusion: We report the first cases of TED following AHSCT for MS. Despite predominantly low CAS scores at presentation, the disease course tended towards moderate-to-severe TED at follow-up. Prolonged multidisciplinary (endocrine, ophthalmic, and neurological) vigilance with concordant radiological surveillance is recommended for this cohort. Newer biologic therapies for MS and TED raise questions about their use in patients with complex immune-modifying and reconstitution therapies.

Introduction

Immune reconstitution therapy (IRT), such as alemtuzumab, an anti-CD52 monoclonal antibody and autologous haematopoietic stem cell transplantation (AHSCT), are effective in ablating immunity to reset pathogenic autoimmunity (1,2) and are widely used in the current treatment of progressive and relapsing multiple sclerosis (MS). Although effective in modifying disease progression (3), both are complicated by secondary autoimmune disease, most commonly thyroid dysfunction, usually Graves' hyperthyroidism (GH).

We report a case series of patients who developed thyroid eye disease (TED) post-IRT for MS managed at a large tertiary centre.

Methods

Patients with a history of MS and TED were identified from a thyroid eye clinic database in multidisciplinary (MDTED) clinics led by thyroid eye specialists (including VL, KM and CF) at Imperial College Healthcare NHS Trust. The MS care was led by MS specialists (including RN).

All patients underwent endocrine evaluation, with optimisation of thyroid status. Hyperthyroidism was managed with antithyroid therapy, typically carbimazole as first-line and propylthiouracil as second-line, either alone or in combination with thyroxine in a block-and-replace regimen or thyroidectomy. Hypothyroid patients and those who had undergone thyroidectomy received levothyroxine titrated according to thyroid function tests.

TED was diagnosed based on clinical assessment, verified by orbital imaging. All patients had their Clinical Activity Score (CAS) (4), EUGOGO severity score (ESS) (5) assigned by a consultant ophthalmologist at each visit. The most severe ESS score was used to determine disease severity for the patient's ongoing care. All patients underwent full ophthalmic, orbital and orthoptic assessment. Gorman diplopia grades and Graves' Orbitopathy Quality of Life (GO-QoL) scores were recorded at each clinic visit. Orbital MRI was performed using a dedicated TED protocol incorporating axial and coronal T2 short-tau inversion recovery, pre- and post-contrast T1 and diffusion-weighted imaging with apparent diffusion coefficient (ADC) mapping (6).

Treatment decisions were based on MDTED consensus, informed by clinical assessment, radiologic evidence and impact on quality of life.

In accordance with EUGOGO guidelines, Mild TED was managed with smoking-cessation advice (where appropriate), selenium supplementation, and ocular lubricants. Active moderate-to-severe TED received intravenous methylprednisolone and mycophenolate (5). Upper eyelid triamcinolone injections were offered for symptomatic upper eyelid retraction in the active phase. Rehabilitative surgery to address disfigurement included orbital decompression, strabismus surgery for intractable diplopia and surgical eyelid lowering once TED became quiescent.

Data were collected from the Trust (Cerner Millennium, Oracle Health, North Kansas City, MO, USA) and ophthalmic (Medisight, Medisoft Limited, Leeds, United Kingdom) records and entered into a standardised worksheet. Data were anonymised at extraction and analysed using descriptive statistics. Missing values were not imputed. Thyroid function was categorised as euthyroid, hyperthyroid or hypothyroid and TSH receptor antibody (TRAb) levels were recorded.

As a non-interventional, retrospective case note analysis using routinely collected data, formal research ethics approval was not required.

Written, informed consent was obtained from case 3 for inclusion of identifiable images in this publication.

Claude (Anthropic, San Francisco, CA, USA) was used to format the author-collected data in the tables and the timelines in the supplementary files. No content or data was AI-generated.

Results

Patient Characteristics

Eight female patients with MS and TED were identified. Four were Caucasian, two South Asian, one African, and one of mixed race ethnicity. Four had never smoked, three were ex-smokers and one was a current smoker. One patient had a family history of GH. The mean age at MS diagnosis was 29.8 years (range 23-43 years) and the median peak Expanded Disability Status Scale (EDSS) was 5.75 (range 1.5-6.5). The pattern of MS was relapsing/remitting in seven patients and progressive in one. Three patients had a history of demyelinating optic neuritis.

MS Treatment

All patients received IRT (alemtuzumab n=6, AHSCT with cyclophosphamide conditioning n=3), including one patient who received both. Additional disease-modifying therapies included natalizumab (n=4), anti-CD20 therapy (ocrelizumab or ofatumumab, n=3), interferon-β (n=1) and glatiramer (n=1). MS preceded GH in all patients by a median of 135.5 (31–299) months. There was no history of thyroid dysfunction prior to IRT. Five patients developed GH at least 10 years after MS onset. The median interval between IRT and GH was 34.5 (12–49) months.

Thyroid Status

All the patients were biochemically euthyroid before GH developed and TRAb levels were raised at presentation in every case, exceeding 30 IU/L in five. GH was managed medically in four patients and with thyroidectomy in four. None underwent radioactive iodine ablation.

TED developed after a median of 12 (2-35) months following GH. Baseline ESS was moderate-to-severe in six patients and mild in two. The median baseline CAS was 1. One patient presented with active disease (CAS 4) and peak CAS exceeded 2 in only two patients.

Patient Reported Outcomes

Baseline Gorman diplopia score (GDS) was 0 (no diplopia) in five patients, 1 (intermittent diplopia) in two and 3 (constant diplopia) in one. GDS deteriorated in one, improved in one and remained stable in the remainder. GO-QoL at presentation was available in six patients (mean appearance score 52.08, median 50, range 25–100, mean visual score 68.84, median 76.31, range 16.67–100) and at final assessment in eight (mean appearance score 50.62, median 41.88, range 25–87.5; mean visual function 65.78, median 70.84, range 16.67–100). Median MDTED follow-up was 44 (25–98) months, calculated from the first to the final clinic attendance date.

Radiological findings

No single MRI imaging phenotype characterised the cohort.

Apical crowding was noted in two patients (Cases 1 and 3), in the latter, only following ofatumumab. Definite extraocular muscle (EOM) enlargement was noted in three cases (Cases 1, 3 and 6) and was equivocal in another patient (Case 2). One patient (Case 5) developed fat-predominant disease without EOM involvement and another (Case 7) had only mild radiologic proptosis. The posterior orbital findings were within normal limits in two patients (Cases 4 and 8). Muscle changes occurred in patients with a low CAS (Cases 1 and 3), whereas the only patient presenting with active disease (Case 8) had repeatedly normal posterior orbital studies.

Case 3 illustrated this radiological heterogeneity over time. Although clinically quiescent (CAS 0–2) for over four years, serial MRI imaging showed EOM involvement that changed over time, beginning with right-sided involvement and a persistently abnormal right inferior rectus that did not resolve radiologically before other muscles and the left orbit became affected. Seven months after starting ofatumumab, she developed an asymmetric, predominantly left-sided pan-extraocular myositis with raised ADC values and new apical crowding.

TED Management

Four patients received systemic intravenous methylprednisolone and three had upper eyelid triamcinolone injections. Case 3 received tocilizumab. Rehabilitative surgery was undertaken in three patients, including elective orbital decompression (n=2), strabismus surgery (n=1), lid lowering/ptosis surgeries (n=1) and blepharoplasty (n=1). Orbital decompression was planned in one more.

Illustrative Cases

Three cases are briefly outlined to highlight clinically disparate patterns. The full cohort dataset is presented in Table 1 and in the Supplementary Files.

Case 2: Rehabilitative burden following AHSCT

A 43-year-old diagnosed with relapsing-remitting MS underwent AHSCT with cyclophosphamide conditioning in 2015 and developed GH 22 months later. TRAb levels were >30 IU/L on diagnosis. TED developed 11 months after GH onset with constant diplopia (Gorman grade 3), bilateral proptosis and a low CAS. A 12-week course of intravenous methylprednisolone produced no measurable change in proptosis or diplopia. She subsequently underwent bilateral orbital decompression, sequential inferior rectus recessions, extraocular muscle botulinum toxin and a Fresnel prism to resolve diplopia (Gorman grade 0).

Case 3: TED reactivation following ofatumumab

A female diagnosed with relapsing–remitting MS at age 28 was treated with alemtuzumab (2015–2016) and developed GH 18 months later. Mild TED was diagnosed 21 months after GH and remained quiescent (CAS 0–2) for over four years, during which time upper eyelid triamcinolone was administered twice for persistent lid retraction. Seven months after starting ofatumumab, she re-presented with a painless reduction in vision and gaze-evoked diplopia. Examination revealed periocular oedema and erythema (Figure 1) and left-sided optic disc swelling. Orbital MRI demonstrated significant, predominantly left-

sided pan-extraocular myositis (Figure 2). This was managed with intravenous methylprednisolone resulting in an improvement of GDS from 3 to 1, but with persistent disease activity, which has improved following the initiation of second-line intravenous tocilizumab.

Case 4: TED after AHSCT with a low TRAb titre

A 25-year-old female diagnosed with primary progressive MS and a family history of Graves' disease underwent AHSCT with cyclophosphamide conditioning. She had previously received IVMP and interferon-β. GH developed 46 months following AHSCT, with a TRAb level of 3.2 IU/L. Moderate-to-severe TED was diagnosed eight months later, with persistently low CAS (0–1). No systemic immunosuppression or surgery has been required during 53 months of follow-up.

Discussion

This case series describes eight female MS patients who developed GH and subsequent TED after exposure to IRT with no prior history of thyroid dysfunction. Half of our cohort was non-Caucasian. IRTs such as alemtuzumab and AHSCT exploit immune depletion to interrupt the autoimmune process in MS. This process of immune reconfiguration carries a well-characterised risk of secondary autoimmune disease (7), most commonly thyroid disease (8). Our experience is consistent with the published literature, which mainly consists of small retrospective case series following treatment, limiting clarity on epidemiology, natural history, and optimal management (9) (Table 2).

All patients developed moderate-to-severe TED by final review, despite 7/8 having a low CAS ≤2 at baseline. GO-QoL scores were low at both baseline and final follow-up, although GO-QoL is non-specific and is less sensitive in patients with overlapping comorbidities, including prior optic neuritis. Case 3 experienced unexpected TED reactivation seven months after starting ofatumumab, despite a previously stable and quiescent disease course for over four years. CD20-targeted therapy has been used to treat TED and is not expected to exacerbate it (10), and two other cases in this cohort received CD20-targeted therapy without any known side effects. Anti-CD20 therapies deplete mature B cells but largely spare plasma cells, allowing continued autoantibody production (11,12). Although causation cannot be established, the increasing use of anti-CD20 therapies, such as ocrelizumab and ofatumumab, in MS emphasises the need for extended MDT clinical and radiological surveillance. Decisions on systemic TED treatment were optimised via consensus between the TED and MS teams.

We additionally report two novel cases who developed GH and TED after AHSCT, with no prior alemtuzumab exposure. AHSCT is a more ablative form of IRT than alemtuzumab (2), associated with a lower frequency of thyroid autoimmunity than alemtuzumab (13,14). TRAb titres were lower in two of three patients treated with AHSCT than in those treated with alemtuzumab, which was typically > 30 IU/L. Serial radiological orbital surveillance showed significant heterogeneity in fat and extraocular muscle involvement, with temporal changes in individual muscle involvement.

This study has several limitations. Its retrospective nature, small sample size and single-centre setting limit generalisability and attribution of causality. MS, GH and TED data points were not uniformly collected and heterogeneity in MS phenotype, DMTs, follow-up duration and clinical course limits attribution of GH and TED aetiology. As a large tertiary centre, referral bias may lead to an overrepresentation of severe or complex cases.

In conclusion, GH and TED are late complications of both AHSCT and alemtuzumab, with a disease course that tends towards moderate-to-severe TED. Prolonged endocrine and ophthalmic surveillance is important, as changes in MS treatments may affect the course of TED. The emergence of biologic agents in TED, such as veligrotug and teprotumumab, adds further complexity regarding whether these therapies can be used in MS-TED patients (15,16).

Declarations

Conflict of Interests

V.L.: Advisor – Viridian Therapeutics, Inc., Amgen, Argenx, Roche; Honoraria for sponsored symposia – Amgen; Institutional financial support – University faculty; Advisory board member – Viridian Therapeutics, Inc., Amgen, Argenx, Roche; Leadership – Royal College of Ophthalmologists Scientific Committee, British Oculoplastic Surgery Society UK Thyroid Eye Lead, EUGOGO Secretary; Financial support – Viridian Therapeutics, Inc., Amgen, Argenx, Lassen, LIDS

The remaining authors declare no competing interests.

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Author Contribution Statement

MM collected and analysed data, generated tables, obtained patient consent for publication of clinical images and drafted the manuscript.

KB reviewed and interpreted orbital imaging, selected images for publication, prepared figure legends and contributed to manuscript preparation.

VL conceived and supervised the project, identified patients for inclusion and contributed to manuscript preparation.

RN reviewed neurologic records and provided specialist input regarding multiple sclerosis management and treatment.

SN reviewed endocrinologic records and contributed to manuscript preparation.

CF provided specialist input regarding potential mechanisms of ofatumumab-associated disease reactivation and contributed to interpretation of findings.

KM provided specialist input regarding thyroid management and contributed to interpretation of clinical records.

All authors critically reviewed the manuscript, made improvements and approved the final version.

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Tables

Table 1: Demographic, neurologic, endocrinology and ophthalmic characteristics of eight patients with MS and therapy-associated TED

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Patient								
Sex	F	F	F	F	F	F	F	F
Age at MS diagnosis	28	43	28	25	26	29	23	36
Smoking	Current	Never	Past	Past	Never	Never	Past	Never
FH of GH	No	No	No	Yes	No	No	No	No
Multiple Sclerosis								
MS phenotype	RR	RR	RR	PP	RR	RR	RR	RR
EDSS (peak)	5.5	4	6.5	6.5	1.5	6	3	6.5
Demyelinating optic neuritis	No	No	Yes	No	Yes	No	No	Yes
MS therapies preceding TED	ALM + NTZ + IVMP	MSS + NTZ + AHSCT/CYC	ALM	IFN + IVMP + AHSCT/CYC	ALM + IVMP	NTZ + ALM	IVMP + ALM + NTZ	IVMP + GLTR + ALM + AHSCT/CYC
MS therapies following TED	None	None	OFA + IVMP	None	OCR	OCR	NTZ	None
IRT → GH / TED (months)	12/36	22/33	18/39	46/54	30/35	44/57	49/85	39/41
Thyroid								
MS → GD (months)	31	132	139	299	55	152	51	169
Thyroid diagnosis	GH	GH	GH	GH	GH	GH	GH	GH
TRAb level at presentation	6.68	>30	>30	3.2	>30	>30	>30	15
Thyroid Eye Disease								
GH → TED (months)	24	11	21	8	5	13	35	2
CAS baseline / peak	1 / 1	2 / 2	0 / 2	1 / 1	2 / 3	1 / 1	1 / 2	4 / 4
Severity (final)	Mod–Sev	Mod–Sev	Mod–Sev	Mod–Sev	Mod–Sev	Mod–Sev	Mod–Sev	Mod–Sev
PROMS baseline / final	A 50 / 31.25 V 16.67 / 66.67 G 1/1	A NA / 31.25 V NA / 42.86 G 3/0	A 100 / 87.5 V 93.75 / 91.67 G 0/1	A 56.25 / 50 V 50 / 16.67 G 1/1	A 50 / 85.71 V 64.29 / 75 G 0/0	A 31.25 / 60.5 V 100 / 83.33 G 0/0	A 25 / 33.75 V 88.33 / 100 G 0/0	A NA / 25 V NA / 50 G 0/0
VA logMAR RE / LE (baseline → final)	0/0.1 → 0/0	0.1/0.1 → 0.1/0.4	-0.1/0.1 → 0/0.3	0.4/0.1 → 0.4/0.3	0.1/-0.2 → 0.1/0.1	0/0 → 0/0	-0.1/0 → -0.1/0.1	0.2/0.2 → 0/0
Proptosis RE / LE (baseline → final)	20/21 → 23/23	25/24 → 22/19	18/18 → 19/22	21/20 → 20/22	26/27 → NA	21.5/21 → 21.5/21	21/19 → 20/20	21/21 → 22/21
ULSS worse eye (baseline → final)	-1mm → -1mm	0mm → -1mm	-1mm → -1mm	-3mm → -3mm	0mm → NA	+1 → -2mm	N/A → 0mm	+0.5mm → 0mm
TED immunosuppression	IVMP	IVMP	TCN, IVMP, TCL	None	None	None	TCN,	IVMP, TCN
TED procedures	None	EOM Botox, SS, OD	None	None	BP, OD	Lid lowering (x2), ptosis (x1)	None	Planned OD

Abbreviations: *MS, multiple sclerosis; GH, Graves' hyperthyroidism; TED, thyroid eye disease; RR, relapsing–remitting; PP, primary progressive; IRT, immune reconstitution therapy; ALM, alemtuzumab; AHSCT, autologous haematopoietic stem cell transplantation; NTZ, natalizumab; OCR, ocrelizumab; OFA, ofatumumab; GLTR, glatiramer; IFN, interferon; IVMP, intravenous methylprednisolone; MSS, mesenchymal stem cells; CYC, cyclophosphamide; FH, family history; GD, Graves' disease; TRAb, thyrotropin receptor antibody; CAS, clinical activity score; PROMS, patient-reported outcome measures; A, appearance (GO-QoL); V, visual function (GO-QoL); G, Gorman grade; VA, visual acuity; RE, right eye; LE, left eye; ULSS, upper lid scleral show; TCN, triamcinolone; TCL, tocilizumab; OD, orbital decompression; EOM, extraocular muscle; SS, strabismus surgery; BP, blepharoplasty.*

Table 2: *Summary of published peer-reviewed reports of therapy-associated TED in MS.*

Study	Number of MS/TED patients	Female, %	Mean age of MS onset (years)	Smoking history, %	MS therapies preceding TED of interest	Thyroid Diagnosis	Time Thyroid Disease → TED	Time MS → GD, TED	Mean interval from study drug → TED (months)	EUGOGO Mod–Severe (%), Final	Systemic TED Immuno-suppression, %
This Study	8	100%	29.8	50%	ALM, AHSCT	GH, 100%	15 months	10.7 years, 11.9 years	47.5	100%	50%
Pariani et al (17)	7	N/A	N/A	43%	ALM	N/A	N/A	N/A	N/A	N/A	N/A
Roos et al (18)	6	33%	36	50%	ALM	GH, at least 50%	33 months	N/A	14.8	50% (baseline)	50%
Nirmalan et al (19)	5	40%	N/A	80% (current)	ALM	GH, 100%	24 months	N/A, 13.8 years	48	N/A	40%
Ueland et al (20)	9	N/A	30.5	N/A	ALM	N/A	17 months	N/A, N/A	40.5	22%	22%
Muller et al (10)	1	100%	37	100%	ALM	GH, 100%	12 months	10 years, 11 years	48	100%	100%
Moon et al (21)	1	0%	N/A	N/A	ALM	GH, 100%	N/A	N/A	36	100%	100%
Trinh et al (22)	1	100%	36	N/A	ALM	GH, 100%	12 months	3 years, 4 years	36	100%	0%
Le Moli et al (23)	1	100%	33	N/A	ALM	GH, 100%	Concurrent	36 months, 36 months	13	100%	0%
Patrizio et al (24)	1	100%	57	100%	IFN	GH, 100%	Concurrent	3 years	20	Unclear	0%
Rodriguez de VeranGomez et al (25)	6	67%	N/A	N/A	ALM	GH, 100%	15.2	N/A	45.9	50% (baseline)	50%
Tsourdi et al (26)	2	50%	34.5	N/A	ALM	GH, 100%	Concurrent	5.5 years	30.5	50%	50%
Sovetkina et al (3)	2	N/A	N/A	N/A	ALM	GH, 100%	N/A	N/A	<12	N/A	N/A
Kazakou et al (27)	4	N/A	N/A	N/A	ALM	N/A	N/A	N/A	N/A	N/A	N/A
Manso et al (28)	2	N/A	N/A	N/A	ALM	N/A	N/A	N/A	N/A	50%	50%
Daniels et al (29)	3	N/A	N/A	N/A	ALM	GH, 100%	N/A	N/A	N/A	N/A	N/A

Abbreviations: *N/A, not available; GH, Graves' hyperthyroidism; ALM, alemtuzumab; AHSCT, autologous haematopoietic stem cell transplantation; IFN, interferon beta.*

Figures



Figure 1

Paired clinical images for case 3, taken before and after starting Ofatumumab in March 2025. Images show worsening left sided periocular oedema and erythema with a new hypertropia. Fundal assessment during the same visit showed left sided optic disc oedema.

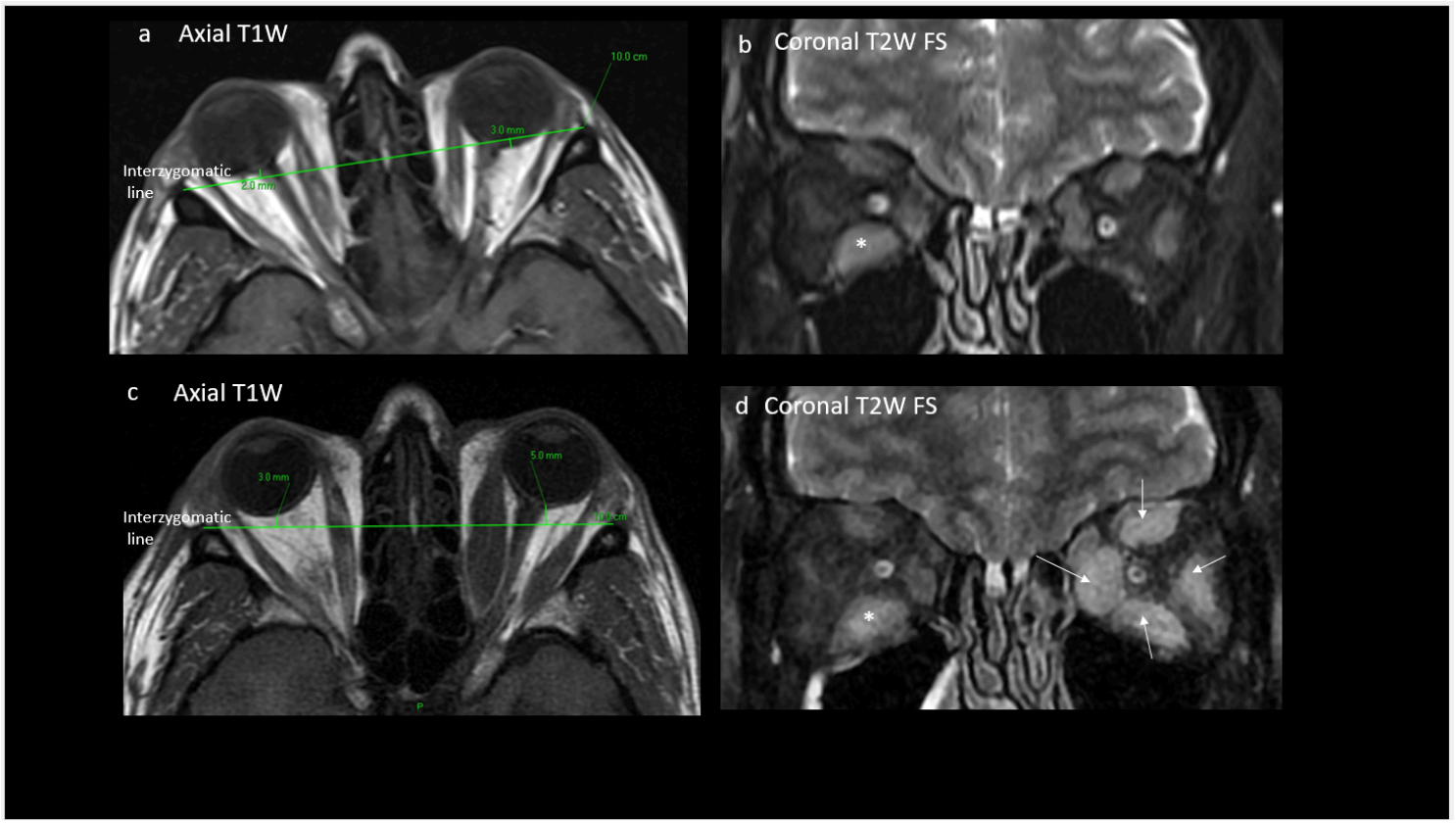


Figure 2

MRI orbits for patient described in case 3 acquired in March 2024 (Top row, a+b) and September 2025 (bottom row, c+d). a) Axial T1-weighted image shows moderate right and mild left proptosis as measured by the perpendicular distance from the posterior sclera to the interzygomatic line. b) Coronal T2-weighted fat saturated image shows moderate right inferior rectus muscle enlargement with mildly increased T2 signal (*) suggestive of oedema.

c) Axial T1-weighted image shows new severe left proptosis. d) Coronal T2-weighted fat saturated image showing persistent enlargement and oedema of the right inferior rectus muscle (*) and new moderate-to-severe enlargement and oedema of the left rectus muscles (arrows).

Supplementary Files

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- SupplementaryCaseFilesFinal.pptx