Endocrinology, Diabetes & Metabolism CASE REPORTS

L Das and others | Thyroid eye disease with orbital lymphoma

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Thyroid eye disease with concurrent orbital lymphoma: a radiological surprise

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Summary

Thyroid eye disease (TED) is the most common extra-thyroidal manifestation in Graves' disease (GD). Additional/concurrent/synchronous pathologies may be present, especially in elderly patients who present with atypical features such as non-axial (or eccentric) proptosis, absence of lid lag and restricted superior extra-ocular movements. A 70-year-old female presented with progressive proptosis of her left eye and diplopia. She was diagnosed with GD a year prior and initiated on carbimazole. On examination, she had eccentric proptosis, restricted superior extra-ocular movements and a palpable mass in the supero-temporal quadrant of the left eye. Her T3 (1.33 ng/mL) and T4 (8.85 µg/dL) were normal with carbimazole. Thyroid-stimulating hormone (TSH)-receptor antibody was positive (3.15 IU/L, reference range <1.75). MRI revealed an enhancing lesion infiltrating the left superior rectus, with concurrent characteristic muscle belly involvement bilaterally. Orbital biopsy showed atypical lymphoid cells (CD20+), suggesting marginal zone lymphoma. CT thorax and abdomen, fluorodeoxyglucose-positron emission tomography and bone marrow examination were normal. The patient was administered orbital radiotherapy for her localised lymphoma and carbimazole was continued. TED is the most common cause of orbital involvement overall and in GD. However, additional or alternative pathology may be present which requires evaluation. MRI can be a useful adjunct in these patients. Orbital lymphoma needs to be staged with workup for disseminated disease. Radiotherapy is the treatment of choice for localized disease. The index case provides evidence for synchronous presentation of dual pathology and highlights the importance of astute clinical examination as well as keeps a low threshold for MRI in selected cases.

Learning points:

- Thyroid eye disease can co-exist with other ocular pathology, especially in elderly individuals.
- Eccentric proptosis, absent lid lag and restriction of eye movements (suggesting tendon involvement) should alert towards the presence of alternative pathology.
- Orbital imaging using MRI not only has greater sensitivity in diagnosing radiologically bilateral disease in patients who have unilateral involvement clinically but is also useful to identify concurrent neoplasms.

Background

Thyroid eye disease (TED) is a frequent complication of Graves' disease (GD) (1). It is usually synchronous and bilateral but may be clinically unilateral in upto 4–14% of cases (2). However, non-TED causes of ocular involvement must be suspected in patients with atypical features such as non-axial (eccentric) proptosis (defined as protrusion of the eyeball with an alignment different from the long axis of the globe, in which the direction is determined by the site of the lesion) and a lack of lid retraction in elderly individuals. The index case represents a rare occurrence

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of a dual pathology for orbital involvement in a 70-year-old female with GD. This case highlights the importance of using orbital imaging for actively investigating atypical ocular features in patients with GD. Orbital MRI can not only diagnose occult bilateral TED but also unearth underlying neoplasms which require definite management.

Case presentation

A 70-year-old female presented with gradually progressive left eye proptosis, xanthopsia, diplopia and redness of both eyes for the past 6 months. There was no history of eye discharge, diminution/loss of vision, diarrhoea, loss of weight, palpitations, fever or night sweats. She did not complain of retro-orbital pain at rest or on movement but had foreign body sensation. She was diagnosed with GD a year prior to the current presentation. Past medical history was otherwise insignificant. On initial evaluation, her vitals were normal. She had pallor and a goitre (WHO grade II). Investigations revealed iron deficiency anemia (Hb 9.6 g/dL, mean corpuscular volume (MCV) 74 and microcytic hypochromic RBCs on peripheral smear). Eye examination showed eccentric proptosis (6 mm on Hertel's exophthalmometry) in the left eye with downward and outward displacement of globe, no lid retraction, mild palpebral conjunctival congestion and restriction of superior and horizontal extraocular movements as shown in Fig. 1. A firm-to-hard immobile mass was palpable in the superotemporal quadrant. Its posterior extent was not assessable. Overlying skin was free with normal temperature. Right eye showed cataract. She had inactive TED in both eyes (left eye clinical activity score (CAS) 1/7, right eye CAS 0/7). Her best corrected visual acuity was 6/60 in left eye and 6/12 on the right. Colour vision was normal.

Thyroid function tests at baseline showed thyroid-stimulating hormone (TSH) <0.01 µIU/L (reference values: 0.4–4.2), total T4 19.6 µg/dL (reference values: 4–12) and total T3 3.55 ng/mL (reference values: 0.8–2). Free fractions were not measured. Antibody titres to thyroid peroxidase (152 IU/L, N <5.4) and TSH receptor (TRAb) were positive (3.15 IU/L, N <1.75). Ultrasonography of the thyroid showed heterogeneous architecture, with multiple hypoechoic nodules. CT scan of the orbit was performed for recent-onset atypical proptosis which showed a homogenously enhancing soft-tissue attenuating mass lesion in the pre- and peri-orbital region of the left eyeball, causing mass effect and extending into the retrobulbar space, with bulky left medial rectus as shown in Fig. 2. Contrast-enhanced MRI orbits showed a well-defined T1, T2 isointense, homogeneously enhancing mass lesion in the superior

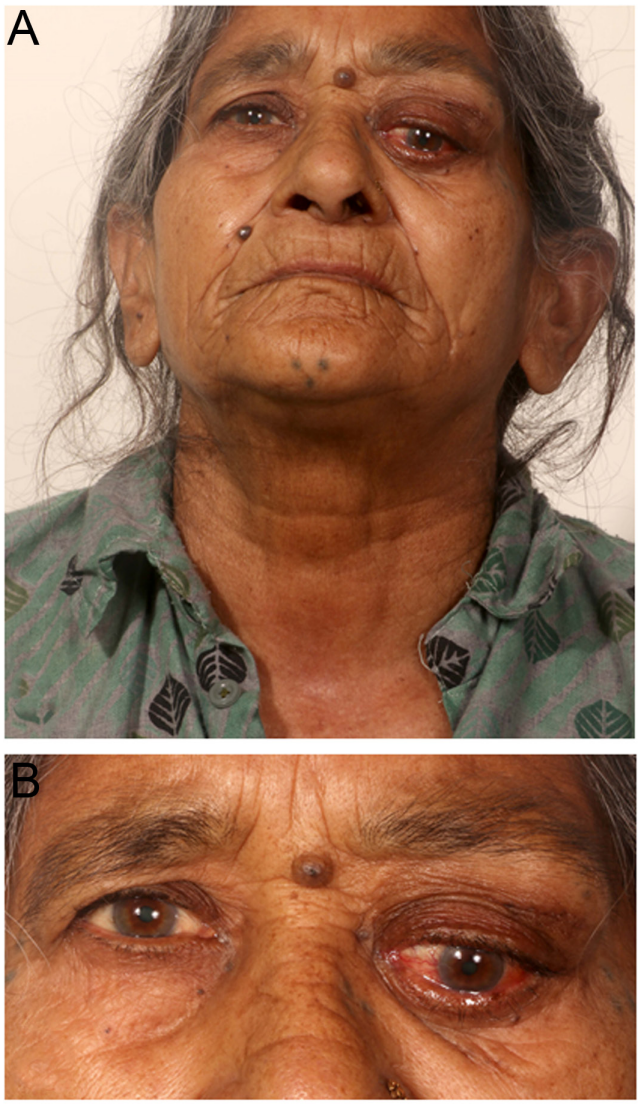

Figure 1
(A and B) Clinical photographs of the patient showing non-axial (eccentric) proptosis of the left eye accompanied by conjunctival erythema with absent lid retraction, favouring a non-TED cause of ocular involvement in the given patient.

region of the left orbit (4.4 × 3.4 × 2.3 cm), predominantly in the extraconal compartment, with minimal extension into the intraconal space and infiltrating the superior rectus (SR) and reduced bulk of the left optic nerve (Fig. 2C and D). The mass was abutting the globe and orbital walls circumferentially from 9 to 3 o'clock position encasing the bulky SR, enlarged lacrimal gland and preseptal tissues in continuity. Bilateral thickened muscle bellies of inferior rectus (IR) and medical rectus (MR) with tendon sparing were noted on both sides. Due to the unusual, asymmetric focal lesion, orbital incisional biopsy was performed, which was uneventful. Histopathology revealed diffuse

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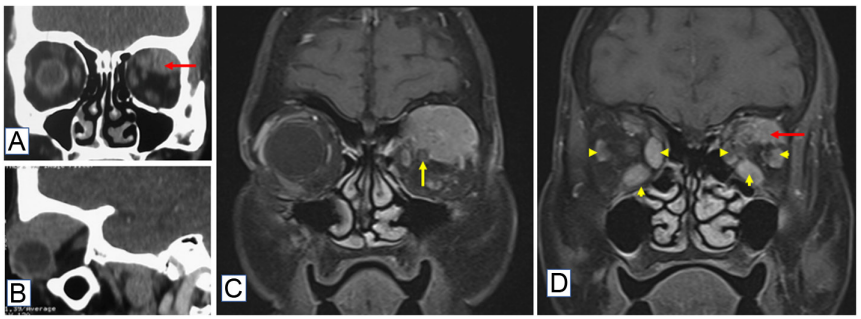

Figure 2
(A, B, C and D) Panel of CT and MRI of the index patient with (A) depicting CT orbit coronal section showing a mass in the superior aspect of the left orbit encasing the superior rectus (red arrow) and sparing of the other extraocular muscles and (B) showing CT orbit sagittal section with the isodense mass without bony erosion. MRI coronal section of the orbit (C) depicts a T1 isointense mass draping along the superior aspect of the globe and encasing the superior rectus muscle with the optic nerve seen separately (yellow arrow). (D) depicts the thickened muscle bellies of the inferior, medial and lateral recti bilaterally marked by yellow arrowheads consistent with bilateral thyroid eye disease associated with the mass in the superior aspect (red arrow), consistent with lymphoma.

infiltration by small-to-medium-sized atypical lymphoid cells seen in Fig. 3. Individual lymphoid cells had round hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm. Scattered mitotic figures were seen. No areas of necrosis were identified. On immunohistochemistry, the tumor cells were diffusely positive for CD20, and negative for CD3, CD5, CD23, cyclin D1, SOX-11 and CD10. Ki-67 index was 10–15%. Overall features were suggestive of extranodal marginal zone B-cell lymphoma. Further workup for staging the disease was negative, with contrast-enhanced CT thorax and abdomen showing only few subcentimetric cervical and mediastinal lymph nodes and fluorodeoxyglucose-positron emission tomography (FDG-PET) showing no activity other than the enhancing left orbital mass. Bone marrow also showed no lymphomatous infiltration.

She was initiated on 20 mg carbimazole twice daily followed by gradual tapering to 5 mg daily. This led

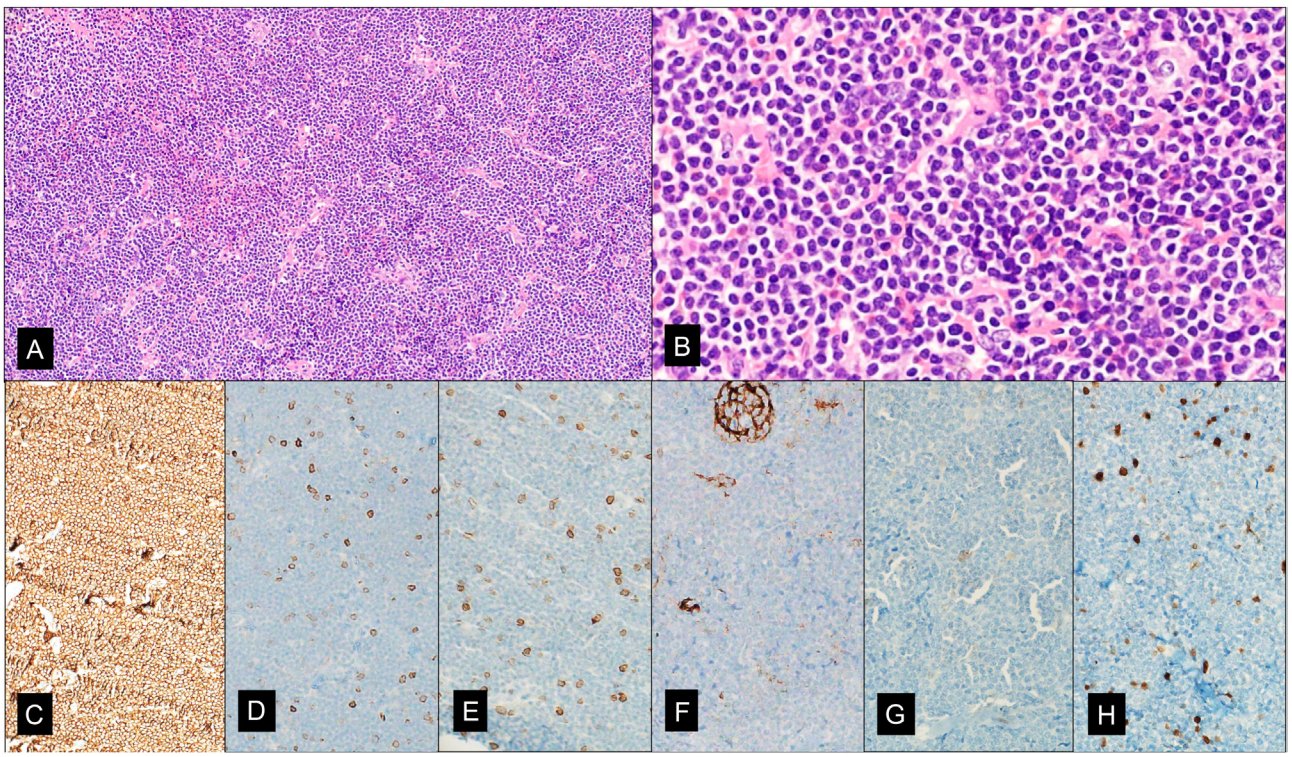

Figure 3
(A, B, C, D, E, F, G and H) Histopathology of the excised mass showing (A) diffuse monomorphic infiltrate of lymphoid cells (H & E, 100×); (B) the lymphoid cells are small-sized (H & E, 600×). The lymphoid cells are positive for CD20 (C) and negative for CD3, CD5, CD23 and cyclin D1 (D, E, F and G, DAB chromogen, Hematoxylin counterstain, 400×). Ki-67 index is 10–15%.

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to normalisation of T3 and T4 levels and subclinical hypothyroidism in the current admission, following 14 months of treatment (TSH 8.09 µIU/L, total T4 8.85 µg/dL and total T3 1.33 ng/mL). In view of localized lymphoma, the patient was administered fractionated orbital external beam radiotherapy. There was a steady improvement in her proptosis with radiotherapy. Ultimately, there was complete and durable resolution of the same. Patient continued to remain euthyroid with 5 mg daily dose of carbimazole (TSH 4.1 µIU/L, T4 7.9 µg/dL and T3 1.5 ng/mL).

Discussion

TED is a frequent complication of GD, with recent evidence estimating a prevalence of 25–50% of this complication in GD (1). Unilateral TED is seen in nearly 4–14% of cases but most cases with clinically unilateral disease are confirmed to have bilateral disease radiologically (2). However, upto 7% patients may be euthyroid, and on the other hand, non-TED inflammatory and neoplastic conditions can cause ocular involvement in a patient of GD (3). Further, asymmetric involvement has been reported in 9–34% cases, but most cases classify as mild asymmetry (2). In the spectrum of TED, disease activity and severity do not always go hand in hand. However, a visible and palpable lump, strictly unilateral or gross asymmetric eye involvement, non-axial (eccentric) proptosis, a lack of lid retraction or lid lag on downward gaze or weakened muscle function (suggestive of tendon involvement) are the clinching features of non-TED mediated ocular involvement in a given patient of GD (4). The presence of two or more of these features is a stronger pointer to additional pathology in a patient with TED and should prompt not only further imaging but also referral to the ophthalmologist and initiate multidisciplinary care in such challenging clinical situations. Recognition of such atypical features of eye disease in a patient with GD is imperative to timely identify an underlying sinister etiology and ensure optimal management.

TED is the most common cause of single or multiple extraocular muscle involvement overall, followed by inflammatory and neoplastic causes (5). However, the relative preponderance of TED decreases with advancing age, when neoplasms gain prominence. The typical pattern of TED is bilateral symmetric muscle involvement and tendon sparing. Radiological evidence of bilateral involvement is much more common than clinical, as was noted in the index case who had clinical signs in the left eye only but typical bilateral involvement on MRI. Atypical findings such as the absence of hyperthyroidism, no upper lid retraction or lid lag and solitary muscle involvement should point towards non-TED causes in a patient of GD (1, 6). The IR and MR are the most commonly involved muscles in TED and isolated involvement of the superior rectus (SR), lateral rectus (LR) or obliques is exceedingly rare (1). Restriction of superior extra-ocular movement and downward displacement of the globe in the index patient suggested isolated SR involvement which was an unusual feature, prompting further evaluation. Low or undetectable TRAb levels are also regarded as a pointer for non-TED pathologies in a patient of GD. The index case is a rare instance of co-occurrence of TED and orbital lymphoma, which has seldom been reported earlier. The unequivocal histopathological evidence of lymphoma along with long-standing history of thyrotoxicosis, elevated TRAb levels and radiological evidence of typical extra-ocular muscle involvement were proof of co-existing pathologies in the index patient.

Primary orbital neoplasms account for nearly 5–10% of all orbitopathies and lymphomas constitute half of them. They can present as localised or multifocal disease. Unilateral (75%) and localised (60%) disease patterns are more common, as seen in our patient. The typical presentation of orbital lymphoma is between the 5th and 7th decades as a painless mass and no gender predilection. Vision is usually spared. Orbital imaging can be a useful adjunctive diagnostic modality to discern the etiology in these patients, especially in those with atypical features or for disease monitoring. MRI has been found to have a higher sensitivity than CT for TED diagnosis, assessment of involvement of non-osseous structures and immunomodulatory treatment monitoring (7). CT orbit showed a soft-tissue mass with retro-orbital extension and MRI confirmed the presence of bilateral TED with concurrent left orbital mass, consistent with lymphoma.

Interestingly, TED patients have reportedly higher propensity to develop periocular lymphoma (8). The mechanism underlying this phenomenon has been ascribed to the emergence of lymphoma in a background of chronic lymphocytic stimulation as seen with other inflammatory diseases, including Hashimoto's thyroiditis. The pathogenesis of TED involves autoimmunity against the TSHR, primarily present on the orbital fibroblasts and adipocytes, which acts as the primary autoantigen. Similarly, orbital lymphoma commonly arises in the retro-orbital adipose tissue and in the extra-ocular muscles. Unilateral marginal zone B-cell Non-Hodgkin's lymphoma (NHL) and MALT-lymphoma have been described in patients with GD (9, 10, 11). But in these reports, the patient did not have concurrent TED, unlike in our case.

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Complete staging using CT thorax and abdomen or FDG-PET and bone marrow are required to stage the disease. In case of localised disease, radiotherapy is the treatment of choice. Prognosis in cases of localised disease is usually good, with overall mortality rates of 5–10%. In the index case, disease was found localised to the orbit, hence she was administered orbital radiotherapy. Carbimazole therapy was continued.

Conclusion

TED is the most common cause of eye involvement in a patient with GD and is the most common cause of orbitopathy overall. However, there may be concurrent presence of other causes, which should be investigated further. Eccentric proptosis and the absence of lid retraction are to be regarded as red flags in this context.

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
Written, informed consent was obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement
All authors contributed equally to the management and clinical care of the patient as well as to the manuscript. The final version of the manuscript has been read and approved by all the authors.

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