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Case report

Euthyroid Graves' orbitopathy and incidental papillary thyroid microcarcinoma

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ABSTRACT

Euthyroid Graves' orbitopathy (GO) combined with incidental papillary thyroid microcarcinoma has rarely been reported. CASE REPORT: A 61-year-old Caucasian woman initially presented with progressive fatigue, exophthalmos, and thyroid function tests within normal limits. She underwent thyroidectomy, was found to have two incidental papillary thyroid microcarcinomas, and received radioactive iodine ablation to eliminate thyroid antigen. In addition to following her eye disease, TSH-receptor antibodies, thyroid stimulating immunoglobulins, and serum thyroglobulin measurements were recorded, demonstrating no evidence of thyroid cancer at four-year follow-up. At first, she had mild GO, developing into moderate-to-severe GO, and at 4 years she had Hertel measurements of 20 mm in both eyes. CONCLUSION: This report underscores the difficulty of managing GO even when thyroid function is normal(ized) and thyroid antigen exposure has been minimized. In addition, it illustrates why antithyroidal antibodies should be considered in cases of concomitant papillary thyroid cancer, as thyroid cells can be stimulated not only by TSH but also by TSH-receptor stimulating antibodies.

Key words: Antibody, Graves' disease, Orbitopathy, Radioactive iodine, Thyroid carcinoma

INTRODUCTION

Graves' orbitopathy (GO) is diagnosed in 10–25% of patients with Graves' disease and a small percentage (1.6-8.6%) of patients with GO are euthyroid or hypothyroid.[1-5] As a multifactorial disorder, GO is influenced by non-preventable factors (age, sex, genetic factors) and exogenous factors (cigarette smoking, thyroid dysfunction, radioiodine treatment).[5,6]

The pathogenesis of GO includes the TSH-receptor as an antigen, fibroblasts, and adipocytes as the main cell contributors, and a specific cytokine-mediated immunologic response.[7,8] Patients with euthyroid

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Graves' disease and GO have high levels of TSH receptor antibodies (TRAb) including thyroid-blocking and thyroid-stimulating immunoglobulins (TSI).[9,10]

Cases of papillary thyroid microcarcinomas (PTMC) and concomitant euthyroid GO have previously been reported.[11] Thyroidectomy specimens have been investigated for possible "incidentalomas" (thyroid microcarcinomas) in multiple studies, with prevalence rates up to 35.3%.[12-18] A few studies have concluded that papillary thyroid cancers (PTC) in Graves' disease patients have a more aggressive behavior due to the presence of high titers of thyroid-stimulating antibodies.[19-23] It is unclear whether the coexistence of differentiated thyroid cancer and thyroid autoimmune disorders such as Graves' and Hashimoto's disease has a causal relationship.[23]

A thorough investigation of patients with Graves' disease can help reduce the risk of missing some of these (incidental) thyroid cancers and other autoimmune disorders that might co-occur in the form of polyglandular syndrome variants.[24,25]

Case Presentation

A 61-year-old Caucasian woman presented to her local primary care physician with a six-month history of progressive fatigue and exophthalmos. Initially, she was asymptomatic but remembered that a friend had commented about an enlargement of her eyes two months prior. She also noted double vision the days immediately before presentation. She described no change in the quality of her voice and denied any preceding stressful events, previous thyroid disease, radioactive iodine therapy, or (active or passive) smoking history along with problems related to eating, drinking or swallowing. Thyroid function tests performed at this time were within normal limits (Table 1). Orbital MRI demonstrated bilateral enlargement of the rectus muscle (inferior, medial, and superior), more prominent in the left orbit than in the right. This appearance was most suggestive of Graves' disease and associated orbitopathy. The patient consented to have pictures taken of her orbitopathy during visits. Figures 1A and 1B show her thyroid-associated orbitopathy on initial presentation.

The patient was then referred to our clinic and examined three months after initial presentation. Over the previous three months, she had received prednisone therapy at 5 mg every other day (prescribed by her ophthalmologist, for a total period of nine months). Laboratory studies now demonstrated a suppressed TSH, free T4, and anti-TPO antibodies within normal limits, elevated anti-TSH receptor antibodies, and undetectable thyroglobulin antibodies (Table 1). A thyroid ultrasound showed two bilobar nodules, each measuring approximately 15 mm in size, without increased vascularity or microcalcifications. Given her thyroid eye disease and the size of the thyroid nodules, a total thyroidectomy was scheduled to obtain definitive histology and reduce antigen-driven inflammation in the orbit.[26]

Before thyroid surgery, a detailed eye exam was performed. Visual acuity and Hertel measurements are shown in Table 1. No color vision errors, edema or pallor of the optic nerve were noted. Strabismus was appreciated as mild to moderate with intermittent diplopia. Total (subtotal) thyroidectomy was performed and considered successful, with less than 3-4 g of thyroid tissue remaining. The pathology report revealed a surprising finding of two conventional PTMCs measuring 0.5 mm and 2 mm, respectively, in the right lobe within two mucoid nodules, 2 and 1 cm maximum dimensions, whereas the left lobe contained multiple benign nodules ranging from 1.1 to 1.5 cm.

Our patient returned for another follow-up visit six weeks after surgery. Evaluation of thyroid function at this time demonstrated an elevated TSH, suppressed free T4, and elevated TSH receptor and anti-TPO antibodies (Table 1). She was diagnosed with postsurgical hypothyroidism and levothyroxine 100 mcg/day was started. She also noted that her diplopia and blurred vision were worsening. At this point, we recommended radioactive iodine ablation to destroy any remaining thyroid tissue and further reduce antigen exposure.[5,27]

RAI ablation (30 mCi) was performed and the patient returned for another follow-up exam. At this time, her TSH and TSH-receptor antibodies had decreased and anti-TPO antibodies were within normal limits (Table 1). Figures 1C and 1D show the patient's GO post-RAI ablation.

Although we were seeing improvement of thyroid function and antithyroidal antibody concentrations,

Table 1. Biochemical and clinical analyses related to our patient's autoimmune thyroid disease over four years

	Thyroid function tests									
Clinical examination	**TSH (uU/mL) N: 0.35-4.50**	**Free T4 (ng/dL) N: 0.89-1.76**	**Anti-TSH-R N: <16%**	**TSI N: 0-1.3**	**Anti-TPO (IU/ml) N: 0-9**	**Tg (ng/ml)**	**CAS**	**VISA**	**Visual Acuity**	**Hertel Measurements (mm)**
03/2008 (Initial)	0.81	1.15	-	-	-	-	-	-	-	-
06/2008 (Referral)	0.035	1.7	44	-	9	-	2/7*	3/8**	L: 20/25 R: 20/20	L: 21 R: 20
10/2008 (Post-thyroidectomy)	>100	0.2	30	-	13	2.3	-	-	-	-
01/2009 (Post-RAI)	40.80	-	25	-	9	<0.1	-	-	-	-
08/2009 (Post eye surgery)	0.573	-	27	-	-	<0.1	4/7[1]	6/8[1]	-	L: 26 R: 25
12/2009	0.087	-	5.42	-	-	-	-	-	L: 20/25 R: 20/25	-
07/2010 (Post left eye surgery)	0.136	-	-	2.5	8	<0.1	-	-	-	-
02/2011	1.550	-	3.14	3.2	-	-	-	-	-	-
08/2011	0.44	-	2.09	1.9	-	-	-	-	-	L: 20 R: 20
04/2012	0.36	-	-	2.0	-	<0.1	3/7	4/8	-	L: 20 R: 20

* positive only for chemosis and eyelid edema, ** 2 points for chemosis and 1 point for eyelid edema
[1]these moderate to high scores may represent an initial increase in orbital inflammation due to trauma caused by eye surgery
CAS: Clinical Activity Score; VISA: vision, inflammation, strabismus, and appearance/exposure score, Tg: thyroglobulin.
Thyroglobulin antibodies were undetectable (<20 IU/ml and <1.8 IU/ml) throughout her course of treatment from 2008 to 2012.

her diplopia continued to worsen and decompressive eye surgery was performed. She returned to our clinic for follow-up one month after surgery. At this time, her TSH was within normal limits, while TSH-receptor antibodies and Hertel measurements remained elevated (Table 1).

The decompressive eye surgery was successful for only a short period before the patient's condition worsened again, possibly as a result of surgical trauma to the orbit. She returned to us for another follow-up appointment six months following eye surgery. Visual acuity at this visit was stable (Table 1). No edema, pallor of the optic nerve or color vision errors were present. The patient noted worsening diplopia in her left eye and was scheduled for a second eye surgery. Figures 1E and 1F show the patient's GO on this visit.

We discussed intravenous glucocorticoid therapy according to the Kahaly protocol[28] and radiotherapy but the patient was not in favor and, instead, underwent a second surgery on her left eye and returned for follow-up four months later. Her clinical presentation had improved at this visit and she noted that her diplopia had resolved. Figures 1G and 1H show her GO four months after left eye surgery. Table 1 shows laboratory studies drawn at this time.

We continued to monitor her GO and maintain surveillance for PTMC by regular follow-ups, serial thyroid function tests, serum thyroglobulin levels, and thyroid ultrasound examinations. We evaluated the

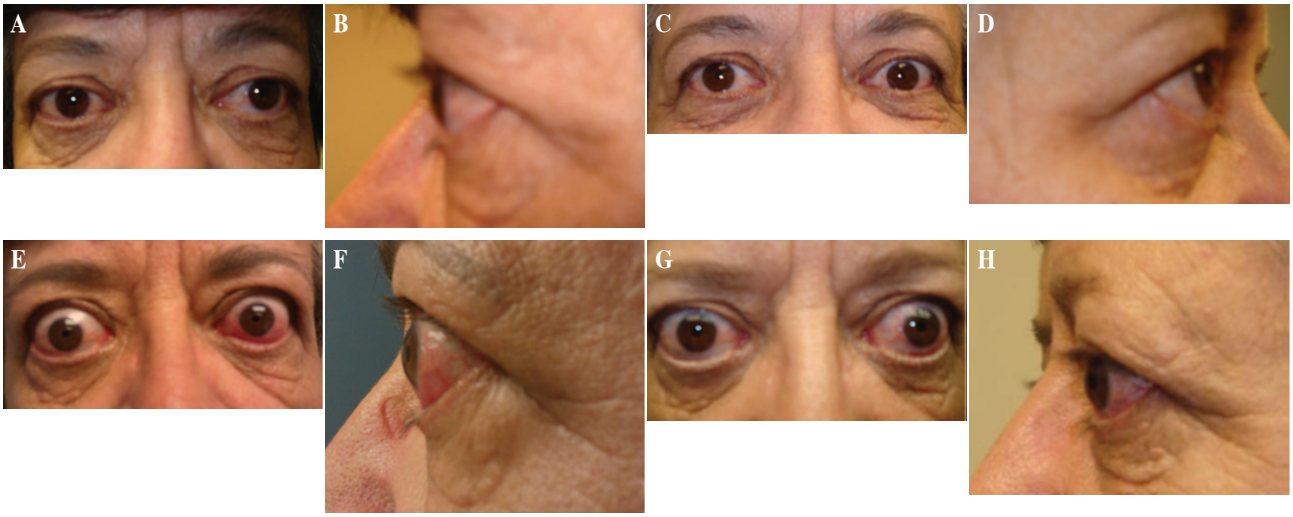

Figure 1. Anterior (**A**) and lateral (**B**) views of our patient's thyroid-associated orbitopathy on presentation. These images can be compared with anterior (**C**) and lateral (**D**) views of her TAO post-RAI ablation, anterior (**E**) and lateral (**F**) views six months after decompressive eye surgery, and anterior (**G**) and lateral (**H**) views four months after second eye surgery.

success of our treatment at various points throughout the patient's course by using the Clinical Activity Score (CAS) and VISA inflammatory score (Table 1). At her final follow-up visit four years after initial presentation, Hertel measurements were within normal limits and TSH was normalized (Table 1). Her GO showed significant improvement as demonstrated in Figures 2A and 2B. She continues thyroid hormone replacement therapy with oral levothyroxine 200 mcg daily.

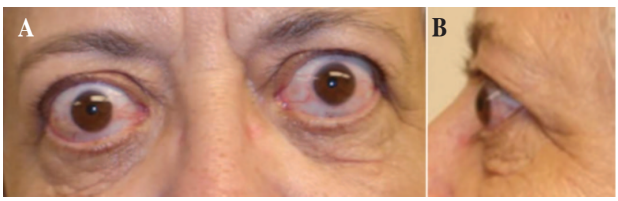

Figure 2. Anterior (**A**) and lateral (**B**) views of her thyroid-associated orbitopathy during final follow-up visit four years after initial presentation.

DISCUSSION

As only a small fraction of patients with GO are euthyroid at the time of presentation, our euthyroid patient, who denied any previous thyroid disease, radioactive iodine therapy, smoking history or preceding stressful events (environmental factors which have been identified as risk factors for exacerbation of Graves' disease[6,29,30]), is unusual. It is important to note her three-month prednisone therapy prior to referral visit, which could explain thyroid-function tests at referral (low TSH and FT4 within normal limits).[31]

The majority of GO cases appear in the context of hyperthyroidism. Luckily, severe GO occurs in less than 5% of patients with Graves' disease. In addition, it is very uncommon to have concomitant PTMCs, which can complicate the management of such patients, as radioactive iodine therapy usually is not recommended for patients with severe or moderate GO since it can aggravate the progression to orbitopathy.[11,32] In assessing the chances of remission in patients with Graves' disease and/or GO, measuring autoantibodies is helpful.[33,34] Thyroid-stimulating immunoglobulins (TSI) are very disease-specific with a detection rate of more than 90% in patients with Graves'disease.[9,10,35] Whereas TSI is measured as an index in a bioassay that is very sensitive, unless there are very high TSI concentrations present (in which case a high-dose hook effect might occur), TSH-R antibodies are recorded in an assay measuring TSH-binding inhibition (TBII). Table 1 demonstrates how both assays compared for our patient, while also comparing both assays with serum levels of thyroglobulin in its function as a tumor marker. Euthyroid GO exists as a mixture between fluctuating amounts of thyroid-stimulating antibodies (measured by TSI) and thyroid-blocking

antibodies (for which there is no direct assay commercially available).[36-38] Thyroid-blocking antibodies are part of the TBII assay, though this assay is blind to the stimulatory or inhibitory nature of each anti-TSH-receptor antibody it measures. In the future, as more specific assays become commercially available, hopefully we will be able to elicit even more information about the biochemical basis for euthyroid GO.

Pazaitou-Panayiotou et al. reviewed the literature on thyroid cancer in patients with hyperthyroidism and found that most carcinomas associated with Graves' disease are small and found incidentally during postoperative histological evaluation of the thyroid.[39] They also concluded that microcarcinomas found in Graves' disease seldom cause metastases or recurrence, leaving the clinical significance of these microcarcinomas as uncertain. Our case correlates well with these findings, as both PTMCs were found incidentally on histological evaluation. These PTMCs did correspond with the thyroid nodules detected on ultrasound, though they occupied only a small portion of the nodules. Following total thyroidectomy and radioactive iodine ablation, our patient has remained free of any evidence of recurrence to this day. In a Scottish patient population with Graves' disease, administering 10 mCi of radioactive iodine was as effective as 15 mCi.[40] Interestingly, patients with Graves' disease and mild to moderate GO, those with large goiter or relapse of hyperthyroidism had had their hyperthyroidism and GO improved following total thyroidectomy alone.[41,42] In retrospect, radioactive iodine ablation was necessary in our case, as multifocal tumors have been identified as a risk factor for high-risk or aggressive PTMC phenotype.[43] For unifocal PTMC without risk factors, RAI ablation often is not necessary.

We utilized most of the treatment modalities available to cope with the undulant evolution of this case. Also, we investigated the possibility of employing new therapies such as rituximab (see http://clinicaltrials.gov/ct2/show/NCT00595335) or cyclosporine should her symptoms return.[44,45] Recent research has shown that peroxisome proliferator-activated receptor-α (PPARα) agonists may exert immunomodulatory effects in GO by inhibiting various chemokines secreted by GO fibroblasts and preadipocytes.[46,47] Perhaps addressing this pathogenic mechanism will help reduce the chance of disease recurrence in the future.

In conclusion, this case underscores the difficulty of treating GO even when thyroid function and antithyroidal antibodies are normal(ized) and thyroid antigen exposure has been minimized. Concomitant incidental papillary thyroid microcarcinoma can complicate management, as TSH-R stimulating antibodies may be present and, at times, TSH suppression may be desired making the patient hyperthyroid instead of euthyroid (the latter more desirable for GO).

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DISCLOSURE

The authors have no financial conflict of interest with this report.

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