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*Case Report*

# Development of Thyroid Associated Eye Disease After Total Thyroidectomy for Recurrent Papillary Thyroid Cancer

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## Abstract

**A 50-year-old woman with locally advanced papillary thyroid cancer was treated with total thyroidectomy, left neck dissection and radioactive iodine ablation. She presented with nodal neck metastases two years later and underwent a radical neck dissection with curative intent. Sixteen months after that, she developed new onset thyroid eye disease in association with elevated thyroid stimulating immunoglobulin. It is extremely rare to develop thyroid eye disease in an athyreotic patient. She has had no visible papillary thyroid cancer recurrence on anatomic imaging for the subsequent 24 months, however the appearance and persistence of thyroid stimulating immunoglobulin remains a concern for thyroid cancer recurrence, and close follow up is indicated.**

**Keywords:** Thyroid eye disease, Graves' disease, papillary thyroid cancer, orbital fibroblasts.

## INTRODUCTION

Thyroid eye disease (TED) is an autoimmune disorder with an unclear pathophysiological mechanism. Thyroid stimulating immunoglobulin is thought to cross-react with orbital fibroblast proteins in addition to activating the TSH receptor and causing hyperthyroidism (Bahn, 2010). Here, we present a rare case of a patient who developed TED years after total thyroidectomy, neck dissection, and radioactive iodine (RAI) for locally metastatic papillary thyroid carcinoma, despite theoretical absence of all thyroid cells at the time of development of the orbitopathy. This research was HIPAA-compliant, and the patient gave written consent.

### Case Presentation

A 50-year-old woman presented with a slowly enlarging left sided neck mass over one year in 2015. She was a non-smoker with no personal history of thyroid disease or radiation and denied family history of thyroid cancer or Graves' disease. Computed tomography (CT) neck at the time of her presentation demonstrated numerous bulky left neck metastatic nodes. Fine needle aspiration cytology was consistent with papillary thyroid cancer. She underwent total thyroidectomy and left-sided neck dissection. Pathology confirmed multifocal papillary thyroid cancer with lymphocytic thyroiditis, suggestive of previously undetected underlying autoimmune thyroid disease. She was treated with 159 mCi of Iodine 131. Post-therapy scan was notable for uptake only in the thyroid bed, with no evidence of distant metastases.

Follow up was complicated by the presence of thyroglobulin antibodies (TGAb), common in patients with lymphocytic thyroiditis, limiting accuracy of thyroglobulin measurements. Rising TGAb titer (from 22 to 71 IU/mL) in 2017 prompted a repeat CT neck, which showed recurrent metastatic papillary thyroid cancer to her left

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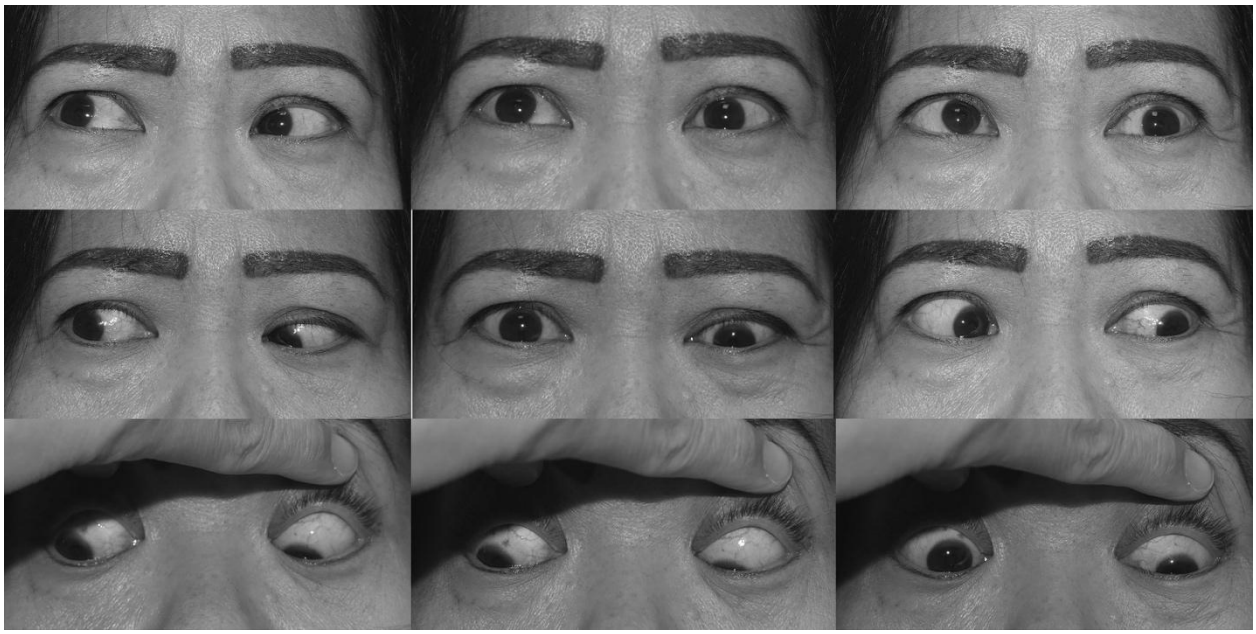

**Figure 1.** External photographs showing 9 gazes of view. In primary gaze, there is right upper eyelid retraction (margin to reflex distance-1, MRD1 7.0mm) and left hypotropia. With supraduction, there is restriction of both eyes, greatest in the left. Horizontal ductions are full while there is slight restricted downgaze of the right eye.

central and lateral neck. She underwent a second neck dissection in December 2017 with involvement of 11 of 38 nodes and extra-nodal extension. She did not receive any further RAI treatment. TGAb titer trended downwards post-operatively, suggestive of successful removal of antigen.

In April 2019, she presented with double vision in primary gaze and noted that her left eye was bulging. Her ophthalmologist detected bilateral restrictive strabismus, proptosis (OD 21 and OD 22), and eyelid retraction (Figure 1). MRI orbits showed mild exophthalmos and enlargement of her extraocular muscles bilaterally (Figure 2B). These findings were new compared to normal extraocular muscles seen on CT of her neck in June 2017 (Figure 2A), reflecting development of TED since her second neck dissection sixteen months prior. She was in a mildly thyrotoxic state while taking levothyroxine 112 mcg for replacement and suppression (TSH 0.03 uIU/mL, fT4 2.13 ng/dL). Her thyroid stimulating immunoglobulin was elevated with >500% basal activity. Based on these laboratory and imaging findings, she was diagnosed with TED despite being supposedly athyreotic.

Her restrictive strabismus improved with conservative management including vision therapy and prisms. At six months follow up after her diagnosis of TED, given quiescent disease, she opted for continued clinical follow up and deferred orbital decompression surgery. Her thyroid cancer has continued in apparent remission; repeat neck ultrasound in November 2019 was negative for recurrent malignancy and her TGAb has continued to trend downward (most recently 5.6 IU/mL in February 2020). However, the presence of thyroid stimulating immunoglobulin may suggest thyrocyte presence.

## DISCUSSION

While Graves' disease has been associated with an increased incidence of thyroid cancer (Wei et al., 2015), it is rare to develop TED after total thyroidectomy for thyroid cancer. The mechanism by which TED occurred in our patient is unclear.

Development of TED with positive thyroid stimulating immunoglobulin may suggest presence of thyroid follicular cells, perhaps heralding another recurrence of our patient's thyroid cancer. A prior case reported a patient who developed TED nine years after initial thyroidectomy, and subsequently was found to have metastases due to papillary thyroid cancer (Katz et al., 1997). A second case reported development of TED after thyroidectomy and I-131 treatment, and was thereafter found to have metastases to the right pelvis (Woeber and Schwartz, 2008). Our patient's negative interval thyroid ultrasound and ongoing reduction in TGAb titer together argue against recurrence of papillary thyroid cancer. There was also a patient who developed TED after thyroidectomy for papillary carcinoma with no detectable metastases, suggestive that thyroid tissue may not be necessary for appearance of thyroid autoantibodies (Giovansili et al., 2011).

Another possibility is that RAI ablation induced autoimmunity to trigger TED. Radioiodine ablation causes destruction of thyroid tissue and liberation of antigen,

Figure 2A.

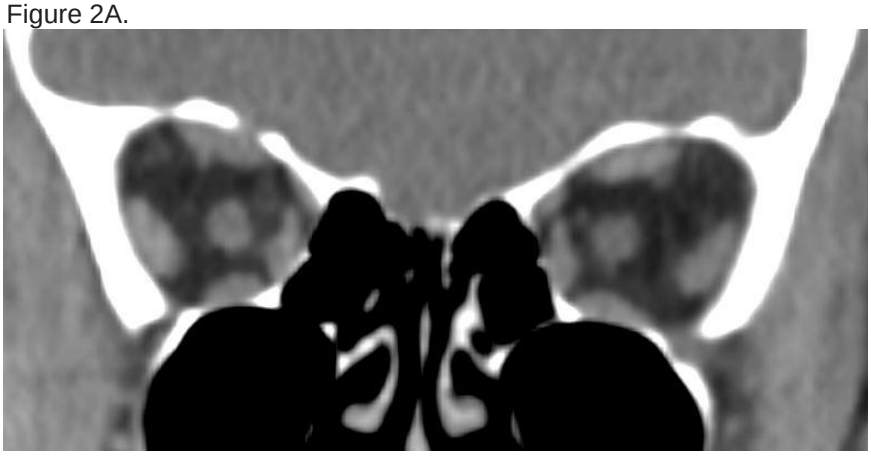

Figure 2B

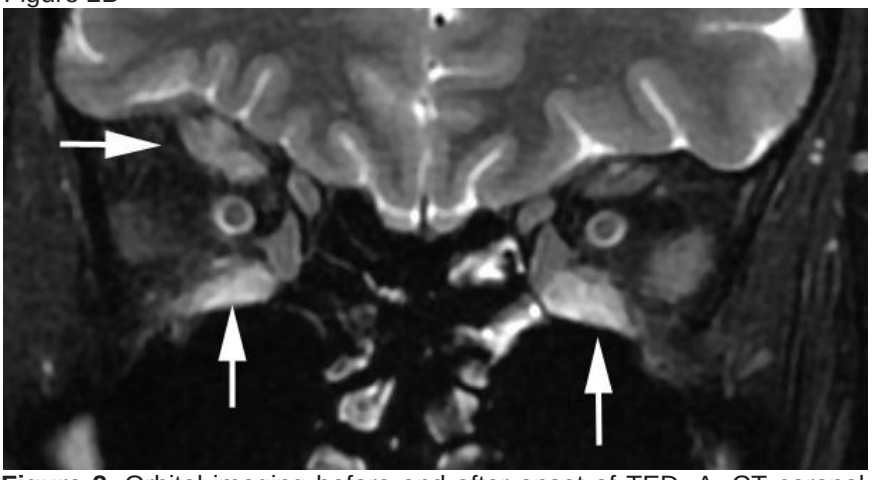

**Figure 2.** Orbital imaging before and after onset of TED. A. CT coronal imaging shows normal caliber of the extraocular muscles. B. MRI coronal imaging shows enlargement of the right superior rectus, right inferior rectus and left inferior rectus with associated contrast enhancement.

which is responsible for triggering the development of autoantibody to the TSH receptor. This has been reported following radioiodine ablation for Graves' disease, perhaps because the thyroid gland is usually sizeable and thus there is destruction of a certain mass of tissue (Karlsson 2006). By contrast, reports of this phenomenon after radioiodine ablation for thyroid cancer are scarce. This may be because thyroidectomy (with or without lymph node dissection) has almost always taken place in advance, thus the volume of disrupted tissue is low. There are several reported cases similar to ours without evidence of metastasis in patients who had undergone thyroidectomy and radioactive iodine ablation (Jang et al., 2015 and Giovansili et al., 2011). At this point, further radioactive iodine ablation would be contraindicated in our patient given radioactive iodine's association with worsening TED (Louvet et al., 2016).

An analogous hypothesis is that the tissue disruption from surgery itself in another way to expose thyroid antigens to the immune system. In a case series of 6 patients who developed TED after thyroidectomy +/- radioactive iodine therapy for thyroid cancer, the authors hypothesized that surgical destruction of thyroid cells increased TSH receptor expression leading to Graves' disease, or that an immune system abnormality was induced by surgery (Jang et al., 2015). By this mechanism, it is possible our patient's second nodal resection triggered TED. However, most patients in the case series did receive both thyroidectomy and radioactive iodine ablation, and thus distinguishing between the two as the etiology of TED is challenging.

In most patients with differentiated thyroid cancer, rise in serum marker thyroglobulin heralds recurrence. However, patients with underlying lymphocytic thyroiditis often

harbor antibodies to thyroglobulin (TgAb) that interfere in laboratory measurement of serum thyroglobulin. In such cases, titer of TgAb itself can be a surrogate marker for thyroglobulin (Spencer and Fatemi, 2013). It is unexplained why our patient developed thyroid stimulating immunoglobulin while her TgAb titer was falling. In the one other case reported with lymphocytic thyroiditis in the pathology specimen after thyroidectomy for papillary thyroid cancer, TgAb was persistently elevated during development of TED and thyroid stimulating immunoglobulin (Woeber and Schwartz, 2008). It may be worth considering a prospective study to measure thyroid stimulating immunoglobulin in thyroid cancer patients that have lymphocytic thyroiditis to consider as a potential alternative tumor marker, although in our patient seems not to reflect cancer recurrence.

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