

## Sight Threatening Thyroid Eye Disease Complicating Hashimoto's Thyroiditis

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**Received date:** September 12, 2017; **Accepted date:** October 3, 2017; **Published date:** October 15, 2017

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### Abstract

A case of sight threatening thyroid eye disease (TED), arising in a 55 year old woman with primary hypothyroidism due to Hashimoto's thyroiditis (HT), is described. TSH receptor antibody (TSHRab) was positive as were orbital antibodies. Initial management consisted of methylprednisone intravenously followed by prednisone orally in a tapering dose, orbital irradiation and decompressive surgery. Visual acuity improved but 9 months later, there was evidence of relapse with features of compressive optic neuropathy, and exophthalmos had worsened. Prednisone dose was increased. At that time, TSHRab was negative. She underwent total thyroidectomy on the understanding that this was experimental therapy, surgery confirmed that thyroid pathology was solely TH without any evidence of Graves' disease. Prednisone was successively tapered without further relapse. Rehabilitative ocular muscle surgery is planned. Whether the improvement seen in TED can be attributed to effect of removal of thyroid antigens following thyroidectomy is purely speculative. Our case illustrates that relapsing sight threatening TED is part of spectrum of TED in HT and demonstrates that clinical features can be severe.

### Introduction

Thyroid eye disease is an inflammatory disorder of the extraocular muscles and surrounding orbital connective tissue and fat, thought to be autoimmune in origin [1-4]. TED most commonly occurs in the presence of Graves disease [2]. Subtle eye signs are not uncommon in HT, when actively sought being found in up to a third of cases [5]. Florid TED however is unusual with HT, with only 5 prior cases reported [6-10].

Although in cases of severe TED, patients with negative TSHRab have been reported [9] a more recent large series found that TSHRab measured with a bioassay was strongly associated with TED in HT, suggesting that the association was due to concurrent Graves' disease [10].

### Case Presentation

A 55 year old woman, diagnosed with primary hypothyroidism 2 months prior, presented with rapid onset of reduced vision. Examination revealed sight threatening TED with bilateral reduction in eye movement in all directions, bilateral exposure keratopathy, right afferent pupillary deficit, and reduced visual acuity, with VA 3/24 on the left, and 6/36 on the right. She was a non-smoker, and of Indonesian heritage. There was a family history of Graves' disease affecting her half brother and an undefined thyroid disease had affected their mother. Her other history included type 2 diabetes mellitus and alopecia totalis.

Initial biochemistry demonstrated modest thyroxine over replacement with serum TSH of 0.076 mIU/L (reference range RR, 0.1-3.8), a free T4 level of 15.7pmol/l (RR, 10.5-17.7) and a free T3 of 3.0 pmol/L (RR, 2.3-7.1).

Thyroid autoantibodies were positive with an antithyropoxidase titre of 1890 units/mL (RR, 0-35), an anti thyroglobulin titre of 981 units/mL (RR, 0-25) and an TSHRab of 20 units/litre (RR, <20) was borderline positive. Antibodies associated with thyroid orbitopathy were both elevated. Calsequestrin antibody was 542 Units (RR, 93-283) and Collagen XIII antibody was 283 Units (RR, 30-112). Units for both calsequestrin and collagen XIII antibodies are calculated on optical density as an ELISA and then multiplied by 100.

A CT orbits revealed marked bilateral proptosis, with diffuse enlargement of all extraocular muscles and tendons at the musculotendinous junction, and some evidence of optic nerve compression. Thyroid ultrasound was typical for HT with increased vascularity suggestive of thyroiditis, and no evidence of nodules.

The patient was admitted for intravenous methylprednisone, and received 1 g daily for 3 days. She was then commenced on prednisone 100 mg daily.

Concurrently she underwent bilateral medial wall surgical decompression on Day 5 of admission, with good improvement in visual acuity to 6/6 bilaterally. Prednisone was reduced from 100 mg to 60 mg daily during the admission.

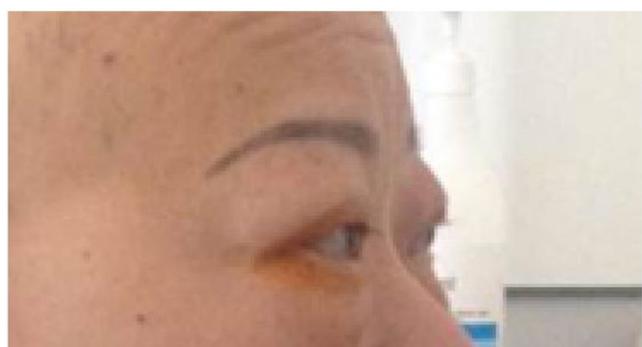
She was discharged on prednisone 50 mg daily, with a weekly taper to 30 mg daily. This was subsequently uptitrated to 40 mg due to a relapse in visual acuity.

This was then progressively tapered again, to a nadir of 3 mg daily, over the following 7 months.

Concurrently she was referred for orbital irradiation (XRT), which was commenced approximately 2 weeks after discharge (Figures 1 and 2).



**Figure 1:** 2 weeks after initial presentation.



**Figure 2:** Lateral view 2 weeks after initial presentation.

She received total dose of 2000 Rad given over 10 fractions. At end of radiotherapy eye findings were an improvement in visual acuity to 6/18 on the right and 6/9 on the left. Her visual fields, pupils and colour saturation had normalised.

Thyroid hormone replacement was repeatedly titrated during her clinical course, aiming to achieve serum TSH in the lower part of the reference range.

Nine months from the original presentation, she represented with a reduced vision on the right and was noted to have a right sided afferent pupillary deficit with reduced colour vision, and an acute reduction in visual acuity to 6/60 on the right. This was thought to represent TED recurrence rather than chronic change. Prednisone was increased from 3 mg to 40 mg daily and she required a right lateral orbital wall decompression. The afferent pupillary deficit resolved. She had an ongoing limitation in eye abduction. Visual acuity improved to 6/12 for the right eye and 6/6 to the left eye. At this presentation, the TSHR ab titre was undetectable, and anti thyroglobulin antibody had reduced to 178 units/ml and anti thyroid peroxidase antibody level reduced to 157 units/ml.

A thyroidectomy was performed 2 months following the second orbital decompression surgery. Visual acuity improved further to 6/9 on the right.

Six months following thyroidectomy, antithyroglobulin antibody had normalised and anti thyroid peroxidase antibody fell to 43

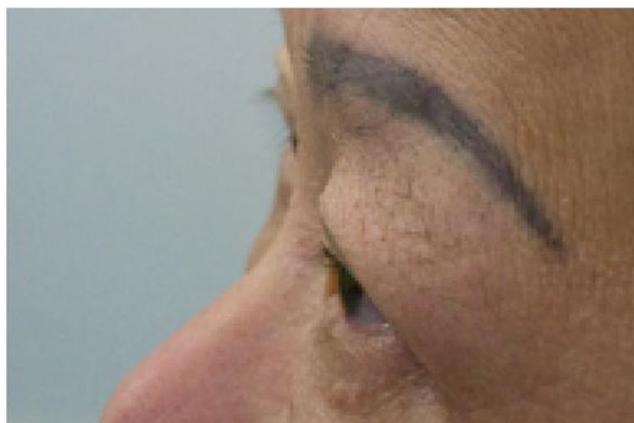
units/mL. Calsequestrin antibody improved to 109 Units and anti collagen XIII to 105 Units, both of which were in reference limits.

Use of prednisone required isophane and aspart insulin in order to maintain glycaemic control. As the dose of prednisone was reduced, she was transitioned to oral agents only.

She subsequently underwent reconstructive surgery, with a Bi-medial rectus recession performed 20 months after her original presentation (Figures 3 and 4).



**Figure 3:** 18 months after presentation.



**Figure 4:** Lateral view 18 months after prevention.

She continues to have regular ophthalmic surveillance and has also developed evidence of non-proliferative diabetic retinopathy.

## Discussion

Sight threatening presents challenges in terms of the management of TED itself; the potential for relapse; the management of any underlying thyroid disorder; and whether any interaction between the two conditions should influence therapeutic decisions. In terms of management of TED, given the severity in our patient, multiple therapeutic modalities were employed including decompression, GC and XRT, particularly since there is evidence to suggest synergy between glucocorticoids (GC) and radiotherapy (XRT) [11,12].

Therapeutic options for severe TED include high dose GC, which is first line treatment. First line therapy for management of severe TED is pharmacotherapy with GC. A recent weekly methylprednisone protocol has been proposed, (0.25-0.5g per week for 6 weeks in the Eugogo protocol) (13) with a highest maximum total dose of 5g methylprednisone. Our patient had received a higher equivalent GC (methylprednisone plus prednisone) within 3 months of commencing treatment.

The active phase of TED is on average 6-36 months. In patients who require GC for less than 3 years, an increase in symptoms may represent increased disease activity rather than relapse. Around 10-20% of patients relapse after GC therapy. This group, similar to our case, represent a therapeutic dilemma. There is no clear recommendation in current guidelines [13,14].

XRT is reserved as second line treatment, in refractory cases or where GC are associated with significant morbidity [13]. Decompression surgery is indicated in sight threatening disease (despite GC and/or XRT) although does not alter the course of disease. Other immunosuppressive agents such as Cyclosporine or Rituximab have been utilised, with Cyclosporine demonstrating some clinical improvement when combined with GC in 2 studies, but with significant morbidity, including renal and liver toxicities [15,16]. Evidence for the clinical utility of Rituximab is limited, with a pilot study demonstrating some benefit [17]. Two subsequent larger trials yielded conflicting results, with one study demonstrating no difference to placebo, and another showing some benefit in ocular motility and quality of life compared to GCs [18,19].

The clinical course of TED can make it difficult to assess the impact of management of thyroid status on the TED. Given the likelihood that a rise in serum TSH may underlie the exacerbation of TED after radioactive iodine for management of Graves disease [20], thyroxine was titrated frequently in our patient. The management of hyperthyroidism in Graves' disease in terms of impacts on presence and progression of TED is debatable. Although there is some evidence to suggest that TED may improve after thyroidectomy for management of Graves' disease [21], there is a lack of randomised clinical trials to provide guidance [13].

It was discussed with the patient that there was no data to support thyroidectomy in the management of TED complicating HT. In particular, there was no difference in the eye symptom domain of THyPRO, a quality of life questionnaire specific for thyroid disease [22]. Our patient undertook thyroidectomy on the understanding that this was experimental therapy. Rationale for surgery was that there is a likely role for TSH receptor antigen in TED, as supported by animal models [23].

In TED complicating Graves disease, TSHR ab levels correlate to TED severity [24] however, in TED complicating HT, TSHRab did not fluctuate but data on whether there was a correlation with severity or activity of TED was not reported [25]. However, mild eye disease, with symptoms such as grittiness, pruritis and upper eyelid retraction occurs in 25% of patients with HT [5] and TRAb levels as measured by TSI/Thyretin are negative [26], indicating the possibility of a different eye disease.

Our patient had a low titre TSHab on presentation, which subsequently normalised, yet still demonstrated a relapse in her orbitopathy. It is unclear whether TSHab may reflect initiation of disease and other factors are responsible for relapse. Orbital antibodies such as calsequestrin and Collagen XII, as measure in this patient are

thought to be implicated directly in the pathogenesis of TED. Subgroups of eye disease have been described, but with some cases displaying features of both. Calsequestrin, G2S (a subunit of a mitochondrial enzyme), and flavoprotein are implicated as candidate autoantigens in the ocular myopathy subgroup, whereas TSHab and Collagen XIII have been implicated as candidate autoantigens in the congestive ophthalmopathy group [2]. Other novel autoantigens have also been described. In conclusion, the role of autoantibodies on the underlying pathogenesis of TED remain unclear, however our case provides anecdotal evidence of improvement in severe TED after total thyroidectomy in HT.

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