

Idiopathic Orbital Inflammation Underlying Drug-Associated Thyroid Eye Disease

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INTRODUCTION

Alemtuzumab has been reported to cause thyroid eye disease in approximately 30% of patients being treated for multiple sclerosis (MS).¹ Treatment of alemtuzumab-induced thyroid ophthalmopathy mimics Graves' ophthalmoplegia regimen, whereas systemic symptoms frequently require thyroidectomy. While Graves' ophthalmoplegia is clinically common, ophthalmoplegia has a wide differential diagnosis, which often can be narrowed via imaging and, of potentially more importance, tissue analysis.² We present an unusual case where thyroid eye disease and idiopathic orbital inflammation co-occurred, resulting in a hazy clinical picture. The unique findings in the combined disease processes are underscored and outcomes of the patient's management are presented.

CASE REPORT

A 41-year-old female presented for evaluation and treatment of thyroid eye disease. Three years prior to presentation, she was treated for relapsing, remitting multiple sclerosis with alemtuzumab. Three months prior to presentation, she developed eye pain, pressure, and binocular diplopia. Review of systems was otherwise negative and family history was unremarkable. Her prior lab work was consistent with Graves' disease and an outside provider began treating her with selenium.

The exam showed 20/25 vision in both eyes, mildly elevated intraocular pressure (25 mmHg in the right eye, 21 mmHg in the left eye) and a 2+ afferent pupillary defect in the left eye. Motility showed -1 deficit with left abduction. Hertel measurements were 19 mm in the right eye and 23 mm in the left eye. Slit lamp exam showed 1+ edema and erythema of both upper eyelids. There was 1+ injection of the conjunctiva and caruncle with 1+ chemosis in both eyes. The remainder of her exam was unremarkable.

Thyroid labs showed a thyroid stimulating hormone of 0.6 mIU/L, low free T4 0.02 ng/dL, elevated thyroid stimulating immunoglobulin 4.9 IU/L, and elevated thyroid receptor antibody 4.78 IU/L. Complete blood count, angiotensin converting enzyme, lysozyme, anti-nuclear antibodies, erythrocyte sedimentation rate, c-reactive protein, myeloperoxidase, and proteinase-3 antibody were within normal limits. IgG subclass 4 was low < 0.3 mg/dL. Computed tomography (CT) of the orbits without contrast showed moderate left greater than right infiltrative soft tissue thickening in the superior and lateral intraconal and extraconal orbits with less involvement in the inferior orbit. These find-

ings were non-specific, but were not suggestive of thyroid eye disease. The patient underwent left orbitotomy with biopsy of the abnormal tissue. The biopsy showed focal lymphoplasmacytic infiltrate, chronic inflammatory infiltrate. The findings were suggestive of a reactive process. Immunoglobulin gene rearrangement was negative, excluding lymphoma.

Oncology and endocrine services were consulted for a lymphoplasmacytic mass, with a concern for lymphoma versus inflammatory mass with concurrent thyroid eye disease. At three-month follow-up, monitoring of Graves' clinical activity scores showed no changes from baseline. Humphrey visual field results were borderline with normal right eye results and non-specific left eye changes. Positron emission tomography (PET) scan showed hypermetabolic activity in the posterior orbits bilaterally corresponding to the region of soft tissue thickening. The PET scan was not concerning for systemic lymphoma. Response to high dose steroids was minimal.

The medical oncology service started a three-week course of rituximab, after which the patient developed worsening proptosis. Prednisone 60 mg resulted in moderate improvement of the proptosis. Follow-up CT two months later showed mild improvement of left muscle thickening. The patient's condition was complicated by active COVID-19 infection during rituximab infusions and severe headaches from vision changes. The oncology service pursued radiation treatment of bilateral extraocular muscles, which resulted in gradual, moderate improvement in double vision, ability to close the eyelids, and proptosis without full resolution.

The patient received 4 Gray in 2 fractions to the bilateral orbits. With the endocrine service suggesting that Graves' disease played a major role in her symptoms, the patient underwent a near-total thyroidectomy one-month later. One-month post-operation, she was clinically euthyroid and the thyroidectomy was unremarkable. She was awaiting retroorbital surgery for continued ocular symptoms, unresolved by thyroidectomy.

DISCUSSION

This case highlighted the similarities between idiopathic orbital inflammation and thyroid eye disease. The patient was presumed to have thyroid eye disease given the associations in the literature with alemtuzumab and lab work was consistent with Graves' disease.¹ However, imaging showed foci consistent with orbital inflammation rather than muscle enlargement seen with Graves' ophthalmopathy.³ Inflammatory workup was negative, as was gene rearrangement. Biopsy demonstrating chronic inflammation confirmed the diagnosis of idiopathic orbital inflammation.

This case emphasized the importance of maintaining a broad differential when evaluating patients with symptoms suggestive of thyroid eye disease. Orbital imaging and histopathological analysis remain important diagnostic steps in distinguishing thyroid eye disease from other inflammatory processes and determining treatment course. This was demonstrated by the decision to administer a lower radiation dose than what would be used typically to treat clear-cut Graves' exophthalmos,⁴ due to reduced suspicion of Graves' disease based on her imaging and tissue analysis.

Case reports describing eye diseases masquerading as Graves'

ophthalmopathy can be found in the literature;^{5,6} however, only a few cases demonstrated idiopathic orbital inflammation and thyroid eye disease occurring concurrently. While clinicians frequently order imaging in these cases, imaging is often inconclusive.² The risk of unnecessarily initiating thyroid disease treatment versus obtaining minimally invasive biopsies under local anesthesia must be considered in each case. Imaging combined with histopathologic analysis tends to efficiently narrow the differential and orient toward a more specific treatment.² Relying on purely non-invasive analysis risks neglecting a secondary inflammatory condition, such as in this patient.

This report described an interesting case where the clinical picture of alemtuzumab-induced thyroid eye disease was disconcerted by an underlying idiopathic orbital inflammation. The two conditions frequently were compared throughout the literature with plentiful discussion of how to distinguish the two diseases.^{5,6} While labs were consistent with thyroid eye disease, imaging suggested idiopathic orbital inflammation, which was proven by biopsy. This resulted in a more reserved style of management, relative to standard thyroid eye disease management, by all consulted providers. This case serves as a reminder of the importance of histopathologic analysis in cases of complicated thyroid eye disease.

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